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Inhaled Nitric Oxide in Preterm Infants

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-Based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. This report was requested and funded by the National Institutes of Health (NIH), Office of Medical Applications of Research (OMAR). The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review prior to their release.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome comments on this evidence report. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to epc@ahrq.gov.

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Structured Abstract

Objectives. To systematically review the evidence on the use of inhaled nitric oxide (iNO) in preterm infants born at or before 34 weeks gestation age who receive respiratory support.

Data sources. We searched MEDLINE, EMBASE, the Cochrane Central Register of Controlled Studies (CENTRAL) and PsycInfo in June 2010. We also searched the proceedings of the 2009 and 2010 Pediatric Academic Societies Meeting and ClinicalTrials.gov. We identified additional studies from reference lists of eligible articles and relevant reviews, as well as from technical experts.

Review methods. Questions were developed in collaboration with technical experts, including the chair of the upcoming National Institutes of Health Office of Medical Applications of Research Consensus Development Conference. We limited our review to randomized controlled trials (RCTs) for the question of survival or occurrence of bronchopulmonary dysplasia (BPD) and for the question on short-term risks. All study designs were considered for long-term pulmonary or neurodevelopmental outcomes, and for questions about whether outcomes varied by subpopulation or by intervention characteristics. Two investigators independently screened search results, and abstracted data from eligible articles.

Results. We identified a total of 14 RCTs, reported in 23 articles, and eight observational studies. Mortality rates in the NICU did not differ for infants treated with iNO versus those not treated with iNO (RR 0.97 (95% CI 0.82, 1.15)). BPD at 36 weeks for iNO and control groups also did not differ (RR 0.93 (0.86, 1.003) for survivors). A small difference was found between iNO and control infants in the composite outcome of death or BPD (RR 0.93 (0.87, 0.99)). There was inconsistent evidence about the risk of brain injury from individual RCTs, but meta-analyses showed no difference between iNO and control groups. We found no evidence of differences in other short term risks. There was no evidence to suggest a difference in the incidence of cerebral palsy (RR 1.36 (0.88, 2.10)), neurodevelopmental impairment (RR 0.91 (0.77, 1.12)), or cognitive impairment (RR 0.72 (0.35, 1.45)). Evidence was limited on whether the effect of iNO varies by subpopulation or by characteristics of the therapy (timing, dose and duration, mode of delivery, or concurrent therapies).

Conclusions. There was a seven percent reduction in the risk of the composite outcome of death or BPD at 36 weeks PMA for infants treated with iNO compared to controls, but no reduction in death or BPD alone. Further studies are needed to explore particular subgroups of infants and to assess long term outcomes including function in childhood. There is currently no evidence to support the use of iNO in preterm infants with respiratory failure outside the context of rigorously conducted randomized clinical trials.

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Executive Summary

Background

Neonatal lung disease is the most common complication of preterm delivery and causes significant morbidity and mortality. Disorders of prematurity and respiratory distress are among the leading causes of infant mortality in the U.S.

The use of inhaled nitric oxide (iNO) has been approved by the U.S. Food and Drug Administration for respiratory failure of the term and near-term infant and is recommended by professional societies, such as the American Academy of Pediatrics. Evidence supporting the use of iNO in term or near term infants is summarized by a Cochrane review that found that use of iNO therapy reduced the need for extracorporeal membrane oxygenation in term and near term (> 34 weeks gestation) infants with respiratory failure, but did not change neurodevelopmental outcomes at two to three years of age. There is a need to consider the evidence about the use of iNO therapy in preterm infants ≤ 34 weeks of gestation.

This report summarizes the available evidence on the use of iNO in preterm infants born at or before 34 weeks gestation age who receive respiratory support. The report addresses the following questions:

1. Does iNO therapy increase survival and/or reduce the occurrence or severity of bronchopulmonary dysplasia (BPD) among premature infants who receive respiratory support?

2. Are there short-term risks of iNO therapy among premature infants who receive respiratory support?

3. Are there effects of iNO therapy on long-term pulmonary and/or neurodevelopmental outcomes among premature infants who receive respiratory support?

4. Does the effect of iNO therapy on BPD and/or death or neurodevelopmental impairment vary across subpopulations of premature infants?

5. Does the effect of iNO therapy on BPD and/or death or neurodevelopmental impairment vary by timing of initiation, mode of delivery, dose and duration, or concurrent therapies?

Methods

We searched MEDLINE, EMBASE, the Cochrane Central Register of Controlled Studies (CENTRAL) and PsycInfo in June 2010. We also searched the proceedings of the 2009 and 2010 Pediatric Academic Societies Meeting and ClinicalTrials.gov. We identified additional studies from reference lists of eligible articles and relevant reviews, as well as from technical experts. Questions were developed in collaboration with technical experts, including the chair of the upcoming National Institutes of Health Office of Medical Applications of Research Consensus Development Conference. We limited our review to randomized controlled trials (RCTs) for the question of survival or occurrence of bronchopulmonary dysplasia (BPD) and for the question on short-term risks. All study designs were considered for long-term pulmonary or neurodevelopmental outcomes, and for questions about whether outcomes varied by subpopulation or by intervention characteristics. Two investigators independently screened search results, and abstracted data from eligible articles.

Results

We identified a total of 14 RCTs, reported in 23 articles, and eight cohort studies addressing our questions. Our major findings are summarized by key question.

Key Question 1. Does iNO therapy increase survival and/or reduce the occurrence or severity of bronchopulmonary dysplasia (BPD) among premature infants who receive respiratory support?

- There is no statistically significant effect of iNO compared to placebo on survival or mortality rates in preterm NICU infants requiring mechanical ventilation.
- There is insufficient evidence to determine whether iNO reduces the rate of bronchopulmonary dysplasia (BPD), as defined by requiring supplemental oxygen at 36 weeks postmenstrual age, in preterm NICU infants requiring mechanical ventilation.
- There is small but statistically significant reduction in the composite variable of death or BPD at 36 weeks PMA for infants treatment with iNO compared to infants in control groups.
- Preterm infants who required mechanical ventilation and were the subjects of randomized controlled trials of inhaled nitric oxide were a high risk population with high mortality and BPD rates during NICU hospitalization.

Fourteen RCTs addressed death or BPD. The definition of outcomes, specifically the time outcomes were assessed, differed across studies. Evidence on the outcome of death was considered of moderate strength as was BPD at 36 weeks PMA.

Key Question 2. Are there short-term risks of iNO therapy among premature infants who receive respiratory support?

- There is insufficient evidence of a neuroprotective effect of iNO in preterm infants.
- There is no evidence that treatment of preterm infants with iNO influences the rates of other complications of prematurity, including patent ductus arteriosus (PDA), sepsis,

necrotizing enterocolitis (NEC), severe retinopathy of prematurity (ROP), pulmonary hemorrhage, or air leaks.
- No study reported accumulation of toxic levels of methemoglobin or nitrogen dioxide.

Fourteen RCTs provided data on short term risks of iNO therapy. There was moderate strength of evidence on IVH, PVL, PVL, PDA and NEC.

Key Question 3. Are there effects of iNO therapy on long-term pulmonary and/or neurodevelopmental outcomes among premature infants who receive respiratory support?

- There is insufficient evidence to determine whether iNO therapy in preterm infants who require respiratory support influences the incidence of cognitive, motor or sensory impairments, or neurodevelopmental disability.
- There is evidence suggesting that iNO therapy in preterm infants who require respiratory support may decrease the need for respiratory medications at one year of age.
- There is insufficient evidence to determine whether iNO therapy in preterm infants who require respiratory support impacts long-term health outcomes such as respiratory symptoms, rehospitalization after NICU discharge, and growth.

Twelve articles reported long term outcomes; nine RCTs and three observational studies. Evidence was considered to be of low strength for neurodevelopmental and coginitive outcomes and for cerebral palsy. Evidence for death as a long term outcome was moderate. Evidence on all of the other long term outcomes was considered low or insufficient.

Key Question 4. Does the effect of iNO therapy on BPD and/or death or neurodevelopmental impairment vary across subpopulations of premature infants?

- There is insufficient evidence to determine whether the effect of iNO therapy on mortality, BPD, or motor impairment differs by the birth weight of the treated infants.
- There is insufficient evidence to evaluate the relationship between iNO therapy and infant sex, race/ethnic group, gestational age, or socioeconomic status.
- There are no published data available to evaluate the association between iNO therapy and, antenatal steroids, chorioamnionitis, multiple birth, or growth restriction.
- There is insufficient evidence concerning the relationship between iNO therapy and the severity of illness.
- There is insufficient evidence that iNO therapy improves outcome of infants suffering respiratory failure from pulmonary hypoplasia, respiratory distress syndrome or pulmonary hypertension.
- There is no consistent pattern of infants that respond to iNO therapy and those that do not.
- There is no consistent pattern of infants that respond to iNO therapy and those that do not.

We identified six RCTs with five followup studies, and six other studies, that addressed this question. The definition of outcomes varied across studies, and many of the subgroup analyses were by post hoc analyses. Death, BPD at 36 weeks PMA and survival without BPD had

moderate strength of evidence. All other outcomes for this question had evidence judged to be low strength.

Key Question 5. Does the effect of iNO therapy on BPD and/or death or neurodevelopmental impairment vary by timing of initiation, mode of delivery, dose and duration, or concurrent therapies?

- There is insufficient evidence to determine if initiating iNO therapy for acute respiratory distress at ≤ 3 days reduces the risk of death or bronchopulmonary dysplasia (BPD) at 36 weeks PMA, or death and neurodevelopmental disability at 1 year of age, corrected for gestational age at birth.
- In infants with developing BPD, there is insufficient evidence to determine if treatment with iNO during the second week after birth improves survival without BPD compared with treatment during the third week after birth.
- There is insufficient evidence to determine the effect of delivery of iNO by high frequency ventilation on either death or BPD, or neurodevelopmental outcome compared with conventional ventilation.
- There is insufficient evidence to support an optimal dose of iNO or duration of exposure to improve outcome or prevent harm.
- There is insufficient evidence to determine the effect of iNO with concurrent therapy.

We identified 14 RCTs addressing this question. No studies allowed for assessment of duration of therapy. Comparison across studies was limited by differences in definitions of outcomes. All but two of the studies provided data based on post hoc analysis, and so should be interpreted with caution. Strength of evidence was moderate for survival without BPD and BPD at 36 weeks. For all other outcomes, evidence was low strength.

Future Research

Current evidence does not support the routine use of iNO to treat premature infants. However, we should not abandon the possibility that iNO may someday become a component of a treatment strategy for some preterm infants receiving respiratory support. Several factors contribute to our recommendation to continue the study of iNO: 1) our finding a small but statistically significant difference in death or BPD at 36 weeks PMA, the common primary outcome variable of 73% of RCT conducted to-date; 2) the statistically significant finding of a diminished need for chronic pulmonary medication at one year corrected age, suggesting less severe lung disease in those treated with iNO, and 3) no studies have been powered to detect meaningful differences in infant functional outcome or quality of life with iNO treatment compared to standard therapy.

Specific considerations for future research are listed below.

Patients

- RCTs must be adequately powered to assess the effect of iNO on subgroups of preterm infants, such as those of varying birth weight.

- Special care must be taken if infants born at the limit of viability are included in RCTs. These infants do not yet have alveoli (gas exchange occurs through their terminal bronchioles) and their brains do not yet have gyri or sulci. They are most vulnerable to organ injury, which may be most evident on long-term follow-up. Every effort must be taken to obtain pulmonary, neurodevelopmental and health follow-up for all infants in this category.
- There may be a value to viewing the use of iNO in terms of postmenstrual age, which is a better measure of degree of maturation and takes into account both gestational age and chronologic age in developing preterm infants.

Intervention

- Since the goal is to support pulmonary and brain development in the NICU, courses of iNO given for weeks, not days, should be studied.
- Mode of ventilation should be considered in randomization schemes for trials restricted to infants < 1500 grams, those at highest risk for death, BPD and neurodevelopmental impairment, to adequately address the question concerning mode of delivery.
- As many of the smallest preterm infants are managed with CPAP or high flow nasal cannula alone, without intubation, information concerning iNO delivery with these devices is needed.

Outcomes

- Future RCTs should require neuroimaging by standardized protocols before trial enrollment, to detect the occurrence and progression of brain injury during iNO treatment.
- Studies should be powered to assess long term neurodevelopmental, pulmonary and other health outcomes.
- Outcomes should focus on functional status and quality of life, as well as neurodevelopmental disabilities.
- Studies are needed to provide information on resource utilization such as rehospitalizations, medications, physicians' visits. Future focus should be on the real pulmonary problems of prolonged hospitalizations, use of supplemental oxygen and pulmonary medications after NICU discharge, prevalence of reactive airway disease and recurrent hospitalizations.
- Consideration should be given to assess longer term childhood outcomes (e.g., pulmonary function tests, school performances).
- Cost benefit analyses should be conducted with multicenter RCTs of iNO.

Evidence Report

Chapter 1. Introduction

Background

Neonatal lung disease is the most common complication of preterm delivery, and results in significant morbidity and mortality.[1] Preterm infants suffer from both acute and chronic respiratory failure as a result of anatomic and biochemical disruption of lung function, lung inflammation and oxidative stress, nutritional deficiencies, and arrest of tracheobronchial and pulmonary vascular growth (see Appendix A[a], List of Acronyms). Treatment for acute respiratory failure often contributes to evolving bronchopulmonary dysplasia (BPD) and chronic respiratory failure, due to barotrauma and oxygen toxicity from prolonged respiratory support, deficient nutrition, as well as immaturity of lung growth, vascular development and immunologic defenses. Pulmonary hypertension may occur in association with acute and/or chronic respiratory failure.[2] Multiple etiologies make finding an effective treatment for respiratory failure in preterm infants challenging. Disorders related to prematurity and respiratory distress are among the leading causes of infant mortality in the U.S.[3]

Treatment Options

Treatment options for respiratory failure in preterm infants include a variety of modalities. Prenatal steroids, antibiotics, exogenous surfactant replacement, tidal volume ventilation, conventional ventilation, continuous positive airway pressure, high flow oxygen administration, and high frequency ventilation are all used as therapeutic modalities. Treatment of preterm infants with inhaled nitric oxide (iNO) as a rescue therapy for refractory hypoxemic respiratory failure is an extension of the relative success of the treatment of term and near term infants with iNO.[4]

Mechanism of Action

Endogenous nitric oxide (NO), produced in vascular endothelial cells, regulates vascular tone. [5] NO diffuses into adjacent vascular smooth muscle cells and activates soluble guanylyl cyclase, leading to the activation of cGMP-dependent protein kinase.[6] The subsequent signal transduction cascade results in vascular smooth muscle cell relaxation and vasodilatation.[6, 7] When exogenous nitric oxide is inhaled, it is a selective pulmonary vasodilator decreasing pulmonary vascular resistance without affecting systemic vascular tone.[8] This occurs because the low molecular weight and high lipid solubility of inhaled NO allows rapid diffusion in the ventilated lung from the alveoli to direct contact with arterioles.[9] In addition, NO has a very short half-life,[5, 10] and NO is rapidly deactivated by heme in hemoglobin reducing its effect on other smooth muscle in the body.[11, 12]

Since 1999, iNO has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of severe hypoxemia and persistent pulmonary hypertension of the newborn

[a] Appendixes and evidence tables for this report can be found at:
http://www.ahrq.gov/downloads/pub/evidence/pdf/inoinfants/inoinfants.pdf

(PPHN) in term and near term infants.[13] PPHN is a syndrome associated with several neonatal cardio pulmonary etiologies, and is characterized by high pulmonary vascular resistance (PVR).[7] High PVR causes extrapulmonary shunting of blood right to left across the ductus arteriosus and/or foramen ovale and may cause critical hypoxemia.[7, 14] In newborns, the use of iNO therapy to selectively lower PVR and reduce extrapulmonary shunting accounts for the acute improvement in oxygenation observed with PPHN.[15]

In severe respiratory failure, hypoxemia may also occur with intrapulmonary shunting, due to atelectasis and ventilation/perfusion inequality.[7] Thus, inhaled nitric oxide may also benefit preterm infants with parenchymal lung disease by redistributing pulmonary blood flow, thereby reducing intrapulmonary shunting and ventilation: perfusion mismatching.[16] Both mechanisms reduce secondary lung injury from barotrauma, volutrauma, and oxygen toxicity by reducing the need for prolonged respiratory support.

Inhaled NO may have other characteristics beneficial to preterm infants. Ballard, 2006 demonstrated that iNO therapy in a preterm baboon model of evolving BPD increased maximal lung volume, decreased the total protein:phospholipid (PL) ratio of surfactant, and had little effect on the composition of surfactant PL or proteins, suggesting that iNO may be associated with less severe lung injury and improved surfactant function.[17] In a companion study, again in a premature baboon model, McCurnin, 2005 reported lung growth after iNO therapy mimicked that seen in utero.[18] Inhaled NO has also been shown to reduce inflammation and oxidant injury in animal models of hyperoxic lung injury.[19, 20] Furthermore, NO may play a role in early lung development. A newborn rat model with both structural and functional characteristics of BPD[21] showed a reduction in pulmonary hypertension and a preservation of lung growth with early introduction of iNO therapy.[21] Similarly, following exposure to hyperoxia in neonatal rats, Lin, 2005 found that iNO exposure during recovery restored distal lung growth and alveolarization.[22]

Inhaled NO has several potential toxic complications from both direct and indirect effects.[23] The preterm infant is particularly vulnerable to reactive oxidant species induced damage due to the relative inadequacy of antioxidant enzymes in the lung.[24] In the presence of oxygen, nitric oxide forms nitrogen dioxide (NO_2), a potent inflammatory agent leading to pulmonary edema and lung injury, but the formation is slow at low levels of NO_2.[11, 25] A NO_2 dose of 5 ppm is considered the maximum environmentally safe dose, necessitating careful monitoring of infants receiving iNO therapy.[26] In simulation, delivery of 20 ppm iNO at high oxygen concentrations resulted in the formation of < 1 ppm NO_2. NO may also adversely affect platelet aggregation and adhesion,[27] although the evidence is conflicting[28] and has not been reported in trials with infants.

Methemoglobinemia, the resultant reaction of nitric oxide with hemoglobin, reduces oxygen carrying capacity at high concentrations. Accumulation of toxic levels of methemogolobin have not been demonstrated when iNO is delivered at < 80ppm,[29] the range in which most infants are treated, but requires constant monitoring during treatment.

FDA Approved Indication and Usage

The U.S. FDA approved iNO for use in intubated full term and late preterm infants with hypoxemic respiratory failure in 1999[13] Current labeling of iNO is for use in respiratory failure in term and near term infants (> 34 weeks gestation). The initial recommended starting dose for these infants is 20 ppm with continued use for 14 days or until improvement in the underlying disease process results in normal oxygen saturations. The dose is weaned incrementally with improving oxygen saturations beginning as soon as four hours after the initiation of therapy, to 5

ppm before discontinuation. For infants that do not respond to initial iNO therapy, the dose may be increased to 40 to 80 ppm. Brief exposure to these higher doses appears to be safe, but sustained treatment with 80 ppm will increase the risk of methemoglobinemia,[7] with little added clinical benefit.

Utilization of iNO

Since the FDA approval for use of iNO in full term and late preterm infants, a number of studies have been conducted on the use of iNO in clinically diverse populations of preterm infants.[30-40] These studies demonstrate significant variability in their clinical indications for the use of iNO, from its prophylactic use in preterm infants with mild acute respiratory distress to prevent BPD and chronic lung disease, to its use as a late rescue therapy for preterm infants with severe BPD, with resulting wide variations in inclusion and exclusion criteria for study samples. There has been considerable variation in dosage and timing of iNO among studies. Differing findings regarding pulmonary effects and effects on the most common primary outcome variable, death or BPD, raises concerns about gaps in our understanding of physiological effects of iNO in the rapidly developing preterm lung. In addition, differences in the direction of effect on the developing preterm brain raise questions as to whether treatment of preterm infants with iNO increases or decreases the incidence of brain injury.

This controversy has resulted in wide variations in clinical practice, as reports of the longer term pulmonary and neurodevelopmental outcomes at ages two to six years are just emerging.

Purpose of This Evidence Report

Inhaled NO has demonstrated efficacy in improving oxygenation and reducing the need for extracorporeal membrane oxygenation (ECMO) in late preterm infants born after 34 weeks gestation and full term infants with respiratory failure, with no evidence of long term benefits.[4] Despite the approved use of iNO in full term and late preterm infants, the developmentally distinct mechanisms of respiratory failure and differing cardiovascular, pulmonary, and pharmacokinetic characteristics of more immature infants require systematic study of the short and long term outcomes for preterm infants treated with iNO to prevent or treat respiratory failure.

A 2006 meta-analysis included five randomized controlled trials (RCTs) with 808 infants born before 34 weeks gestation.[32] The authors concluded that while preterm infants treated with iNO had reduced treatment failure (death or chronic lung disease (CLD); RR 0.81 (0.70, 0.93)) further research was needed on risks and on later neurodevelopmental outcomes. A 2007 Cochrane review of 11 RCTs analyzed data on 3,251 preterm infants (defined as < 35 weeks gestation) in terms of illness severity, dose and timing of iNO. [31] The Cochrane review concluded that iNO has no proven efficacy as a rescue therapy to treat very ill ventilated preterm infants, and it may increase the incidence of brain injury (one trial was stopped early).[31] It did not appear to prevent chronic lung disease or BPD in preterm infants. Subgroup analyses in some of the multicenter RCTs of iNO in preterm infants suggest that iNO may be beneficial in some preterm infants (e.g., those with higher birth weights, milder respiratory illness, or persistent pulmonary hypertension).[32, 40-42]

The Cochrane review acknowledged very limited data on long term outcomes of preterm infants treated with iNO. If iNO is beneficial, the number need to treat would be very large.

Papers published or presented from 2007 to present report conflicting results as to whether, in preterm infants, iNO has beneficial, adverse, or no effects on long term neurodevelopmental and pulmonary outcomes.[30, 43-46]

Despite the ongoing controversy, iNO continues to be used for hypoxemic respiratory failure in preterm infants < 34 weeks gestation even with potential harm to the developing lungs and brain.[47] There is an urgent need to weigh the current evidence as to whether iNO is a safe and effective treatment in preterm infants.

The Office of Medical Applications of Research (OMAR) at the National Institutes of Health (NIH) scheduled an NIH Consensus Development Conference: Inhaled Nitric Oxide in Preterm Infants to be held in October 2010. The Evidence-based Practice Center at the Johns Hopkins University (JHU) was asked by OMAR and the Agency for Healthcare Research and Quality (AHRQ) to prepare an evidence report for this conference.

Key Questions

We sought to identify and synthesize evidence addressing the following questions:

1. Does inhaled nitric oxide (iNO) therapy increase survival and/or reduce the occurrence or severity of bronchopulmonary dysplasia (BPD) among premature infants who receive respiratory support?
2. Are there short term risks of iNO therapy among premature infants who receive respiratory support?
3. Are there effects of iNO therapy on long term pulmonary and/or neurodevelopmental outcomes among premature infants who receive respiratory support?
4. Does the effect of iNO therapy on BPD and/or death or neurodevelopmental impairment vary across subpopulations of premature infants?
5. Does the effect of iNO therapy on BPD and/or death or neurodevelopmental impairment vary by timing of initiation, mode of delivery, dose and duration, or concurrent therapies?

For the purposes of our review, we sought studies that included infants less than or equal to 34 weeks gestation age. The outcomes of interest are described in detail in Chapter 2.

Chapter 2. Methods

Our objective was to review and synthesize the evidence on the use of inhaled nitric oxide (iNO) in preterm infants born at or before 34 weeks gestation age who require respiratory support. This review addresses the short term outcomes bronchopulmonary dysplasia, cardiopulmonary risks, infectious risks, neurological risks, as well as short term survival and death. Long term outcomes including pulmonary outcomes, neurodevelopmental outcomes, growth, chronic medical conditions, and survival to childhood were also assessed. The results of this report will be presented to an NIH Consensus Panel in October 2010.

Topic Development

The core team worked with technical experts, the NIH Consensus Panel Chair, to develop and refine the Key Questions that are presented in Chapter 1 (Introduction). Prior to searching for literature, we clarified the definitions of these key questions and the types of evidence which we would include in our review. Topic development was facilitated by the results of preliminary searches, discussions among team members, and input from our Technical Expert Panel.

Key Questions 1 and 2 address short term impact of iNO use on preterm infants. Key Question 1 addresses the impact of iNO on survival and/or bronchoplulmonary dyplasia. Key Question 2 addresses short term risks to preterm infants receiving iNO therapy. Based on discussion with our experts, we decided to limit our review to randomized controlled trials for these two questions.

Key Question 3 addresses long term outcomes of iNO use in preterm infants. This question focuses on pulmonary and neurodevelopmental outcomes. We did not limit the consideration of studies by study design. We identified, and abstracted separately case reports and case series. However, we ultimately chose not to include case reports and case series in our formal review as the level of detail in these reports was generally insufficient.

The impact of iNO therapy on bronchopulmonary dyplasia, death, and/or neurodevelopmental outcomes across subpopulations of premature infants is addressed in Key Question 4, and influence of the timing of initiation, mode of delivery, dose and duration, or concurrent therapies is addressed in Key Question 5. Included studies for this question were not limited by study design except for the exclusion of case reports and case series, as for Key Question 3.

Analytic Framework

We developed a framework (Figure 1) to illustrate the components of the key questions, including the population, intervention and outcomes. The framework also delineates the subgroups; treatment characteristics, such as dose of iNO; and specific short and long term outcomes of interest. Short term outcomes were defined as adverse events and clinical outcomes associated with iNO treatment that occur during the initial hospitalization after birth. Long term outcomes were defined as the effects of iNO treatment on infant health and functional outcome in early childhood and include measures of chronic pulmonary disease, growth, developmental delay and disability, and survival.

Search Strategy

Searching the literature involved identifying reference sources, formulating a search strategy for each source, and executing and documenting each search. For the searching of electronic databases we used controlled vocabulary terms (i.e., MeSH, EMTREE), combined with text words for iNO (see Appendix B[b], Detailed Search Strategies) We also looked for eligible studies by reviewing the references in pertinent reviews, by scanning conference proceedings, by querying our experts, and through knowledge shared at core team meetings.

Sources

Our search included electronic and hand searching. On November 9, 2009, we ran searches of MEDLINE® (using PubMed), EMBASE®, the Cochrane Central Register of Controlled Studies (CENTRAL), and PsycInfo databases. These searches were run again on June 23, 2010. We also searched the references of articles included in this study and those tagged as of interest during the screening process. As information on long term outcomes for infants treated with iNO is just emerging, we also scanned the proceedings of the Pediatric Academic Societies Meetings in 2009 and 2010. ClinicalTrials.gov was searched for ongoing or completed trials. Investigators of ongoing trials were not contacted for information. We decided that the investigators conducting ongoing trials would only be contacted if they were studying outcomes with no published information. There were no limits used in the searches, including any based on publication date.

Search Terms and Strategies

We developed a strategy for MEDLINE, accessed via PubMed, based on an analysis of the MeSH terms and text words of key articles identified *a priori*. The PubMed strategy formed the basis for the strategies developed for the other electronic databases (see Appendix B).

Organization and Tracking of the Literature Search

The results of the searches were downloaded into ProCite® version 5.0.3 (ISI ResearchSoft, Carlsbad, CA). Duplicate articles retrieved from the multiple databases were removed prior to initiating the review. From ProCite, the articles were uploaded to Distiller SR © (Evidence Partners, Ottawa, Ontario). We used this software to store full articles in portable document format (PDF) and to track the results of the abstract screen, article screen, and data abstraction.

[b] Appendixes and evidence tables for this report can be found at:
http://www.ahrq.gov/downloads/pub/evidence/pdf/inoinfants/inoinfants.pdf

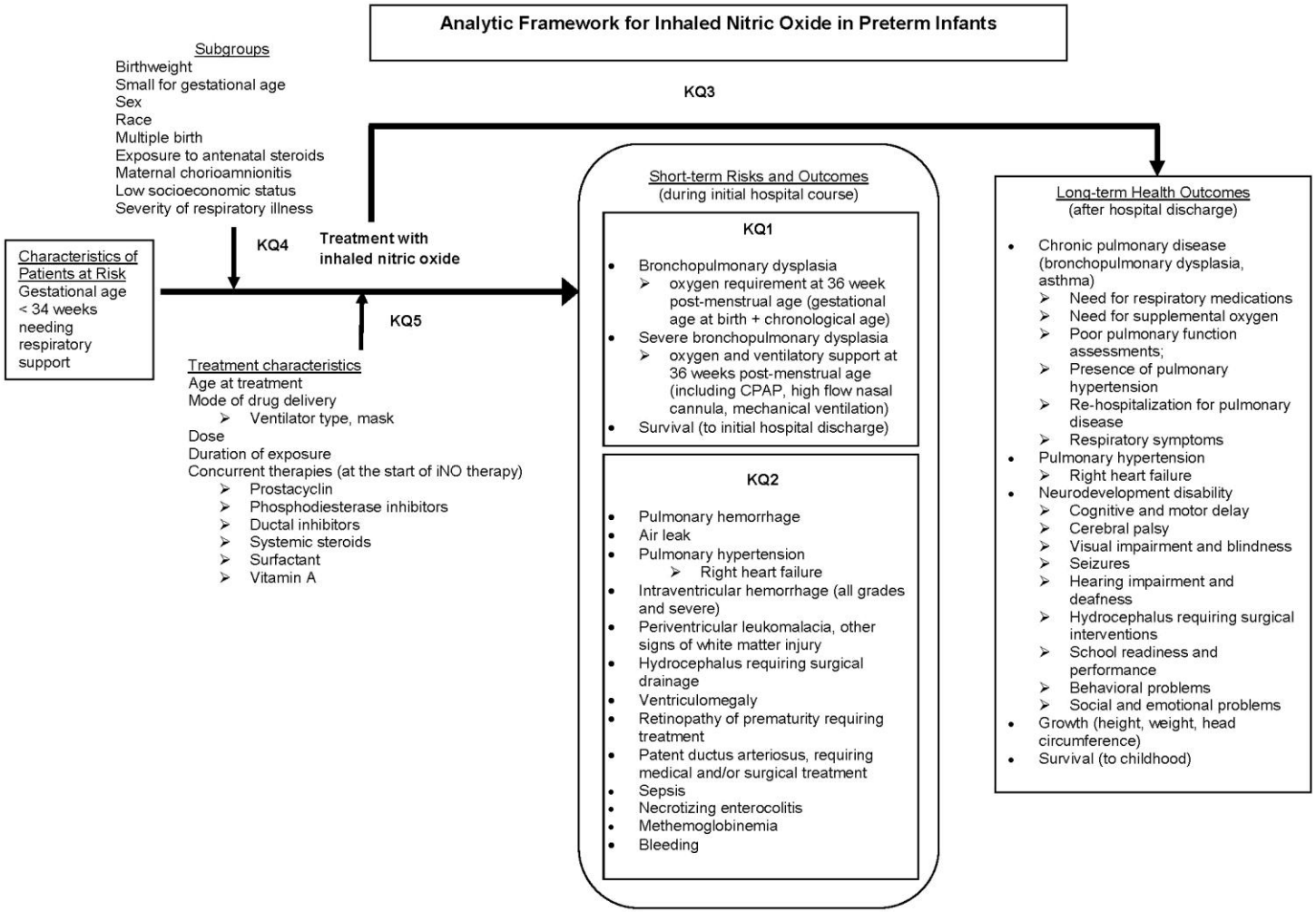

Figure 1. Analytic framework

Study Selection

Abstract Screen

Each abstract was independently screened by two reviewers. An abstract was excluded at this level if it did not reporting any original data, did not include human data, did not include infants born at less than or equal to 34 weeks of gestation, did not include preterm infants requiring respiratory support, did not include preterm infants treated with inhaled nitric oxide, did not address any of the key questions, or addressed Key Question 1 and or 2 but was not a randomized controlled trial. An option was provided for reviewers to indicate other reasons for exclusion. Articles tagged as non English were reviewed by individuals fluent in the language of publication to determine eligibility. (Appendix C, Abstract Review Form).

Abstracts were promoted to be screened using full text article if both reviewers agreed that the abstract could apply to one or more of the key questions. An abstract could be excluded for different reasons by the two reviewers. Disagreements about the eligibility of an abstract were resolved by discussion between the two reviewers or by adjudication of a third reviewer.

Article Screen

Full text articles underwent another independent review by paired investigators to determine whether they should be included in the full data abstraction (see Appendix C, Article Inclusion/Exclusion Form). If articles were deemed to have applicable information, they were included in the data abstraction. Articles could be excluded at this level for the same set of reasons used at the abstract screen level with an additional exclusion criterion of no abstractable data. Articles that had English language abstracts that were promoted to this level but were tagged for exclusion as “not English language” were reviewed by investigators fluent in the specific language for eligibility.

Articles were promoted to data abstraction if both reviewers agreed. An article could be excluded for different reasons by the two reviewers. Disagreements about the eligibility of an article were resolved by discussion between the two reviewers or by adjudication of a third reviewer.

Data Abstraction

We used an independent review process to abstract data from the included articles. In this process, both a clinical expert and a research assistant completed all relevant data abstraction forms independently. Reviewers were not masked to the articles’ authors, institutions, or journal.[48] Disagreements that could not be resolved between the reviewers were resolved through consensus adjudication at team meetings.

For all articles, reviewers extracted information on general study characteristics: study design, whether the study was a followup or additional analysis of another study, location, recruitment start and end dates, inclusion and exclusion criteria, description of the study intervention, iNO dose and duration, and length of followup (see Appendix C, Study

Characteristics Form). Participant characteristics were also abstracted: number of participants, gestational age, birth weight, participant age, sex, and relevant background data such as disease severity, mode of ventilation, and concurrent medications. Maternal characteristics were also collected on this form (see Appendix C, Participant Characteristics Form).

Reviewers abstracted data, for all study arms and subgroups, on a predefined set of outcomes (see Appendix C, All Outcomes). Case reports were abstracted separately to identify whether they included data relevant to this study (see Appendix C, Case report form). These data were ultimately not included as the level of detail in these reports was generally insufficient.

Quality Assessment of Individual Studies (Risk of Bias Assessment)

In order to assess the risk of bias in randomized controlled trials, we used the Cochrane Collaboration Tool for Assessing Risk of Bias from the Cochrane Handbook for Systematic Reviews of Interventions.[49] This tool was used to assess six categories of potential bias; (1) sequence generation, (2) allocation concealment, (3) blinding, (4) incomplete data reported, (5) selective reporting bias as well as (6) other sources of bias. For each bias category reviewers answered one or more questions and entered "Yes" for a low risk of bias, "No" for a high risk of bias or "Unclear."

For the observational studies we adapted the Newcastle-Ottawa Scale in order to determine the risk of bias of the reported data in both cohort and case control studies.[50] This form assessed possible sources of bias including (1) representativeness of the study cohort, (2) selection of the control cohort (if applicable), (3) selection of treated patients, (4) presence of the outcome of interest at the start of the study, (5) comparability of the cohorts, (6) reporting bias, (7) whether the followup was long enough for outcomes to occur, and (8) incomplete data reported. Similar to the risk of bias forms for randomized control trials, we used question based forms where reviewers entered "Yes" for a low risk of bias, "No" for a high risk of bias or "Unclear" for questions about each source of bias.

The risk of bias forms were completed independently by paired reviewers. In the case of a disagreement, the two original reviewers conferred and agreed upon a single answer. These assessment instruments are included in Appendix C, Risk of Bias Forms.

Grading of the Body of Evidence

At the completion of our review, we assessed the quantity, quality and consistency of the body of available evidence addressing Key Questions 1 through 5. We used an evidence grading scheme recommended by the GRADE Working Group, and adapted by AHRQ in their Draft Methods Guide,[51] and recently published in the Journal of Clinical Epidemiology.[52] We considered the strength of the study designs with randomized controlled trials as the highest level of evidence, followed by observational studies. If an outcome was evaluated by at least one randomized controlled trial as well as observational studies our evidence grade was based on the randomized controlled trials and followed by the quality of the cohort studies. If an outcome was

evaluated by one or no randomized controlled trials, our evidence grade was based on the single randomized controlled trial in addition to the best available observational study.

We assessed the quality and consistency of the best available evidence, including assessment of the risk of bias in relevant studies, as well as aspects of consistency, directness, and precision as described in the Draft Methods Guide[51] and Owens, 2010.[52]

For each outcome of interest, two investigators graded the major outcomes for each Key Question and then the entire team discussed their recommendations and reached consensus.

Data Synthesis

We created a set of detailed evidence tables containing information extracted from eligible studies. We stratified the tables according to applicable key question. Once evidence tables were created, we rechecked selected data elements against the original articles. If there was a discrepancy between the data abstracted and the data appearing in the article, this discrepancy was brought to the attention of the investigator in charge of the specific data set and the data were corrected in the final evidence tables.

Meta-analyses were completed using MetaAnalyst. The program was developed by the Tufts Evidence-based Practice Center under contract with AHRQ.[53] The analyses were performed using a Der-Simonian Laird random effects model.[54] In this program, a Woolf-Haldane continuity correction of 0.5 was used when a cell contained zero events.[55] In all analyses, we examined the risk ratio for each outcome. Sensitivity analyses were performed to determine stability of the results. In general, meta-analyses were completed for outcomes reported across more than one study where the definition and measurement of the outcome was determined to be similar. Where relevant, further details regarding the decision to conduct or not conduct meta-analyses, the inclusion and exclusion of articles from the meta-analysis, and any sensitivity analyses, are provided in the results section.

Peer Review

We recruited external technical experts from diverse professional backgrounds, including neonatology, pulmonology, cardiology, and neurodevelopment. The technical experts were asked for input regarding key steps of the process, including development of the analytic framework, outcomes, and search strategies. In addition to the technical experts, three peer reviewers were recruited from various clinical and methodological settings.

Throughout the project, the core team sought feedback from the external technical experts and the NIH Panel Chair. A draft of the report was sent to the technical experts and peer reviewers, as well as to representatives of AHRQ, and the NIH Office of Medical Applications Research Panel Chair for this project. In response to the comments from the technical experts and peer reviewers, we revised the evidence report and submitted a summary of the comments and their disposition.

Chapter 3. Results

Literature Search/Abstract/Article Review

The literature search process identified 3104 unique citations. During the abstract review process, we excluded 2650 citations that did not meet one or more of the eligibility criteria (see Chapter 2 for details). At article review, we excluded an additional 423 articles that did not meet one or more of the eligibility criteria (see Appendix D[c], Excluded Articles). Thirty-one articles were eligible for inclusion in the review. There were 14 RCTs described in 23 articles, and eight observational studies (Figure 2).

Description of the Types of Studies Retrieved

There were 14 articles that applied to Key Question 1. Fourteen articles (all RCTs) applied to Key Question 2. Twelve articles applied to Key Question 3; three original RCTs with six followup studies, and three observational studies. Seventeen articles applied to Key Question 4; six RCTs with four followup studies, and seven cohort studies. Twenty-one articles applied to Key Question 5; 14 RCTs with seven followup studies (Table 1). Eight studies containing 13 case reports were also examined. As mentioned in Chapter 2, we reviewed the case reports and determined that the data were not of sufficient detail to be considered further.

Risk of Bias

As described in Chapter 2, we assessed each individual study for risk of bias using a study design specific tool. (See Appendix E, Evidence Tables 1 and 2.)

The RCTs and their followup studies were not assessed separately for risk of bias. Six of the 14 RCTs (along with their five followup studies) were assessed as having low risk of bias.[30, 34, 36, 37, 39, 40, 44, 56, 57, 58, 59] Three of the RCTs were determined to be at fair risk of bias.[60-62] The remaining five RCTs were assessed as having a high risk of bias.[63-67] Figure 3 provides a summary of the risk of bias for the RCTs. (Appendix E, Evidence Table 1).

None of the eight observational studies were considered to have a low risk of bias. Five received a fair risk of bias assessment, and received this score for a variety of reasons.[38, 68-71] Three observational studies were assessed at high risk of bias.[72-74] (Appendix E, Evidence Table 2).

[c] Appendixes and evidence tables for this report can be found at: http://www.ahrq.gov/downloads/pub/evidence/pdf/inoinfants/inoinfants.pdf

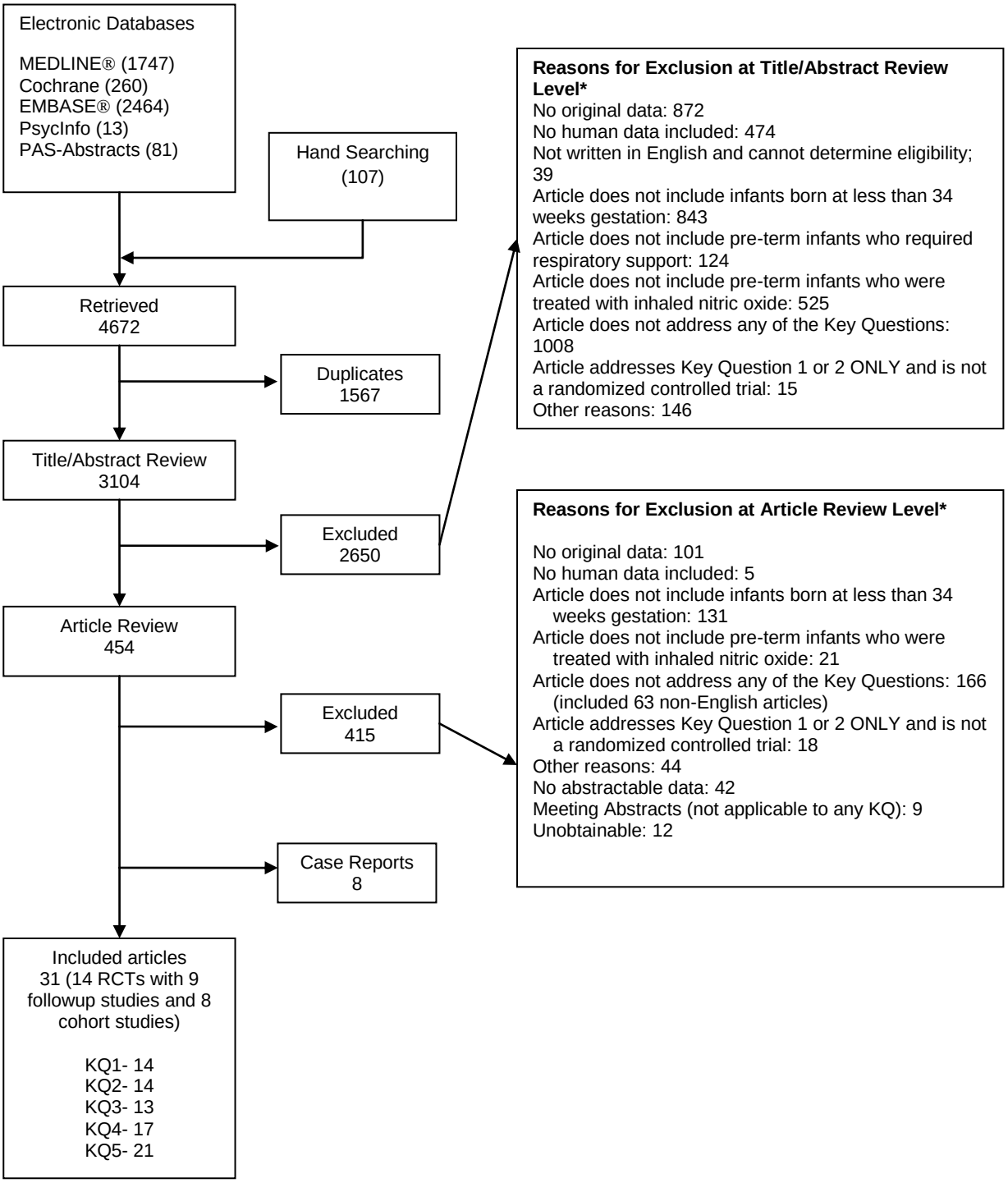

Figure 2. Summary of literature search (number of articles)

* Total may exceed number in corresponding box, as articles excluded by two reviewers at this level.

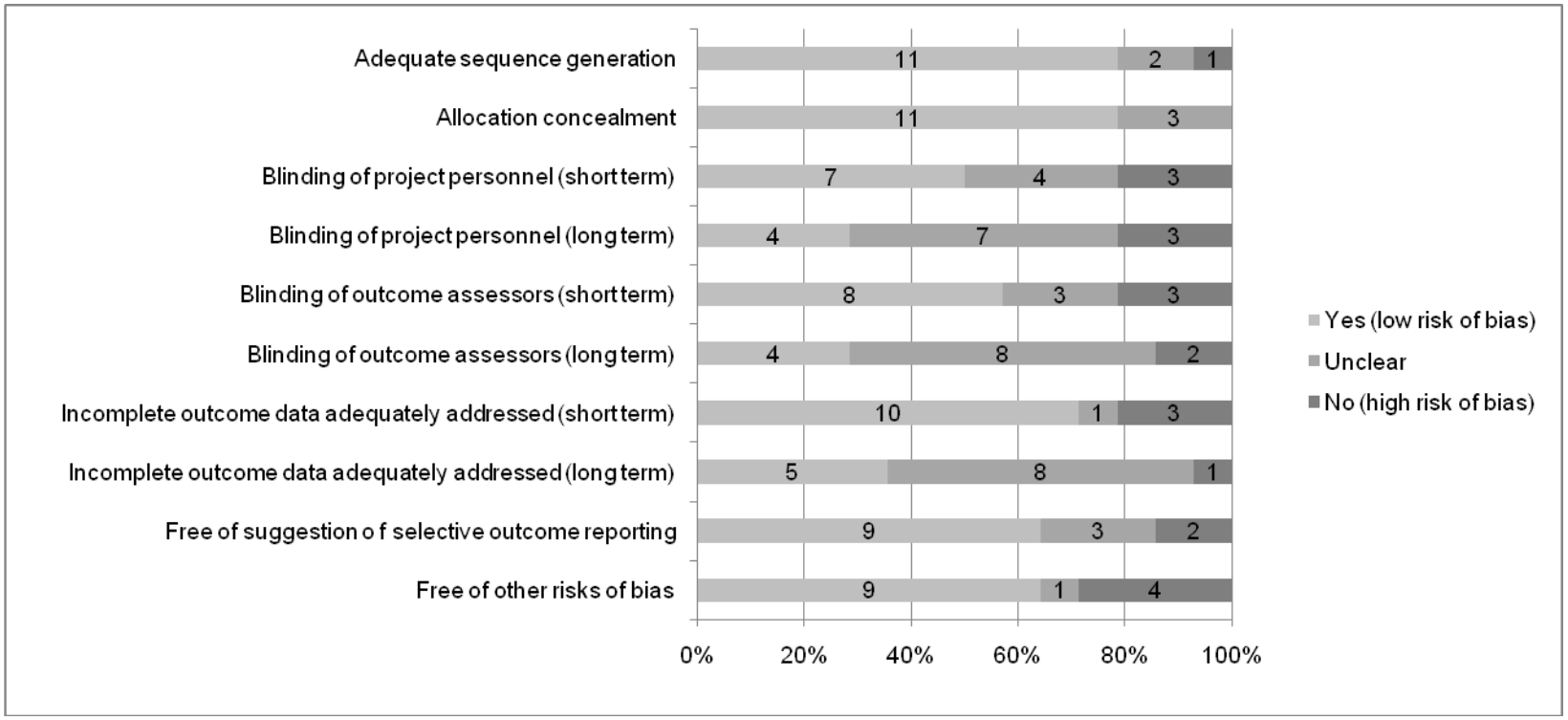

Figure 3. Summary of risk of bias for RCTs

Table 1. Included articles

Author, year	Design	Followup of	KQ1	KQ2	KQ3	KQ4	KQ5
Ballard, 2006[34, 75]	RCT		x	x		x	x
Banks, 1999[70]	Phase II pilot study					x	
Bennett, 2001[76]	RCT	Subhedar, 1997[64]			x		x
Cheung, 1998[72]	Prospective cohort				x		
Chock, 2009[77]	RCT	Van Meurs, 2005, 2007[39, 40]				x	
Clark, 2002[71]	Prospective cohort				x		
Dani, 2006[67]	RCT		x	x			x
Dewhurst, 2010[74]	Pilot study					x	
Franco-Belgium, 1999[60]	RCT		x	x			x
Field, 2005[63]	RCT		x	x	x	x	x
Hamon, 2005 [78]	RCT	Hascoet, 2005[61]					x
Hascoet, 2005[61]	RCT		x	x			x
HIbbs, 2007[44]	RCT	Ballard, 2006[34]			x		
Hintz, 2007 [30]	RCT	Van Meurs, 2005[40]			x	x	x
Huddy, 2008[35]	RCT	Field, 2005[63]			x		x
Kinsella, 1999[59]	RCT		x	x			x
Kinsella, 2006[37]	RCT		x	x		x	x
Kumar, 2007[68]	Retrospective cohort					x	
Mercier, 2010[62]	RCT		x	x		x	x
Mestan, 2005[56]	RCT	Schreiber, 2003[58]			x	x	x
Schreiber, 2003[58]	RCT		x	x		x	x
Srisuparp, 2002[66]	RCT		x	x			x
Su, 2008[65]	RCT		x	x			x
Subhedar, 1997[64]	RCT		x	x			x
Tanaka, 2007[38]	Retrospective cohort				x	x	
Uga, 2004[69]	Retrospective cohort					x	
Van Meurs, 2005[40]	RCT		x	x		x	x
Van Meurs, 2007[39]	RCT		x	x	x		x
Walsh, 2010[57]	RCT	Ballard, 2006[34]			x	x	x
Watson, 2009[36]	RCT	Kinsella, 2006[37]			x	x	x
Yadav, 1999[73]	Retrospective cohort					x	

Key Question 1: Does inhaled nitric oxide (iNO) therapy increase survival and/or reduce the occurrence or severity of bronchopulmonary dysplasia (BPD) among premature infants who receive respiratory support?

Major Findings

- There is no statistically significant effect of iNO compared to placebo on survival or mortality rates in preterm NICU infants requiring mechanical ventilation.
- There is insufficient evidence to determine whether iNO reduces the rate of bronchopulmonary dysplasia (BPD), as defined by requiring supplemental oxygen at 36 weeks postmenstrual age, in preterm NICU infants requiring mechanical ventilation.
- There is a small but statistically significant reduction in the composite variable of death or BPD at 36 weeks PMA for infants treated with iNO compared to infants in control groups.
- Preterm infants who required mechanical ventilation and were the subjects of randomized controlled trials of inhaled nitric oxide were a high risk population with high mortality and BPD rates during NICU hospitalization.

Detailed Analysis

We identified 14 RCTs that compared treatment with iNO to standard treatment in preterm infants requiring mechanical ventilation (Table 2). They varied as to inclusion and exclusion criteria; age of enrollment; dose, timing and duration of iNO; and outcome variables reported. Current labeling of iNO is for use in infants born after 34 weeks gestation with respiratory failure, so we included two RCTs of preterm infants born *at or before 34* weeks gestation.[59, 79] All but one RCT began enrollment and started iNO during the first week after birth; the RCT that differed from the others enrolled infants and started iNO at seven to 21 days after birth.[34] The 14 RCTs varied widely as to severity of respiratory illness, birth weight (BW), gestational age, chronological age from birth, and postmenstrual age (PMA, gestational age plus chronological age, a proxy for degree of prematurity) when treatment was initiated (Table 3). Their study designs varied widely in terms of dose (5 to 40 parts per million (ppm)), duration (1 to 24 days), and mode of delivery. The 14 RCTs varied so widely that it was difficult to group them together in a way that took these important variables into account. For Key Question 1 (and Key Question 2), we viewed the aggregation of these 14 RCTs as providing data on a continuum of exposures to iNO (as listed above). This discussion of death and BPD includes all 14 RCTs that provide data for the variables we were charged with systematically reviewing: death or survival, BPD and the composite variable of death or BPD at 36 weeks PMA. Key Questions 4 and 5 explore data regarding subgroups and variations in administration of iNO, respectively.

Each of the 14 RCTs reported mortality data (three reported only death at 7 or 28 days), and 11 reported data on BPD (Table 2). Three studies focused on changes of oxygenation index (OI) at 2 to 24 hours after starting iNO therapy.[60, 61, 65] Six RCTs reported using placebo gas in the control group and keeping NICU staff masked as to study arm assignment.[34, 37, 39, 40, 58, 62] There were four multicenter RCTs and one single center RCT that had at least 100 infants per study

Table 2. Summary of outcomes for RCTs addressing KQ1

Outcomes	Number of studies	Total Sample size
Survival / Death	14[34, 37, 39, 40, 58-67]	4754
BPD at 36 weeks PMA	12[34, 37, 39, 40, 58-60, 62-65, 67]	2655
BPD other measures	11[34, 37, 39, 40, 58-60, 62, 63, 65, 67]	3315
Death or BPD	12[34, 37, 39, 40, 58-60, 62-65, 67]	3301

BPD = Bronchopulmonary dysplasia; PMA= Postmenstrual age

arm.[37, 62] The findings of the 14 RCTs are discussed below by outcome variable: death/survival, BPD rate, severity of BPD and the composite variable of death or BPD (Appendix E, Evidence Tables 3 and 4; Table 2 and 3).

Survival and death. Each of the 14 RCTs reported mortality data, but there was some variation as to the time point cutoff they used for reporting death (e.g., 7 days, 28 days, 36 weeks PMA, death while in the NICU, or death while in the NICU or in the first 365 days for infants who had prolonged NICU stays). We assumed that death occurred in the NICU in the few studies that did not specify the time point cutoff they used for reporting death as they reported only NICU outcomes. One pilot study for a larger single center RCT focused on toxicity of iNO, and reported only death in the first seven days.[66] One study that focused on physiologic response to iNO reported death at seven and 28 days.[61] For the INNOVO RCT, Field, 2005 reported death in the first day after birth, at two to six days, at seven to 27 days and at 28 days to one year corrected for degree of prematurity.[63] We included these three RCTs in the Evidence Table for death (Appendix E, Evidence Table 5). No matter how the 14 RCTs defined and reported death or survival, none of the 14 RCTs reported a statistically significant difference between iNO and control groups.

Our discussion and meta-analysis focuses on the 11 RCTs that report death by 36 weeks PMA or in the NICU, a specified variable we were asked to include in our systematic review. Six of the RCTs used the composite variable, death or BPD, as their primary outcome variable,[37, 39, 40, 58, 64, 67], and two RCTs used survival without BPD at 36 weeks PMA as their primary outcome variable.[34, 62] All three RCTs, Su 2008, Hascoet, 2005, and Srisuparp, 2002, that focused on immediate physiologic found no significant differences in mortality between the iNO and control groups. [60, 61, 65] Survival to NICU discharge was the primary outcome in only one study, an early multicenter RCT published by Kinsella, 1999.[59] A lower than expected recruitment rate, in combination with an interim analysis that suggested they were unlikely to find a difference in survival, prompted them to terminate this trial early. The survival rates for the iNO group and controls were 25 percent versus 20 percent, respectively with a Relative Risk (RR) of 1.11 (95 percent confidence interval 0.70, 1.80). To make their data comparable to the other RCTs, we report not survival to NICU discharge, but their NICU mortality rates (i.e., 75 percent versus 80 percent) (Appendix E, Evidence Table 5).

The largest multicenter RCT (the EUNO trial), Mercier, 2010, was conducted at 36 centers in nine European countries.[62] They enrolled 800 preterm infants born between 24 weeks and 28 6/7 weeks gestation with a BW at or above 500 g who were treated with surfactant and mechanical ventilation or continuous positive airway pressure (CPAP) for respiratory distress syndrome. Within 24 hours after birth, infants were enrolled and treated with low dose iNO (5 ppm) or placebo gas for a minimum of seven days. There was no statistically significant difference in survival at 36 weeks PMA between the iNO group and controls, 86 percent versus 90 percent, respectively, RR 0.74 (0.48, 1.15), adjusted for gestational age, baseline severity of illness, mode of ventilation and country. For comparison with the other RCTs, we present their data in Table 3

and our meta-analyses in terms of death by 36 weeks PMA, 14 percent versus 10 percent for iNO and control groups, respectively.

The second largest multicenter RCT, published by Kinsella, 2006, enrolled 793 preterm infants born at or before 34 weeks gestation with birth weight below 1250 g on mechanical ventilation in the first two days after birth.[37] Study infants were treated with low dose iNO (5 ppm) or placebo gas for 21 days or until extubation. The NICU mortality rates were 20 percent in the iNO group and 25 percent in the placebo group, RR 0.79 (0.61, 10.3) (p-value = 0.08) (Appendix E, Evidence Table 5).

Ballard, 2006, enrolled 582 infants born before 33 weeks gestation or less with birth weight below 1250 g who were on positive pressure ventilation (ventilator or CPAP) beyond the first week, seven to 21 days after birth.[34] Since preterm mortality is highest during the first week after birth, this RCT had the lowest mortality rates at 36 weeks PMA of all the RCTs of iNO in preterm infants, 5.4 percent in the iNO group and 6.3 percent in placebo controls. Mortality rates were only slightly higher after term, at 44 weeks PMA (6.9 percent versus 6.8 percent) (Appendix E, Evidence Table 5).

In the NICHD Neonatal Research Network's two RCTs of preterm infants born before 34 weeks gestation (BW 401 to 1500 g in the 2005 study and BW > 1500 g in the 2007 study), Van Meurs reported death before discharge to home or 365 days for preterm infants still hospitalized.[39, 40] For both RCTs, the Data Safety and Monitoring Committee noted higher than expected mortality rates, and recommended lowering the OI inclusion criteria. Despite this change to include infants with less severe respiratory failure, mortality rates for preterm infants with BW 400 to 1500 g were 52 percent for the iNO group versus 44 percent for placebo controls (RR 1.16 (0.96, 1.39)), adjusted for study center, BW group, and OI group.[40] As might be expected, mortality rates were somewhat lower for infants with birth weight above 1500 g, 36 percent in the iNO group versus 27 percent in controls (RR 1.26 (0.47, 3.41)) when adjusted for OI stratum.[39] (Appendix E, Evidence Table 5).

In the largest single center RCT with 207 infants born before 34 weeks gestation with BW below 2000 g, Schreiber, 2003 found no differences in death in the NICU or by six months: 15 percent for iNO versus 23 percent for placebo gas controls (RR 0.68 (0.38, 1.2)), adjusted for type of ventilation. [58] There were no statistically significant differences in NICU mortality in the Franco-Belgium, 1999 RCT (27 percent in the iNO group and 35 percent in controls), despite having an initial OI that was higher in the iNO group (median 20.2, interquartile range (IQR) 8.3) than in the control group (median 18.0, IQR 7.4) [60] Neither of two small single center RCTs that each enrolled 40 to 42 infants found statistically significant differences between the iNO and control groups: mortality was 20 percent versus 30 percent, respectively, as reported by Dani, 2006, and 50 percent versus 32 percent with RR 1.57 (0.76, 3.38) as reported by Subhedar,1997[64, 67] (Appendix E, Evidence Table 5).

Table 3. Study design of randomized controlled trials of inhaled nitric oxide in preterm infants*

Author, year	Birth Years	Sample Size	Age	GA, wks	BW, gm	Respiratory	Exclusion Criteria†	Placebo/ Mask Staff	Start/ Max iNO, ppm	Duration of iNO, days	Sites, n
Mercier, 2010[62]	2005-2008	800	<24 hr	24-28.9	>500	Inborn, MV, surfactant, $FiO_2 \geq 0.3$	FiO_2>0.5, lung hypoplasia, lethal congenital anomaly	Yes/Yes	5/5	7-21	36
Su, 2008[65]	2000-2006	65	Mean 24-25 hr	<32	≤1500	RDS, MV + OI≥25	Severe IVH or IPH	No/No	5/20	Mean 4.9	1
Van Meurs, 2007[39]	2001-2003	29	24-25 hr	<34	>1500	MV, OI≥15/12.5 + surfactant	Platelets<50k	Yes/Yes	5/10	Max 14	16
Ballard, 2006[34 80]	2000-2005	582	7-21 d	≤32	500-1250	MV (or CPAP if BW<800 g) for lung disease	Lethal congenital anomaly, bilateral IPH, prior iNO exposure	Yes/Yes	20/20	Min 24	21
Kinsella, 2006[37]	2001-2005	793	<48 hr	≤34	500-1250	MV	Lethal congenital anomaly, active air leak	Yes/Yes	5/5	Max 21	16
Dani, 2006[67]	2001-2004	40	<7 d	<30		Inborn, RDS, MV, surfactant, FiO_2> 0.5 + a/AO_2 <0.15	Hydrops fetalis, major congenital anomaly, Platelet<50k	No/No	10/10	Mean 4.1	1
Hascoet, 2005[61]	1999-2001	145	6-48 hr	<32		MV, FiO_2>40% + a/AO_2<0.22	FiO_2 1.0 pO_2<50 + PCO_2 <50, major congenital anomaly, platelets<50k	No/No	5/10		10
Field, 2005[63]	1997-2001	108	<28 d, med 1 d	<34		MV + severe resp failure	Platelets<50k, IPH, lethal congenital anomaly	No/No	5/40	Mean 3.5	15

Table 3. Study design of randomized controlled trials of inhaled nitric oxide in preterm infants (continued)*

Author, year	Birth Years	Sample Size	Age	GA, wks	BW, gm	Respiratory	Exclusion Criteria†	Placebo/ Mask Staff	Start/ Max iNO, ppm	Duration of iNO, days	Sites, n
Van Meurs, 2005[40]	2001-2003	420	Mean 26-28 hr	<34	401-1500	MV, OI≥ 10/7.5 + surfactant	Congenital lung anomaly, platelets<50k	Yes/Yes	5/10	Max 14	16
Schreiber, 2003[58]	1998-2001	207	<72 hr	<34	<2000	RDS, MV + surfactant	Hydrops fetalis, major congenital anomaly	Yes/Yes	10/10	7	1
Srisuparp, 2002[66]	1997-1998	34	<72 hr		<2000	MV, surfactant, RDS, + OI≥4-12 (based on BW)	Hydrops fetalis, major congenital anomaly, no arterial catheter	No/No	20/20	Max 7	1
Kinsella, 1999[59]		80	≤7 days	≤34		MV, a/AO_2<0.1 + surfactant	Lethal congenital anomaly	No/Yes	5/5	7-14	12
Franco-Belgian, 1999[60]	1995-1997	85	<7 days	<33		MV + OI=12.5-30	OI>30, severe asphyxia, septic shock, IVH, IPH, lung or lethal congenital anomaly	No/No	10/20		33
Subhedar, 1997[64]	1995-1996	42	4 days	<32		MV, surfactant + high CLD score‡	Sepsis, IVH with IPH, major congenital anomaly, platelets<50k	No/No	20/20	3-4	1
TOTAL: 14	1995-2008	3,425	Birth to 21 days	≤34	401-2000			6 with placebo gas	5-20 /5-40	<1 to 21	1-36

* All included infants were on either on a mechanical ventilator (MV) or continuous positive airway pressure (CPAP).
†All RCTs excluded infants with uncorrected bleeding problems, severe congenital heart disease or a decision to not provide full treatment (or contraindication of continuing intensive care).
‡high CLD score = chronic lung disease score that is composed of risk factors for chronic lung disease.[81]

a/AO_2 = alveolar/arterial oxygen ratio; BW – birth weight; CLD = chronic lung disease; CPCAP = continuous positive airway pressure; GA = gestational ages; IPH = intraparenchymal hemorrhage; MV = mechanical ventilator; OI = Oxygenation index; RDS = Respiratory distress syndrome; severe IVH = Intraventricular hemorrhage with ventricular dilation

There were no statistically significant differences (neither increase nor decrease) in NICU mortality rates with iNO in any of the individual fourteen RCTs that reported on death or survival. A meta-analysis of the 11 RCTS that reported death by 36 weeks PMA or in the NICU found no statistically significant differences between the iNO and control groups (RR 0.97 (0.82, 1.15)) (Figure 4).

The relatively high mortality rates for infants enrolled in most of these RCTs are striking. Regardless of group assignment, seven studies reported mortality rates as high as 25 percent to 65 percent,[39, 40, 59-61, 63, 64] and another four reported mortality rates of 15 to 30 percent.[37, 58, 65, 67] The Ballard, 2006 RCT reported the lowest mortality rates (5.4 percent for the iNO group and 6.3 percent for controls).[34] Most preterm infants who die in the NICU die during the first week after birth. The low mortality rates reported in Ballard, 2006 reflects a difference of study design in that they enrolled preterm infants on mechanical ventilation or CPAP at one and to three

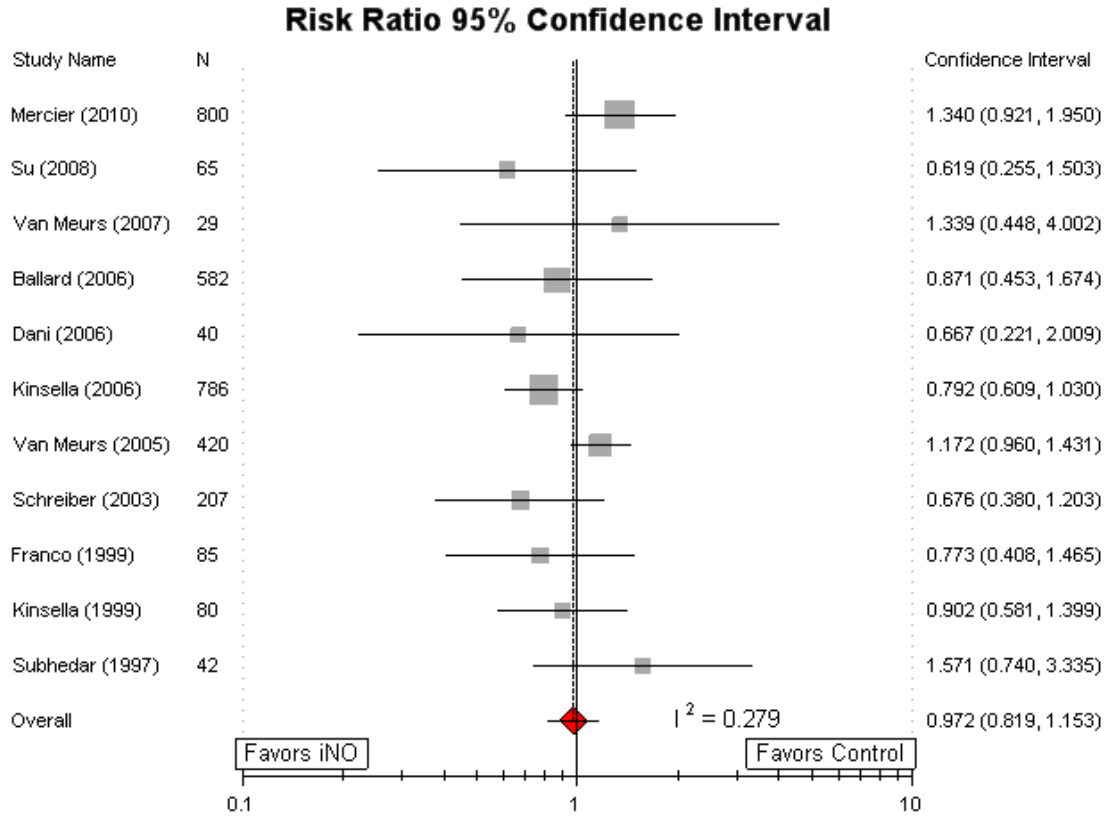

Figure 4. Meta-analysis of 11 studies describing death at 36 weeks PMA or in the NICU

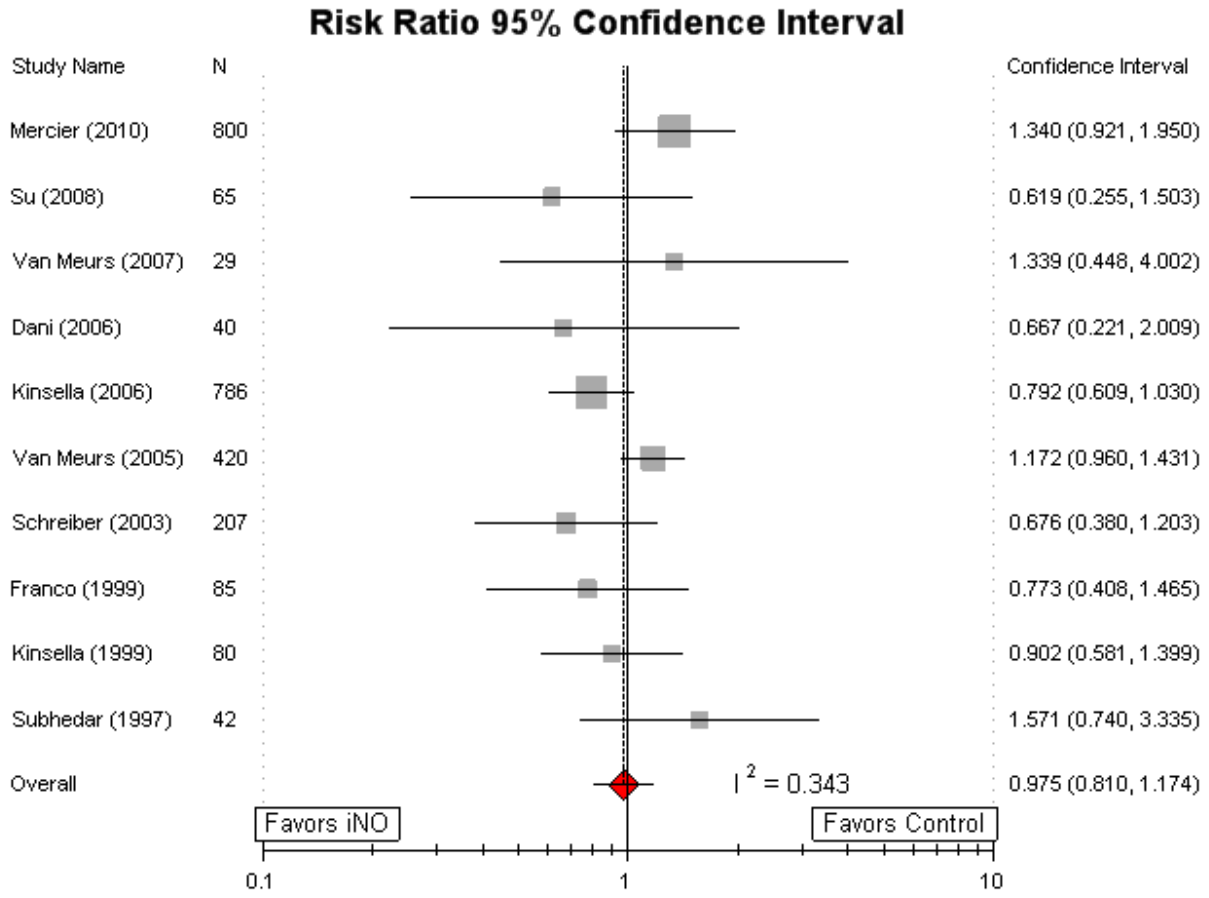

Figure 5. Meta-analysis of 10 studies describing death at 36 weeks PMA or in the NICU without Ballard, 2006

weeks after birth. We therefore removed the data from the Ballard RCT, and repeated the meta-analysis for the remaining ten RCTs. The results did not change: RR 0.98 (0.81, 1.17) (Figure 5). This sensitivity analysis confirmed no statistically significant effect of iNO compared to control on NICU death or survival to discharge from the NICU in preterm infants requiring positive pressure ventilation.

Bronchopulmonary dysplasia. The term bronchopulmonary dysplasia was introduced in 1967 when Northway reported a case series of preterm infants with respiratory distress syndrome (RDS) who developed a chronic lung disease with characteristic radiographic and pathologic features.[82] Although it has always been defined clinically, the definition of BPD has evolved with neonatal intensive care.[83] The clinical, radiographic and pathologic features of BPD have changed as new technologies, medications and management strategies have been introduced, leading to dramatic reductions in gestational age specific neonatal mortality and a lowering of the limit of viability to now 22 to 24 weeks gestation. The evolution of BPD is reflected in its various definitions, including definitions based on persistent respiratory symptoms, radiographic features, and treatments (e.g., requiring supplemental oxygen at 28 days from birth, or a more severe BPD, requiring oxygen at 36 weeks PMA).

Twelve RCTs provide data on BPD at 36 weeks PMA, but there was some variation in how each RCT defined BPD. Six RCTs defined BPD simply as requiring supplemental oxygen at 36 weeks PMA.[39, 40, 59, 60, 63, 67] One multicenter study[37] and three single center studies[58, 64, 65] refined

the definition of BPD by adding the requirement of radiological evidence of BPD. Although there is general agreement that infants on mechanical ventilation or supplemental oxygen above 30 percent FiO_2 at 36 weeks PMA have BPD, some question whether infants on low flow nasal cannulas with a FiO_2 of 30 percent or less should be included in the BPD at 36 weeks PMA category.

Walsh published in 2003 an algorithm for physiologic BPD at 36 weeks PMA that includes an oxygen challenge test for infants on less than 30 percent FiO2.[84] Four RCTs used these criteria for categorizing BPD at 36 weeks PMA.[34, 39, 40, 62] Van Meurs, 2005 and 2007 reported that the rate of BPD as defined by Walsh was somewhat lower than the rate of BPD defined as on supplemental oxygen at 36 weeks PMA.[39, 40] In the NICHD trial of infants born before 34 weeks gestation with birth weight below 1500 g, physiologic BPD rates, 50 percent in the iNO group and 60 percent in controls, RR 0.87 (0.68, 1.10), were lower than rates of BPD defined as requiring oxygen at 36 weeks PMA, 60 percent versus 68 percent, RR 0.90 (0.75, 1.08) (both RR were adjusted for study center, BW group and OI group).[40] In the NICHD RCT of infants with birth weight above 1500 g, the physiological definition classified one more infant treated with iNO as having BPD, and one less control infant as having BPD, resulting in BPD rates of 36 percent versus 40 percent respectively, RR 0.74 (0.26, 2.09) adjusted for OI stratum.[39] (Appendix E, Evidence Table 6). Using the physiologic definition at 36 weeks PMA, Mercier, 2010[62] reported lower BPD rates, 24 percent in the iNO group compared to 27 percent in controls, RR 0.84 (0.58, 1.17), adjusted for gestational age, baseline severity of illness mode of ventilation, and country. Their inclusion criteria differed from two RCTs reported by Van Meurs[39, 40] (Table 3) in their focus on gestational age (i.e., gestational age 24 to 28 6/7 weeks) rather than BW and lower severity of initial illness (mechanical ventilation with FiO_2 at or above 30 percent).

The twelve RCTs also vary as to the denominator used when calculating rate of BPD at 36 weeks PMA: Five used the total number of infants in each group,[34, 63-65, 67] and seven RCTs used the number of *survivors* in each group.[37, 39, 40, 58-60, 62, 85] The small single center Subhedar, 1997 RCT reported BPD rates both for the total group (50 percent for the iNO group versus 64 percent for controls) and for survivors (100 percent versus 90 percent).[64]

Dani, 2006 noted that infants treated with iNO had half the rate of BPD at 36 weeks PMA than the controls (30 percent versus 60 percent, respectively, p-value = 0.067, BPD rate for the total group).[67] An unplanned interim analysis revealed a statistically significant reduction in their primary outcome, death or BPD (p-value = 0.016). On the recommendation of their consulting statisticians and two independent observers, the study was terminated early, with enrollment of only 40 of the anticipated 52 infants. Another small single center RCT found no statistically significant differences in rate of BPD at 36 weeks PMA (31 percent for the total iNO group and 33 percent for the total control group).[65] Field, 2005 reported that 26 of 55 infants in the iNO group and 15 of 53 infants in the control group had BPD at 36 weeks PMA, 47 percent versus 28 percent. Ballard, 2006 reported rates of BPD at 36 weeks PMA for the total iNO group as compared with the total placebo gas control group: 50.7 percent versus 56.9 percent, respectively (Appendix E, Evidence Table 6).

In addition to the Mercier and two Van Meurs NICHD Neonatal Research Network RCTs, Kinsella, 2006 reported BPD rates using as denominator the number of infants alive at 36 weeks PMA[37, 39, 40] There was no statistically significant differences between the iNO and placebo gas control groups, 65 percent versus 68 percent, respectively, RR 0.96 (0.86, 1.09). Using the number of survivors as denominator, Kinsella, 1999 and Schreiber, 2003 reported differences in

rates of BPD at 36 weeks PMA that were not statistically significant.[58] Kinsella, 1999 reported that 60 percent of survivors in the iNO group had BPD at 36 weeks PMA as compared with 80 percent of control survivors.[59] Schreiber, 2003 reported that 39 percent of iNO group survivors compared to 53 percent of control group survivors had BPD at 36 weeks PMA, RR 0.74 (0.53, 1.03) (Figure 6).[58] (Appendix E, Evidence Table 6).

Despite variations in how BPD was defined and calculated, there were no statistically significant differences in rates of BPD at 36 weeks PMA between the iNO group and controls in any of the RCTs. Subhedar, 1997[64] demonstrated how drastically BPD rates can differ when they are calculated using survivors as compared with the total group as denominator. For this reason, we did not do a meta-analysis with all 12 RCTs. We included eight studies in a meta-analysis of the rate of BPD at 36 weeks PMA in *survivors*. The small difference was not statistically significant (RR 0.93 (0.86, 1.003)) (Figure 6) (Appendix E, Evidence Table 6). [37, 40, 58, 59, 64]

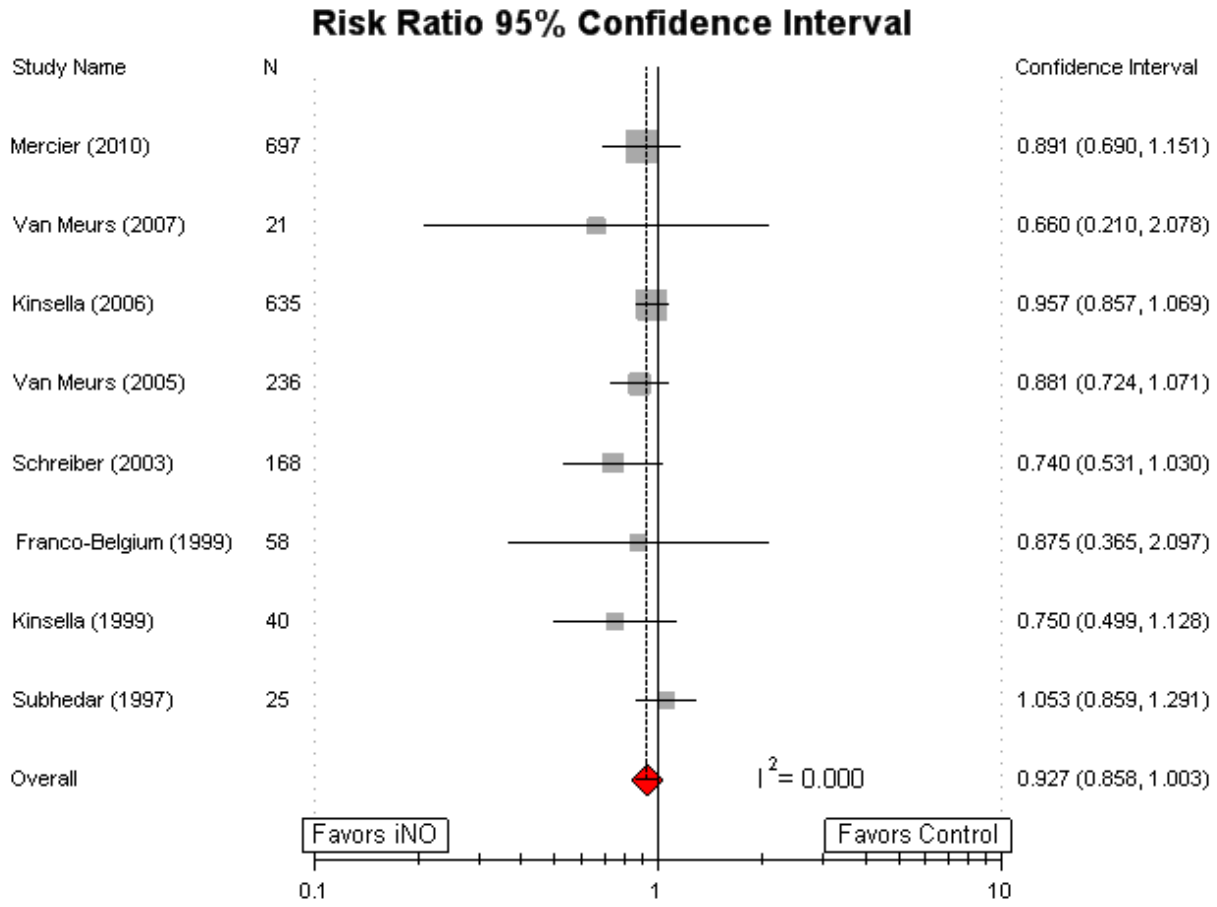

Figure 6. Meta-analysis of eight studies describing BPD at 36 weeks PMA among survivors

Other measures of severity of bronchopulmonary dysplasia. Although the most accepted BPD definition is based on being on supplemental oxygen at 36 weeks PMA, there are other measures of severity of lung disease (e.g., duration of mechanical ventilation and oxygen supplementation, treatment with medications for lung disease), and other time points for reporting the need for mechanical ventilation of supplemental oxygen (e.g., at 40 weeks PMA, 44 weeks PMA and NICU discharge). We found no RCTs that reported number of infants on mechanical ventilation at 36 weeks PMA.

Ballard, 2006 reported statistically significantly fewer infants in the iNO group than controls remained in the hospital, and on mechanical ventilation, nasal continuous positive airway pressure (CPAP) or supplemental oxygen at 40 weeks PMA (p-value = 0.01), and at 44 weeks PMA (p-value = 0.03).[34] At 40 weeks PMA (i.e., full term), six percent in the iNO group and 10 percent of controls were hospitalized and on mechanical ventilation, and 22 percent versus 29 percent were hospitalized and on supplemental oxygen. Kinsella, 1999 reported that 54 percent of infants in the iNO group were discharged home on oxygen as compared with 80 percent of control infants, RR 0.65 (0.41, 1.02).[59] In contrast, only nine percent of all infants in each group were discharge home on supplemental oxygen in Field, 2005.[63]

Kinsella, 2006 reported no differences between the iNO group and controls in proportion of infants ever treated with postnatal corticosteroids (60 percent versus 56 percent).[37] There were no statistically significant differences in proportion of survivors at 36 weeks PMA who were on bronchodilators (20 percent versus 20 percent), corticosteroids (15 percent versus 12 percent) or diuretics (37 percent versus 38 percent). In Franco-Belgium, 1999 there were also no statistically significant differences between the 29 survivors in the iNO group who were treated with steroids (54 percent versus 72 percent) or beta-mimetics (21 percent versus 39 percent) than the 29 control survivors.[63] Field, 2006 reported that 40 percent and 34 percent of the iNO versus control group were treated with corticosteroids[63] (Appendix E, Evidence Table 6). Eight RCTs reported mean duration of supplemental oxygen, mechanical ventilation or CPAP.[39, 40, 58, 60, 62, 63, 65, 67] Dani, 2006 reported a statistically significant lower mean duration of supplemental oxygen reached statistical significance for all infants in the iNO compared to all in the control group (47.3+/-39.4 versus 69.4+/-30.2, p-value = 0.05), but no statistically significant differences in mean days of mechanical ventilation or CPAP .[67] Two other RCTs found no statistically significant differences between the total iNO group and controls in mean duration of mechanical ventilation [60, 65] nor mean duration of supplemental oxygen.[60] (Appendix E, Evidence Table 6). The largest multicenter RCT published in 2010 by Mercier reported no statistically significant differences in mean duration of mechanical ventilation between the iNO group and controls, 44+/-26 versus 45+/-29, respectively, p-value = 0.68, but did not specify whether these data were for the total groups or survivors.[62] Three RCTs reported mean duration of supplemental oxygen or mechanical ventilation in *survivors.*[39,40, 58] Van Meurs, 2007 RCT of preterm infants with birth weight above 1500 g, the mean duration of mechanical ventilation was 8.7+/-5.4 days for the nine survivors in the iNO group and 16.8+/-13.9 for the 11 controls (p-value = 0.08).[39] In their RCT of preterm infants with birth weight 400 to 1500 g, there were no statistically significant differences between the iNO and control groups in mean duration of mechanical ventilation (39+/-45 versus 47+/-53) or supplemental oxygen (84+/-63 versus 91+/-61).[40] In Schreiber, 2003, the median duration of mechanical ventilation was 16 days for the iNO group (the interquartile range was 8 to 48) and 28.5 days (IQR 8 to 48) for controls p-value = 0.19.[58] (Appendix E, Evidence Table 6).

As a part of their analyses of costs and resource utilization, Field, 2005 reported data regarding mechanical ventilation and supplemental oxygen for infants who survived and for the total group.[63] Median (interquartile range) for days on mechanical ventilation after randomization was 7.0 (2.0, 28.0) for all infants in the iNO group versus 4.0 (1.0, 9.0) in all controls, and 15.0 (6.0, 28.0) for survivors in the iNO group versus 12.0 (5.0, 36.0) in surviving controls. The data for days on supplemental oxygen after randomization were similar.[63] (Appendix E, Evidence Table 6).

Of the eight RCTs that reported various measures of severity of BPD, only two reported differences between the iNO and control groups that approached statistical significance, and both favored iNO. Ballard, 2006 reported a statistically significant reduction in hospitalization and respiratory support at 40 and 44 weeks PMA with iNO (p-value = 0.01 and p-value = 0.03, respectively).[34] Dani, 2006 reported a lower duration of supplemental oxygen with iNO (p-value = 0.05).[67] There are insufficient data to perform a meta-analysis for any measure of severity of BPD due to lack of uniformity in definitions used. Although a number of RCTs reported duration of mechanical ventilation and/or supplemental oxygen, they varied as to whether they used mean +/- standard deviation or median (interquartile range), and whether the data were calculated for the total group or only for survivors.

Death or bronchopulmonary dysplasia at 36 weeks PMA. The composite outcome of death or BPD at 36 weeks PMA was reported in 11 RCTs: it was the primary outcome variable for six RCTs[39]; its complement, survival without BPD at 36 weeks PMA, was the primary outcome variable in the Mercier, 2010 RCT[34, 62]; in two RCTs the primary variable was OI at a specified time[60, 65]; in one RCT the primary outcome variable[34, 37, 40, 58, 64] was survival to discharge from the NICU[59]; and for one RCT the primary outcome variable was death or severe neurodevelopmental impairment.[59, 63] In one multicenter RCT and two single center RCTs, there were statistically significant differences between the iNO group and controls in the composite outcome of death or BPD.[34, 58, 67] All eleven RCTs were included in our meta-analysis. (Appendix E, Evidence Table 7).

Ballard, 2006 found a statistically significant benefit in their primary outcome, survival without BPD at 36 weeks PMA, for the iNO group compared to placebo controls, 44 percent versus 37 percent, RR 1.23 (1.01, 1.51).[34] The number needed to treat was 14. Although their study sample was similar to other RCTs (birth before 33 weeks gestation with birth weight at or below 1250 g), infants were enrolled later than in other studies (at 7 to 21 days, compared to within the first week), and the minimum duration of treatment for the Ballard study was 21 days. For comparison with the other RCTs, we used the complement composite variable, rates of death or BPD at 36 weeks PMA, 56 percent of the iNO group versus 63 percent of the placebo control group) in Appendix E, Evidence Table 7 and Figure 7.

Schreiber, 2003, the largest single center trial, reported a statistically significant difference in rate of death or BPD.[58] In the iNO group (n = 105), 49 percent died or developed BPD compared to 64 percent in the placebo control group (n = 102), RR 0.76, (0.60, 0.97). This RCT enrolled infants born before 34 weeks gestation as other RCTs but with birth weight below 2000 g, and they treated study infants with iNO for seven days (Appendix E, Evidence Table 7).

The other single center RCT that found a statistically significant difference between the iNO group and controls in the outcome of death or BPD was reported by Dani, 2006.[67] This RCT was stopped early (n = 40) because an unplanned interim analysis found a statistically significant difference (p-value = 0.02) in death or BPD, their primary outcome. Only 50 percent of infants in the iNO group died or developed BPD, compared to 90 percent of infants in the control group,

RR 0.11 (0.02, 0.61). In this study, the controls were not treated with placebo gas but received standard care and NICU staff was not masked as to study status. The mean duration of treatment with iNO was 98.5 +/- 21.4 hours (4.1 days) (Appendix E, Evidence Table 7).

The largest multicenter RCT published in 2010 by Mercier reported no statistically significant difference between 395 infants in the iNO group compared to 400 in the placebo gas control group in their primary outcome variable, survival without BPD at 36 weeks PMA.[62] They used low dose 5 ppm iNO for seven to 21 days and the physiologic definition of BPD, as published in 2003 by Walsh.[57] Sixty-five percent of the infants in the iNO group and 66 percent of infants in the placebo gas control group survived without BPD at 36 weeks PMA, RR 1.05 (0.78, 1.43). For comparison with other RCTs, we use the complement combined variable death or BPD at 36 weeks PMA, 35 percent versus 34 percent, respectively (Appendix E, Evidence Table 7 and Figure 7.

Just as they found no statistically significant differences in mortality or BPD rates, the two Van Meurs Neonatal Research Network RCTs, the large multicenter Kinsella, 2006 RCT, and Subhedar's small single center RCT found no statistically significant differences in the composite variable of death or BPD at 36 weeks PMA.[37, 39, 40, 64] Both NICHD trials were terminated at the second interim data analysis of this study, at the recommendation of their data safety monitoring committee, based on no statistically significant differences in death or BPD and concerns about significantly higher rates of severe intracranial hemorrhage or periventricular leukomalacia (PVL) in the larger RCT.[39, 40] Rate of death or BPD at 36 weeks PMA was 80 percent for the iNO group and 82 percent for controls, RR 0.97 (0.86, 1.06) adjusted for study center, birth weight group and OI group.[40] The NICHD trial of infants birth weight above 1500 g reported that rate of death or BPD at 36 weeks PMA was 50 percent for the iNO group and 60 percent for controls, RR 0.80 (0.43, 1.48) adjusted for OI.[39] The rate of death of death or BPD in the large Kinsella, 2006 multicenter RCT was 72 percent in the iNO group compared to 75 percent in controls, RR 0.95 (0.87, 1.03).[37] Kinsella, 1999, a trial that included infants with more severe respiratory failure, reported much higher rates of death or BPD at 36 weeks PMA, 77 percent versus 91 percent, RR 0.85 (0.70, 1.03), but no significant differences between groups.[59] Subhedar, 1997 reported even higher rates of death or BPD at 36 weeks PMA, 95 percent in the iNO group and 100 percent in controls, RR 1.04 (0.92, 1.19).[64] (Appendix E, Evidence Table 7).

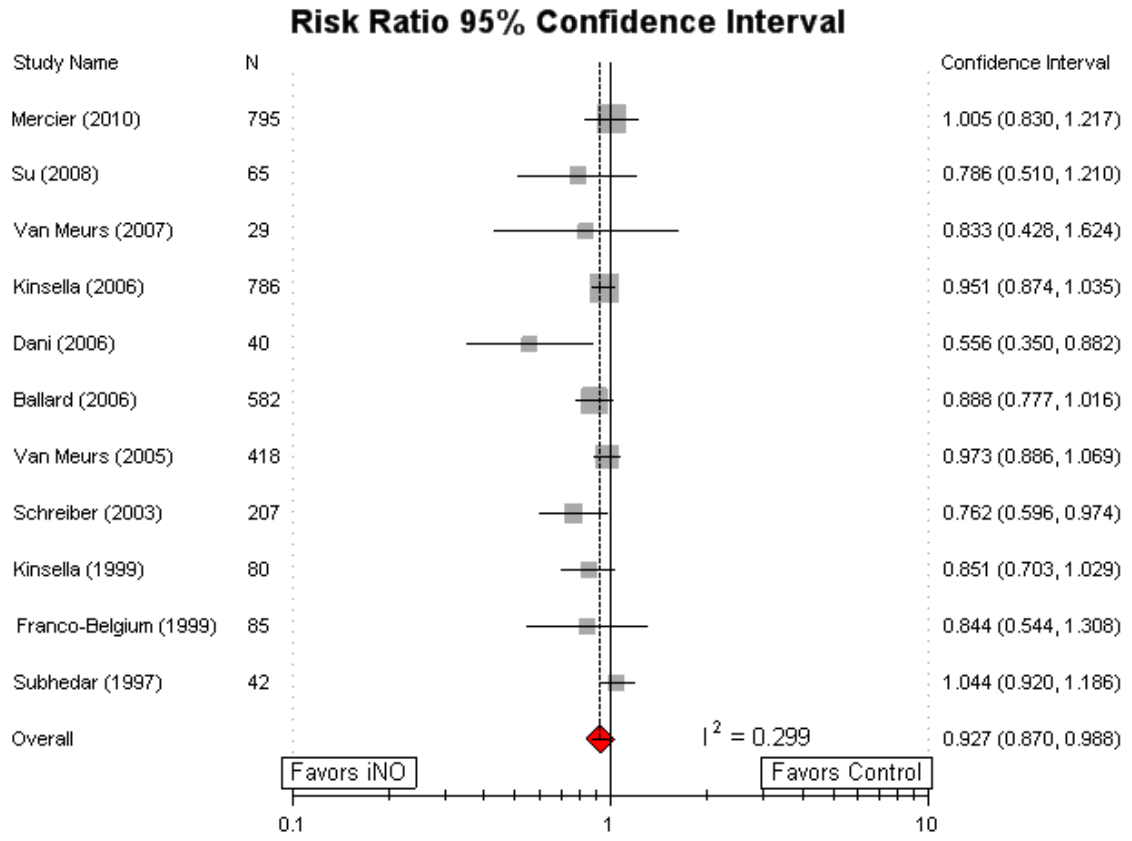

Figure 7. Meta-analysis of studies describing death or BPD at 36 weeks PMA

Two RCTs focused on early physiologic response to the administration of iNO gas. They both had oxygen index (OI) as their primary outcome variable, and differed only as to timing. Franco-Belgium, 1999 found no statistically significant differences in OI at two hours after administration of iNO,[60] whereas Su, 2008 reported an OI at 24 hrs after administration of iNO that was statistically significantly lower in the iNO group.[65] Rates of the composite variable, death or BPD at 36 weeks PMA, in the iNO versus control groups were 45 percent versus 53 percent, respectively, for the Franco-Belgium, 1999 and 50 percent versus 64 percent, respectively, for Su, 2008.

Our meta-analysis of pooled data from all 11 RCTs for death or BPD at 36 weeks PMA found a small but statistically significant difference in favor of iNO, RR 0.927 (0.870, 0.988) (Figure 7). It has been suggested that the study by Ballard, 2006,[34] should not be included in meta-analyses as it had a very different study design as well as the lowest mortality rates when compared to the other RCTs. In a sensitivity analysis, removing Ballard, 2006 from this meta-analysis did not change the effect estimate (RR 0.93). However, not surprising given the size of this study, removing it from the analysis did influence the confidence intervals; the confidence interval for the meta-analysis without Ballard, 2006 included 1 (0.87, 1.000). Running the analysis without Ballard, 2006 did not reduce the statistical heterogeneity, as measured by I^2 (Figure 8).

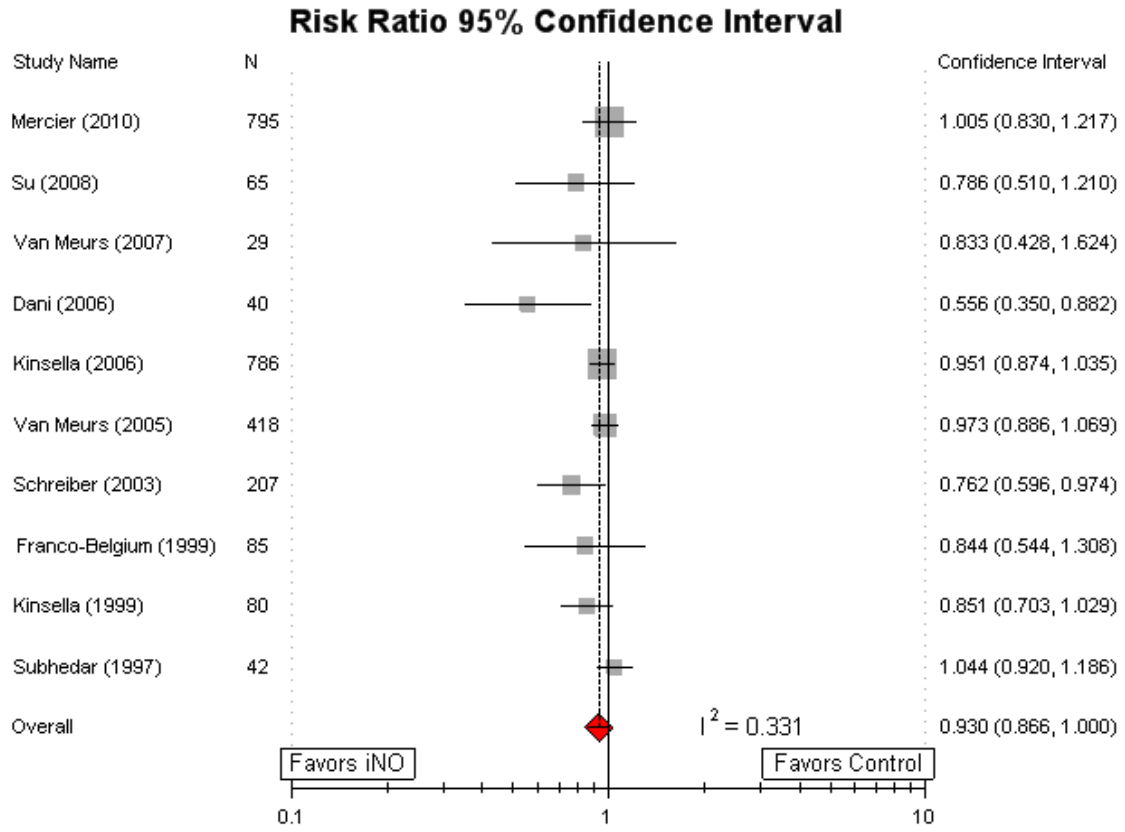

Figure 8. Meta-analysis of 10 studies describing death or BPD at 36 weeks PMA, without Ballard, 2006

Conclusion

Neither our meta-analysis nor any of the fourteen RCTs found any statistically significant differences in death in the NICU or survival to NICU discharge with iNO. Similarly, there were no statistically significant differences in any of the 12 RCTs that reported rates of BPD at 36 weeks PMA. Our meta-analysis of eight RCTs that reported rate of BPD at 36 weeks PMA for survivors did not find a statistically significant difference between the iNO or control groups, though most of these studies favored the iNO group. Two of eight RCTs that reported other pulmonary outcomes reflecting severity of BPD reported statistically significant findings in favor of iNO: a reduction in rates of hospitalization and respiratory support at 40 and 44 weeks PMA,[34] and a statistically significant reduction in mean duration of supplementary oxygen.[67] Three of 11 RCTs reported a statistically significant reduction of the composite variable, death or BPD at 36 weeks PMA or its complement, improved survival without BPD at 36 weeks PMA.[34, 58, 67] There was a small but statistically significant reduction in favor of iNO in our meta-analysis of all 11 RCTs that reported data for the composite variable, death or BPD at 36 weeks PMA. Ballard, 2006 is considered by some as different from the other studies in terms of study design (i.e., not enrolling or initiating treatment until a week or more after birth, and a minimum treatment duration of 21 days), and it had the lowest mortality rate of all 14 RCTs. Excluding data from the Ballard, 2006 and rerunning the meta-analysis resulted in the same effect estimate but a wider confidence interval that included 1. A meta-analysis with all 11 trials may provide a more

complete picture of the available evidence, when considering the effect of iNO in a continuum of exposure at various postmenopausal ages. When death or BPD at 36 weeks PMA is viewed in terms of its complement, the pooled estimate of risk favors iNO with a small but statistically significant improvement in survival without BPD at 36 weeks PMA by seven percent. This finding leads to questions about short term risks, longer term neurodevelopmental, pulmonary and other health outcomes, whether iNO is more effective in certain subgroups, and optimal doses, and methods of drug administration, which are discussed in Key Questions 2, 3, 4 and 5.

Key Question 2: Are there short term risks of iNO therapy among premature infants who receive respiratory support?

Major Findings

- There is insufficient evidence of a neuroprotective effect of iNO in preterm infants.
- There is no evidence that treatment of preterm infants with iNO influences the rates of other complications of prematurity, including patent ductus arteriosus (PDA), sepsis, necrotizing enterocolitis (NEC), severe retinopathy of prematurity (ROP), pulmonary hemorrhage, or air leaks.
- No study reported accumulation of toxic levels of methemoglobin or nitrogen dioxide.

Detailed Analysis

Preterm birth requires infants to utilize organ systems that are not yet fully mature.[86] The many complications of prematurity are multifactorial in etiology, but the highest risk factor is degree of prematurity. Infants born at 22 to 23 weeks gestation, the lower limit of viability, have the highest risks of all the complications of prematurity. Many biologic and environmental risk factors have been identified, and often overlap. For example, inflammation is associated with preterm birth and the development of BPD, white matter brain injury, necrotizing enterocolitis (NEC), and retinopathy of prematurity (ROP). How iNO exposure will influence the incidence of these complications of prematurity has been a major concern. Laboratory data suggest iNO may increase or decrease inflammation, cause bleeding by interfering with platelet aggregation and adhesion, and/or lead to accumulation of toxic substances (e.g., methemoglobin, formed by reaction of NO with hemoglobin, or nitrogen dioxide).

All 14 RCTs that compared treatment with iNO to standard treatment in preterm infants reported data regarding short term risks, including methemoglobin levels, and many complications of prematurity. The complications of prematurity we review in this section include brain injury, patent ductus arteriosus (PDA), sepsis, NEC, ROP, pulmonary hemorrhage, air leak, and pulmonary hypertension. Evidence of brain injury, obtained by serial head ultrasounds, includes intraventricular hemorrhage (IVH), intraparenchymal hemorrhage (IPH), hydrocephalus, periventricular leukomalacia (PVL), and other signs of white matter injury, including ventriculomegaly (Appendix E, Evidence Tables 3 and 4; Table 4). Meta-analyses were performed for all short term outcomes and are presented in a table at the end of this section. Not all RCTs reviewed in the text are included in the meta-analyses because of differences in the denominators across studies (e.g., all infants enrolled versus only survivors), and in the definition

Table 4. Summary of outcomes for RCTs addressing KQ2

Outcomes	Number of studies	Total Sample size
Brain Injury	13[65, 34, 37, 39, 40, 58-62, 64, 66, 67]	2936
PDA	11 [34,37, 58, 59, 61-67]	2870
Sepsis	8[34,37, 58, 62, 63, 65-67]	2958
NEC	8[34, 37, 58, 61, 62, 64, 65, 67]	2683
ROP	8[34, 37, 39, 40, 58, 59, 63, 64]	2025
Pulmonary hemorrhage	7[37, 58, 59, 62-65]	2089
Air leak or pneumothorax	10[37, 39, 40, 58, 59, 62-66]	2361
Methemoglobinemia	12[34, 37, 39, 40, 58, 59, 62-67]	3190

PDA = Patent ductus arteriosus, NEC = Necrotizing enterocolitis, ROP = retinopathy of prematurity, treated

of the condition (e.g. any air leak versus only new air leak occurring after randomization). We grouped trials for analysis of each condition based on similar measurement characteristics, and indicate which trials were included in the table.

Evidence of brain injury. The nomenclature that describes injury to the preterm infant's brain has changed since the publication of the earliest RCTs of iNO in preterm infants in 1997. Severity of IVH was often reported using the grading system proposed by Papile, 1978.[87] Grade 1 is a germinal matrix hemorrhage (GMH), grade 2 is blood in the ventricle but not filling or dilating the ventricle, grade 3 is a large amount of blood in the ventricle and ventricular dilation, and grade 4 is blood in the brain parenchyma, i.e., intraparenchymal hemorrhage (IPH). In terms of its association with neurodevelopmental outcome, GMH is the most benign form of IVH, and despite the IVH grading system, it does not denote blood in the ventricle. In the very immature infant's brain, the germinal matrix is a rich capillary network adjacent to the lateral ventricles, and very vulnerable to injury. Hemorrhage in the germinal matrix can extend into the ventricle, causing an intraventricular hemorrhage (IVH). The hemorrhage can also originate in the choroid plexus of the ventricle, and extend into the ventricle, causing an IVH. Blood in the ventricle may fill the ventricle and dilate it (Papile grade 3 IVH), or blood may be present in the ventricle with no ventricular dilation (Papile grade 2 IVH). However, there may be other causes of enlarged ventricles (called ventriculomegaly). Resorption of injured brain parenchyma can produce ventriculomegaly, as well as cysts in the brain parenchyma. Intraparenchymal hemorrhage (IPH) is more often caused by hemorrhagic infarction of brain tissue than by blood from an IVH extending into the brain parenchyma (Papile grade 4 IVH). An IPH may be due to blood filling the ventricles and compressing the venous network, or may be an injury to the brain that is unrelated to IVH. Periventricular leukomalacia (PVL) is seen when injured brain tissue, especially white matter, is resorbed and replaced by fluid. PVL manifests as small cysts, large cysts, larger ventricles with irregular borders, or any combination of these findings. PVL may be in the frontal, parietal or occipital lobes, and it may be on one side (unilateral) or bilateral. Some preterm infants who did not have an IVH develop ventriculomegaly due to resorption of injured brain. IVH with ventriculomegaly (Papile grade 3 IVH), IPH, PVL with or without ventriculomegaly are each associated with a high risk of neurodevelopmental impairment (NDI).[87]

Thirteen RCTs compared rate of brain injury on serial head ultrasounds in the iNO and control groups.[34, 37, 39, 40, 58-62, 64-67] Brain injury may occur in utero, during labor and delivery, and immediately after birth, and is common in preterm infants on mechanical ventilation. Studies that compared head ultrasounds before treatment with head ultrasounds obtained after treatment can best determine whether exposure to iNO has a toxic or neuroprotective effect on brain injury. Few studies were able to obtain pretreatment head ultrasounds due to logistical problems. Only

four RCTs obtained head ultrasounds at or before enrollment, and compared these to serial ultrasounds obtained during the remainder of the infant's NICU hospitalization[34, 37, 59, 64] (Appendix E, Evidence Table 8). The other seven RCTs did not obtain head ultrasounds before study entry.

Kinsella, 2006, enrolled 420 preterm infants born at and before 34 weeks gestation with a birth weight (BW) of 500 to 1250 g on mechanical ventilation within the first two days after birth, and treated them with low dose iNO (5 ppm) or placebo gas for 21 days. [37] Head ultrasounds at study entry revealed no statistically significant differences between the iNO and placebo control groups in rates of GMH or IVH without ventriculomegaly (Papile grades 1 or 2 IVH, 18.4 percent versus 21.9 percent, respectively) or of IVH with ventriculomegaly (Papile Grade 3 IVH) or IPH (6.1 percent versus 6.6 percent, p-value = 0.41). Infants with GMH, IVH with or without ventriculomegaly or IPH (Papile grades 1 to 4 IVH) at study entry were reported in the outcome data if their condition worsened during or after treatment. Ultrasonographers were masked as to treatment category. They found no statistically significant differences of IVH with ventriculomegaly or IPH between iNO and placebo control groups, 12.3 percent versus 16.0 percent, RR 0.77 (0.54, 1.09) or of ventriculomegaly, 5.2 percent versus 8.9 percent, RR 0.58 (0.37, 1.01), p-value = 0.05. There was a statistically significant reduction of PVL in infants in the iNO group (5.2 percent) compared to placebo controls (9.0 percent), RR 0.58 (0.33, 1.00), p-value = 0.048. The infants in the iNO group had a statistically significant reduction in the rate of the composite variable of IVH with ventriculomegaly (Papile grade 3 IVH), IPH, PVL or ventriculomegaly than placebo controls, 17.5 percent versus 23.9 percent respectively, RR 0.73 (0.55, 0.98), p-value = 0.03 (Appendix E, Evidence Table 8).

Ballard, 2006 enrolled infants with a BW at or below 1250 g on ventilator support or CPAP at seven to 21 days, and treated them for a minimum of 21 days.[34] Most preterm infants develop IVH or IPH within the first seven days after birth. Head ultrasounds were performed before enrollment and during and/or after administration of iNO or gas placebo. At baseline, there were no statistically significant differences in rate of unilateral IVH with ventriculomegaly or IPH, 11.9 percent versus 15.6 percent respectively; infants with bilateral IVH with ventriculomegaly or IPH were excluded. There were no differences between the iNO group and controls in the evolution of neurologic findings on head ultrasounds, 5.0 percent versus 4.1 percent, RR 1.21 (0.53, 2.76). (Appendix E, Evidence Table 8).

Two smaller RCTs were also able to perform head ultrasounds before initiating treatment. Kinsella, 1999 found that at study entry, 15 percent in the iNO group and 19 percent of controls had IVH with or without ventriculomegaly or IPH (Papile's grades 2 to 4 IVH). [59] There were no statistically significant differences in rate of IVH or IPH with or without ventriculomegaly in survivors in the iNO group compared to controls, 28 percent versus 33 percent. They reported no statistically significant differences in rates of new or higher grade of IVH or IPH (44 percent versus 42 percent) [59] (Appendix E, Evidence Table 9). In Subhedar, 1997, 42 infants born before 32 weeks gestation were enrolled at four days after birth and randomized to iNO or a control group.[64] They obtained head ultrasounds at baseline and at weekly intervals for a month. No infant in either the iNO or the control group had an extension of an existing IVH[64] (Appendix E, Evidence Table 8).

The small pilot RCT reported by Srisuparp, 2002 is the only RCT whose primary outcome variable was IVH with ventriculomegaly (Papile grade 3 IVH or IPH).[66] They were unable to obtain head ultrasounds in all infants before study entry, however, as most were enrolled on the

day of birth. They found no statistically significant differences between the iNO and control groups in brain injury, 25 percent versus 28 percent respectively.

Schreiber, 2003, enrolled 207 infants born before 34 weeks gestation with BW below 2000 g on mechanical ventilation for respiratory distress syndrome during the first week after birth.[58] After randomization to the iNO or the gas placebo group, infants in the iNO group were given iNO at 10 ppm for 12 to 24 hours then 5 ppm for six days. They did not obtain head ultrasounds before study entry; all ultrasounds were interpreted by a pediatric radiologist masked to treatment assignments. Infants in the iNO group had statistically significantly lower rates of the composite variable, IVH with ventriculomegaly (Papile grade 3 IVH), IPH or PVL than placebo controls, 12.4 percent versus 23.5 percent respectively, (RR 0.53 (0.28, 0.98), p-value = 0.04). They found no statistically significant differences in the rate of posthemorrhagic hydrocephalus, 11.4 percent versus 9.8 percent, RR 1.17 (0.53, 2.58). (Appendix E, Evidence Table 8).

The secondary hypothesis of the Van Meurs 2005 RCT of infants born before 34 weeks gestation with BW 401 to 1500 g who had severe respiratory failure was that iNO would not increase the incidence of the composite variable, IVH with ventriculomegaly (Papile grade 3 IVH), IPH or PVL.[40] This study was terminated after the second planned analysis because of a higher rate of the composite brain injury variable in the iNO group than in controls reached statistical significance. However, when outcomes were analyzed for all 420 enrolled infants (the plan was for 440 infants) there were no statistically significant differences in rates of the composite brain injury variable (Papile grade 3 IVH, IPH or PVL) whether ultrasounds were read by each center's local radiologists, 39 percent in the iNO group and 32 percent in controls, RR 1.25 (0.95, 1.66); or when they were read by a central masked reader after the study was terminated, 37 percent versus 38 percent, RR 0.97 (0.74, 1.27). Infants enrolled in this RCT had similar BW as in Kinsella 2006, and both RCTs had lower BW than in Schreiber, 2003.[37 58] However, infants in Van Meurs, 2005 were sicker than those in either Schreiber, 2003 or Kinsella, 2006, with OI 22 to 23 compared to five to seven at enrollment (Appendix E, Evidence Table 8).

In a meta-analysis of five RCTs[34, 37, 39, 40, 58] that reported the composite brain injury variable, defined by a combination of IVH with ventriculomegaly, IPH, or PVL (Kinsella, 2006 included ventriculomegaly as a separate variable), there was no statistically significant difference between infants treated with iNO and controls, RR 0.86 (0.58, 1.29). Results were unaffected by removal of the Ballard trial,[34] a study that enrolled infants much later than the other trials included in the analysis and reported only new or worsening brain injury: RR 0.79 (0.50, 1.27) (Figure 9). There was a substantial degree of heterogeneity among the five studies in this meta-analysis of brain injury ($I^2 = 0.657$). The two RCTs with the lowest RR of brain injury (Van Meurs, 2007 and Schreiber, 2003) differed from the other studies by including larger preterm infants, with BW above 1500 g.[39, 58] Brain injury tends to occur during the first week after birth and is associated with cardiovascular instability in sick preterm infants. We can speculate that the larger preterm infants derived greater benefit from the effect of iNO on cardiovascular stability, as is seen with more mature full term infants. Smaller, more preterm infants may not benefit as much from this effect, due to immature autoregulation of their cerebral blood flow.

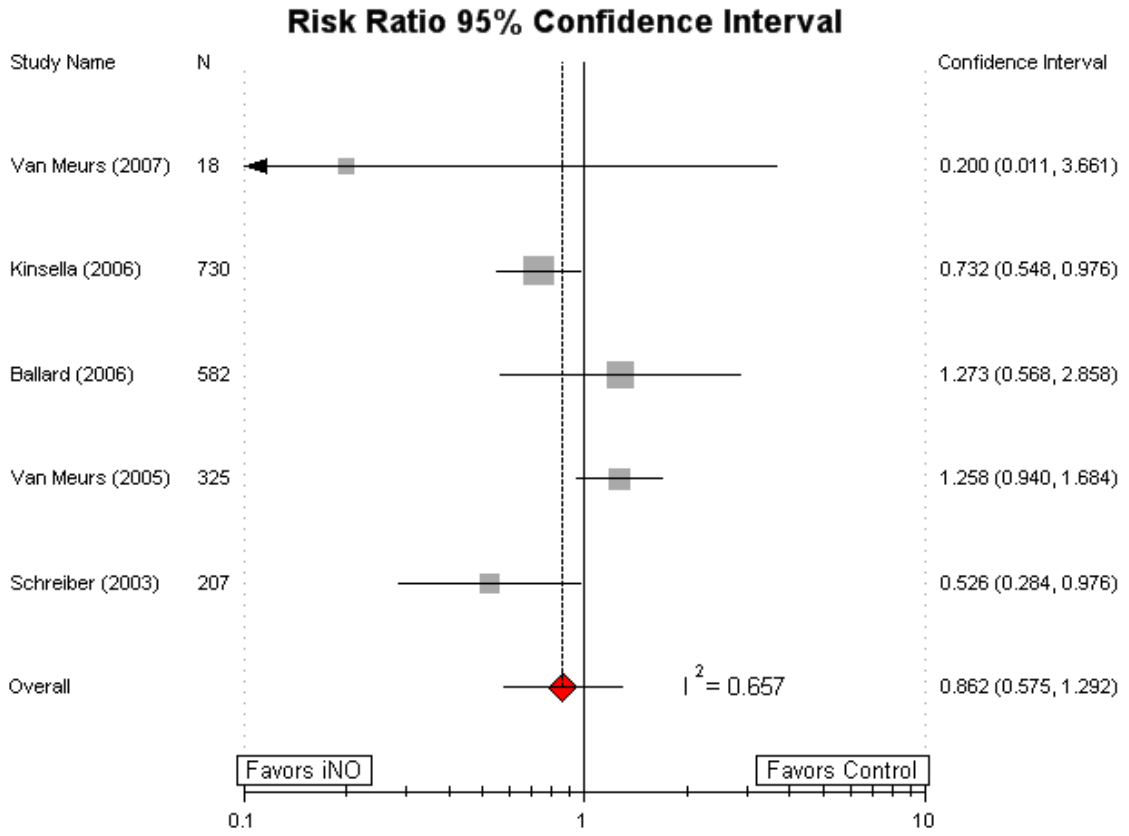

Figure 9. Meta-analysis of five studies describing brain injury

Similarly, a meta-analysis of RCTs that reported the incidence of PVL showed no difference between the iNO and control groups, RR 0.78 (0.37, 1.62) (Table 5).

In summary, one large multicenter RCT and one large single center RCT found a lower rate of brain injury (IVH with ventriculomegaly, IPH, PVL, +/- ventriculomegaly) in infants treated during the first week after birth with iNO compared to placebo controls. Another large multicenter RCT was terminated early for concern that the iNO group had a higher rate of IVH with ventriculomegaly, IPH or PVL than controls, but on final analyses, there were no statistically significant differences between the iNO and control groups. All the other RCTs found no statistically significant differences between the iNO and control groups in rates of all IVH (Papile grades 1 to 4), IVH with ventriculomegaly IPH, PVL, hydrocephalus, or combinations of these variables. What makes these findings important is that these signs of brain injury on serial head ultrasounds in the NICU are some of the best predictors for neurodevelopmental impairment in preterm infants. Key Question 3 addresses more long term outcomes, at a year or more, including cerebral palsy (CP), cognitive abilities, and neurodevelopmental impairments.

Patent ductus arteriosus. In the fetus, the ductus arteriosus allows most of the blood to bypass the lungs (and circulate through the placenta). In preterm infants, especially the most immature, failure of this duct to close can interfere with their transition to extrauterine life and lead to heart failure. By altering pulmonary blood flow, iNO may influence duct closure. Eleven RCTs described in 12 articles compared incidence of PDA in the iNO group and controls.[34, 37, 58,

[59, 61-67, 78] Some trials reported only those infants who underwent surgical ligation of their PDA, and others included all infants diagnosed with PDA, whether they were treated medically or surgically. Kinsella, 2006 reported rates of symptomatic PDA that were medically treated (54.0 percent in the iNO group versus 53.7 percent of controls), and rates of PDA treated with surgical ligation (21.6 percent versus 21.8 percent).[37] None of the eleven RCTs (Appendix E, Evidence Table 9) or a meta-analysis (RR 1.01(0.86, 1.19); Table 5) found a statistically significant difference in incidence of PDA between the iNO groups or controls.

Sepsis. Eight RCTs reported data on infants who developed sepsis. Schreiber, 2003 reported the incidence of sepsis diagnosed after the first day, to distinguish between infants who were septic at birth from those that developed sepsis during their NICU course.[58] Some studies reported sepsis only if the infant's blood culture was positive.[34, 63, 66, 67] None of the eight RCTs[34, 37, 58, 62, 63, 65-67] that reported rate of sepsis found statistically significant differences between their iNO and control groups (Appendix E, Evidence Table 9). All eight trials were included in a meta-analysis that found no difference in the development of sepsis between infants treated with iNO and controls, RR 1.06 (0.95, 1.18) (Table 5).

Necrotizing enterocolitis. NEC is an acute inflammation of the intestines that can lead to intestinal perforation, surgical resection of injured bowel and placement of an ostomy. Bowel perforation is generally associated with sepsis, and treatment consists of intravenous antibiotics, bowel rest, parenteral nutrition, and cautious refeeding. NEC can therefore have an impact on subsequent health and growth. Eight RCTs reported in nine articles[34,37, 58, 61, 62, 64, 65, 67,78] compared the incidence of NEC in iNO and control groups. Ballard, 2006 was the only study to distinguish between NEC treated medically and infants who needed surgery. The They found no statistically significant differences in incidence of NEC, 7.8 percent in the iNO group versus 6.6 percent in controls, RR 1.17 (0.64, 2.13) or NEC requiring surgery (3.4 percent in the iNO group and 2.8 percent in controls, RR1.20 (0.46, 3.13).[34] None of the eight RCTs (Appendix E, Evidence Table 9) nor our meta-analysis (RR 1.23 (0.94, 1.62; Table 5)) found any statistically significant differences in NEC between iNO and control groups.

Table 5. Meta-analyses of short term risks of iNO therapy

Variable	Studies included	Pooled RR	95 % CI
Brain injury, IVH, IPH and/or PVL	Ballard, 2006[34] Kinsella, 2006[39] Schreiber, 2003[58] Van Meurs, 2005[40] Van Meurs, 2007[39]	0.86	0.58, 1.29
PVL alone	Dani, 2006[67] Kinsella, 1999[59] Kinsella, 2006[39] Mercier,2010[62] Su, 2008[65]	0.78	0.374, 1.62
PDA, medically or surgically treated*	Ballard, 2006[34] Field, 2005[63] Kinsella, 1999[59] Kinsella, 2006[39] Mercier, 2010[62] Schreiber, 2003[58] Srisuparp, 2002[66] Su, 2008[65] Subhedar, 1997[64]	1.01	0.86, 1.19
Sepsis, clinical or culture positive	Ballard, 2006[34] Dani, 2006[67] Field, 2005[63] Kinsella, 2006[39] Mercier, 2010[62] Schreiber, 2003[58] Srisuparp, 2002[66] Su, 2008[65]	1.06	0.95, 1.18
NEC, medically or surgically treated[†]	Ballard, 2006[34] Dani, 2006[67] Kinsella, 2006[39] Mercier, 2010[62] Schreiber, 2003[58] Srisuparp, 2002[66] Su, 2008[65]	1.23	0.94, 1.62
ROP, surgically treated	Ballard, 2006[34] Field, 2005[63] Kinsella, 1999[59] Kinsella, 2006[39] Schreiber, 2003[58] Subhedar, 1997[64] Van Meurs, 2005[40] Van Meurs, 2007[39]	1.01	0.82, 1.24
Pulmonary hemorrhage [‡]	Field, 2005[63] Kinsella, 2006[39] Mercier, 2010[62] Su, 2008[65]	0.89	0.60, 1.33
Air leak or pneumothorax [§]	Field, 2005[63] Kinsella, 2006[39] Mercier, 2010[62] Schreiber, 2003[58] Srisuparp, 2002[66] Su, 2008[65] Subhedar, 1997[64]	0.96	0.71, 1.28

Table 5. Meta-analyses of short term risks of iNO therapy (continued)

*Studies excluded: Hascoet,[61] outcomes measured at 28 days; Dani[67] PDA diagnosed prior to treatment
†Studies excluded: Hamon[78] and Hascoet[61] outcomes measured at 28 days
‡ Included only studies that excluded infants with bleeding disorders from enrollment.
§ Included only studies where all enrolled infants were considered in the denominator.

Retinopathy of prematurity. Retinopathy of prematurity is a neovascular retinal disorder, which can result in severe visual impairment. Serial eye examinations determine whether ROP is present as the retina is vascularized, and if it is progressing. Visual outcomes are improved for severe ROP, especially if there are dilated, tortuous blood vessels in the posterior pole of the eye (i.e. plus disease) with laser surgery. Eight RCTs report the incidence of severe ROP treated with laser surgery.[34, 37, 39, 40, 58, 59, 63, 64] Ballard, 2006 found a high incidence of any degree of ROP in their high risk study population, 83.7 percent in the iNO group and 81.9 percent in controls, RR 1.00 (0.93, 1.07).[34] Their incidence of severe ROP requiring treatment was 24.5 percent in the iNO group versus 23.6 percent in controls, RR 0.97 (0.72, 1.31). This is similar to the incidence of ROP requiring treatment in the other seven RCTs, and none found statistically significant differences between iNO and control groups (Appendix E, Evidence Table 9). A meta-analysis confirmed no statistically significant difference in ROP between infants treated with iNO and controls, RR 1.01 (0.82, 1.24; Table 5).

Pulmonary complications. In Key Question 1, we addressed the primary pulmonary complication of prematurity, BPD. In this section, we report other pulmonary complications: pulmonary hemorrhage, air leak or pneumothorax, pulmonary hypertension or right heart failure. An important consideration is whether infants were excluded from studies if they had evidence of bleeding or air leak before entry into the study. If they were not excluded, the most meaningful data are the rate of pulmonary hemorrhage or air leak once entered into the study. Five RCTs, described in six articles, excluded infants with low platelets or bleeding problems,[40, 61, 63, 65, 67, 62] and four excluded infants with severe intracranial or pulmonary hemorrhage.[34, 37, 60]

Seven RCTs report data on pulmonary hemorrhage. Whether they excluded infants with bleeding problems[37, 63, 65 ,74] or not[58, 59, 64] they did not find any statistically significant differences between iNO and control groups in rates of pulmonary hemorrhage (Appendix E, Evidence Table 9). Our meta-analysis with trials that excluded infants with bleeding problems showed no difference in pulmonary hemorrhage between iNO treated infants and controls, RR 0.89 (0.60, 1.33) (Table 5).

Ten RCTs reported rates of air leak or pneumothorax, and none found any statistically significant differences between the iNO and control groups.[37, 39, 40, 58, 59, 62-66] Schreiber, 2003 reported pneumothorax and pulmonary interstitial emphysema separately, finding no statistically significant differences in rate of pneumothorax (10.5 percent versus 16 percent, respectively) or pulmonary interstitial emphysema (27 percent versus 34 percent, respectively).[58] The rates of air leak varied from a low of four to six percent[58, 64, 65] to as high as 35 to 38 percent[40, 63] (Appendix E, Evidence Table 9). Our meta-analysis with trials that included all infants in the denominator also found no difference in the risk of air leak between the iNO treated infants and controls, RR 0.96 (0.71, 1.28) (Table 5).

The only trial that reported pulmonary hypertension as an outcome variable documented 50 percent of infants in the iNO and control group with the condition.[67] No study specifically documented right heart failure (Appendix E, Evidence Table 8).

Methemoglobinemia. Twelve RCTs measured methemoglobin levels, and some measured nitrogen dioxide levels in administered gas.[34, 37, 39, 40, 58, 59, 62-67] Most reported that

methemoglobin levels in all infants were not elevated,[34, 59, 66, 67] or were below 2.5 percent,[65] three percent,[64] or four percent.[39] The Van Meurs, 2005 RCT of infants born before 34 weeks gestation with BW 400 to 1500 g found two infants (1 percent) in each group who had methemoglobin levels above four percent.[40] One infant in the iNO group had a methemoglobin level of at least eight percent, and the nitrogen dioxide level was at or above 3 ppm in two percent, and at or above 5 ppm in one percent. The multicenter Kinsella, 2006 trial reported a transient mild elevation of methemoglobin level in two of 398 (0.05 percent) infants, but elevation was not defined.[37] Three infants treated with iNO in the Schreiber, 2003 RCT had elevation in methemoglobin level that never rose above seven percent, and nitrogen dioxide was never above 2 ppm.[58] The Field RCT allowed the highest maximum dose of iNO, up to 40 ppm, and as many as eight of 55 (14.5 percent) preterm infants had methemoglobin levels above two percent; only one infant (1.8 percent) had nitrogen dioxide above 2 ppm for 30 minutes[63] (Appendix E, Evidence Table 9).

Conclusion

Key Question 2 analyzed 14 RCTs of iNO in preterm infants on mechanical ventilation for evidence of toxicity or short term risks of iNO. None of the 14 RCTs reported statistically significant effects of iNO on rates of PDA, sepsis, NEC, treated ROP, pulmonary hemorrhage, or air leaks. No study reported toxic accumulations of methemoglobin. None of the 13 RCTs that reported head ultrasound evidence of brain injury reported a statistically significant increase with iNO treatment. Two large RCTs, with more than 100 subjects in each group, reported a statistically significant reduction of a composite brain injury variable (IVH with ventriculomegaly, IPH or PVL) in the iNO group compared with placebo gas controls.[37, 58] These two RCTs raise the question as to whether iNO has neuroprotective effects. There was no statistically significant difference between the iNO and control groups in a meta-analysis that pooled data from five RCTs that reported rates of the composite brain injury variable (IVH with ventriculomegaly, IPH or PVL). There was also no statistically significant difference in our meta-analysis of four RCTs with data on rates of PVL. However, not only do the RCTs vary widely in study design, but there is also little uniformity among studies as to when head ultrasounds were performed, who interpreted them (locally at each center or at more uniformly at one site), categories reported, and criteria used for each category. These RCTs were generally powered for death and BPD, and not for short term risks or brain injury. There is insufficient evidence for assessing the effect of iNO on the preterm infant's brain. There is a need for RCTs that obtain neuroimaging before initiation of treatment and at regular prespecified intervals, provide for uniform interpretation of neuroimaging studies, carefully define categories of types of brain injury, and clearly report rates of each type, and composites of brain injury in terms of surviving infants. Because they are so vulnerable as they are rapidly maturing, the effects of any intervention on the brain should be studied in every RCT involving preterm infants. Key Question 3 reviews the evidence of effects of iNO on longer term neurodevelopmental, pulmonary, and other health outcomes.

Key Question 3: Are there effects of iNO therapy on long term pulmonary and/or neurodevelopmental outcomes among premature infants who receive respiratory support?

Major Findings

- There is insufficient evidence to determine whether iNO therapy in preterm infants who require respiratory support influences the incidence of cognitive, motor or sensory impairments, or neurodevelopmental disability.
- There is evidence suggesting that iNO therapy in preterm infants who require respiratory support may decrease the use of respiratory medications at one year of age.
- There is insufficient evidence to determine whether iNO therapy in preterm infants who require respiratory support impacts long term health outcomes such as lung growth and development, pulmonary morbidity, rehospitalization after NICU discharge, and growth.

Detailed Analysis

Nine articles representing six RCTs report long term followup of health and neurodevelopmental outcomes at one year corrected for degree of prematurity or later (see Table 6). Field, 2005 reported on some health and neurodevelopmental outcomes at one year corrected for degree of prematurity of the multicenter INNOVO RCT.[63] Mestan, 2005 reported neurodevelopmental outcomes and growth at two years of the infants enrolled in Schreiber, 2003, the largest single center RCT.[56] Hintz, 2007[58] reported on survival, CP, cognitive abilities and neurodevelopmental impairment (NDI) in 18 to 22 month old survivors enrolled in the NICHD RCT of infants born before 34 weeks gestation with birth weight below 1500 g.[30, 40] Neurodevelopmental impairment at one year corrected for degree of prematurity is included in the Van Meurs, 2007 paper that reported results from the NICHD RCT on infants born before 34 weeks gestation with birth weight above 1500 g.[39] For surviving infants in Ballard, 2006, Walsh, 2010 reported on neurodevelopmental outcomes and growth at two years of age, corrected for degree of prematurity, and Hibbs, 2008 reported on pulmonary and health outcomes at one year.[34, 44, 57] In a paper focused mostly on economic costs and resource utilization, Watson, 2009 reported on survival and some neurodevelopmental outcomes at one year of age, corrected for degree of prematurity, for infants enrolled in Kinsella, 2006.[36, 37] Bennett, 2001 reported on 30 month survival for all study participants who were discharged from the NICU, and neurodevelopmental outcomes for 21 of the 22 children alive at 30 months, corrected for degree of prematurity.[76] Huddy, 2008 followed the group of infants in Field, 2005 up to four to five years, and reported on several health and neurodevelopment related outcomes; this is the longest followup for any of the RCTs[35] (Appendix E, Evidence Tables 3 and 4; Table 6).

Trials that reported comparable neurodevelopmental outcomes were included in meta-analyses. There was some variability in the incidence of outcomes among the few trials that reported conditions such as CP, vision, and hearing impairment. The variability is likely due to the low prevalence of these conditions and small samples, as studies were not powered to detect difference in these outcomes. Few trials reported other long term health outcomes in a consistent manner, making pooled estimates of risk impossible, with the exception of pulmonary outcomes.

Table 6. Summary of outcomes for RCTs addressing KQ3

Outcomes	Number of studies	Total Sample size
Death and Survival	6[30, 35, 36, 39, 44, 56, 57, 63, 76]	2635
Cerebral palsy	7[30, 35, 38, 39, 56, 57, 76]	914
Cognitive outcomes	5[30, 35, 39, 56, 57]	896
Sensory impairment	7[30, 35, 36, 39, 56, 57, 63, 76]	951
NDI	7[39, 30, 35, 36, 56, 57, 76]	1312
Death or NDI	4[30, 36, 39, 76]	1236
Seizures	2[35, 63]	81
Growth	6[30, 35, 56, 57, 63, 72]	978
Oral feeding	1[63]	43
Pulmonary and other health outcomes	6[35, 36, 44, 63, 71, 72]	1344

Death and survival beyond the NICU. Followup studies of two RCTs reported survival into early childhood. Huddy, 2008[35] followed children from Field, 2005[63] until four to five years of age. A total of 108 infants were enrolled in the RCT, 44 survived to their first birthday. Overall survival to four to five years was 44 percent in the iNO group and 36 percent in controls. Mestan, 2005[56] reported that 85 percent of the iNO group and 77 percent of placebo controls from Schreiber, 2003[58] were alive at two years. Additionally, seven followup studies reported long term mortality rates for six RCTs. Study results are displayed in Table 7. None of the studies revealed a significant difference in mortality when comparing infants treated with iNO to controls. (Appendix E, Evidence Table 10).

Table 7. Studies addressing death and/or survival beyond the NICU

Author, Year	Original Trial	Followup	Control, n/N (%)	iNO, n/N (%)
Walsh, 2010[57]	Ballard, 2006[34]	2 years	23/288 (8.9)	24/294 (9.0)
Watson, 2009[36]	Kinsella, 2006[37]	1 year	98/384 (25.5)	80/385 (20.8)
Huddy, 2008[35]	Field, 2005[63]	4-5 years		
Hibbs, 2007[44]	Ballard, 2006[34]	1 year	2/230 (0.87)	2/225 (0.89)
Van Meurs, 2007[39]		18 – 22 months	4/15 (26.7)	5/14 (35.7)
Hintz, 2007[30]	Van Meurs, 2005[40]	18 – 22 months	98/210 (47)	109/210 (52)
Mestan, 2005[56]	Schreiber, 2003[58]	2 years	23/102 (22.5)	16/105 (15.2)
Field, 2005[63]		1 year	30/55 (54.5)	34/53 (64.2)
Bennett, 2001[76]	Subhedar, 1997[64]	30 months	10/22 (32)	7/20 (50)

A meta-analysis was conducted with all the trials that reported death at any time after NICU discharge, regardless of the age of the children at the time of the measurement. Two studies were excluded (Hibbs[44] and Huddy[35]) because there was more than one followup study for the Ballard and Field trials. The pooled estimate shows no difference in mortality with iNO therapy compared to placebo, RR 1.02 (0.86, 1.20) (Figure 10).

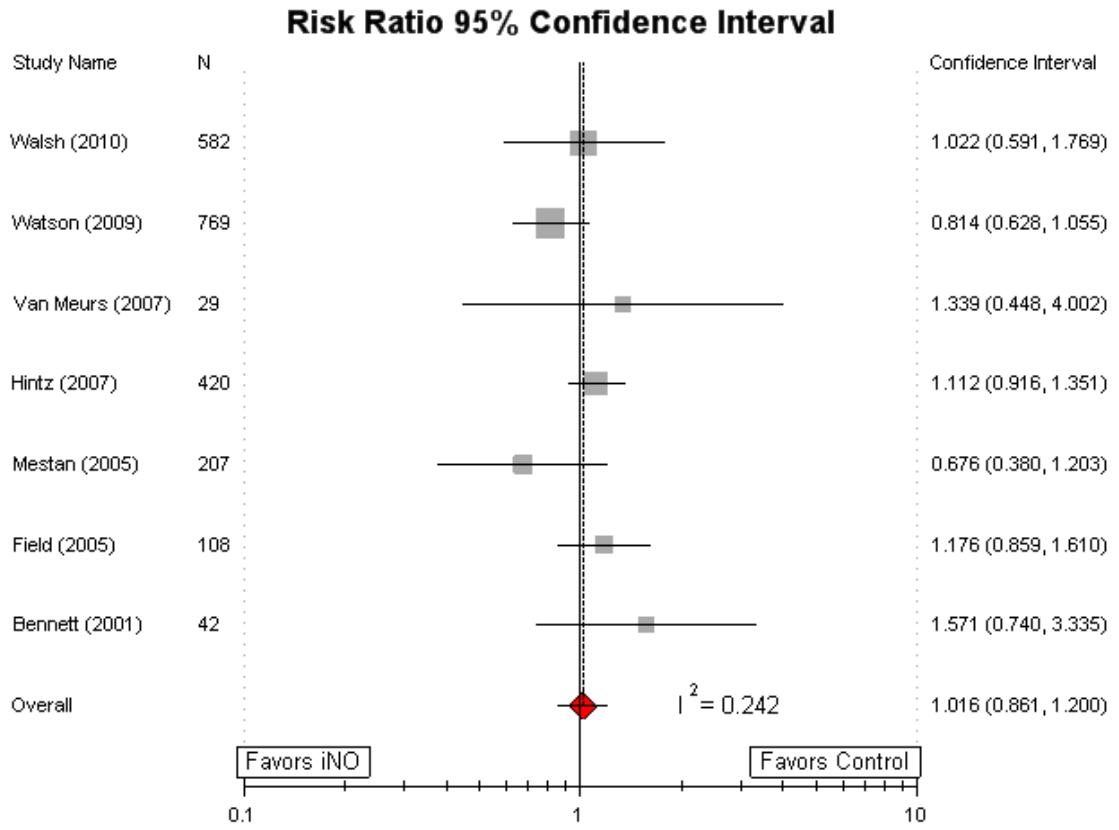

Figure 10. Meta-analysis of death at followup after NICU discharge

Cerebral palsy and motor outcomes. Cerebral palsy is a disorder of movement and posture caused by malformation or injury to the developing brain that cannot be diagnosed in the neonate, but requires a neurological examination and assessment of motor function at one or more years after birth. Cerebral palsy varies in terms of type (spasticity, extrapyramidal or mixed), anatomic distribution (diplegia, hemiplegia, etc.) severity, and associated disabilities (cognitive and/or sensory impairments). The more severe the CP, the earlier it can be diagnosed; diagnosis of mild CP is generally not made until two years or more. Diagnosis of CP requires a comprehensive neurodevelopmental examination focusing on abnormalities of muscle tone, deep tendon and other reflexes, movement and posture, as well as an assessment of motor function. The most common type of CP in preterm infants is spastic diplegia, which involves increased muscle tone and reflexes in both lower extremities with little or no involvement of the upper extremities. CP prevalence increases with decreasing gestational age and birth weight. Most studies reported moderate to severe CP. The functional classification for CP is included in the description of each study that reported this outcome.

The Hintz, 2007[30] 18 to 22 month followup study of Van Meurs, 2005[40] RCT of infants with birth weight 400 to 1500 g found CP in 20 percent of the iNO group and 11 percent of controls. CP functional impairment was defined as the ability to sit independently or with support but not ambulate independently (moderate CP), or the inability to sit or walk without support (severe CP). The initial RR was not significant at 1.85 (0.93, 3.71). When adjusted for birth weight, OI entry criterion strata, sex, BPD, IVH 3 or 4 or PVL, postnatal steroid exposure, study center, and

length of iNO exposure, the RR was significant at 2.41, indicating a higher rate of CP in iNO treated infants, but with a wide 95 percent confidence interval (1.01, 5.75) (Appendix E, Evidence Table 11).

Tanaka, 2007[38] evaluated a cohort of children at three years of age who had received iNO or 100 percent oxygen in the neonatal period for hypoxic respiratory failure with pulmonary hypertension. Cerebral palsy, defined as abnormal muscle tone in one extremity and abnormal control of movement and posture, was diagnosed in 12.5 percent of those treated with iNO compared to 46.7 percent who had been treated with 100 percent oxygen (p-value = 0.054) (Appendix E, Evidence Table 11). There was also a significantly lower odds of CP in children who had received iNO versus 100 percent oxygen (OR=0.16; 0.03, 0.98). This association persisted in several multivariate models.

The other five RCTs that evaluated for CP found no significant differences in the incidence of CP in the iNO group compared to controls. The Van Meurs, 2007 RCT of infants with birth weight above 1500 g found that none of the 17 infants who were followed to one year corrected for degree of prematurity developed CP.[39] In the Mestan, 2005 paper that reported two year outcomes of survivors of the Schreiber, 2003 RCT, CP rates were virtually the same, nine percent in the iNO group and 10 percent in controls.[56] They based their diagnoses of CP and its type on abnormalities in neuromotor tone, deep tendon reflexes, primitive reflexes, postural reactions, movement or coordination, and delay in motor milestones.[58] Walsh, 2010 reported similar findings from the Ballard, 2006 cohort: six percent of iNO treated infants and five percent of control infants developed CP by two years.[34, 57] Motor functional impairment for CP was determined by Palisano's Gross Motor Function Classification Scale (at or above 2).[88] Of the seven infants in the iNO group of Subhedar, 1997 that were followed to 30 months none developed CP, compared to two of 14 controls (14 percent), who had significant abnormalities of tone or movement.[64, 76] In the Huddy, 2008 report of four to five year outcomes of Field 2005, the CP rate (moderate to severe disability of motor function) was 13.6 percent in the iNO group and 12.5 percent in controls.[35, 63]

A meta-analysis of the seven trials that evaluated motor outcome found no statistically significant difference in CP among infants treated with iNO compared with controls, RR 1.07 (0.67, 1.71) (Figure 11). A separate meta-analysis was performed with four trials that used the Bayley Scales Psychomotor Developmental Index below 70 to define motor delay.[30, 39, 56, 76] Individually, none of these trials found a statistically significant difference in the incidence of motor delay when comparing those who had received iNO to controls. Similarly, the meta-analysis showed no statistically significant difference in the incidence of a motor delay with iNO therapy, compared with controls, RR 0.95 (0.66, 1.36) (Figure 11).

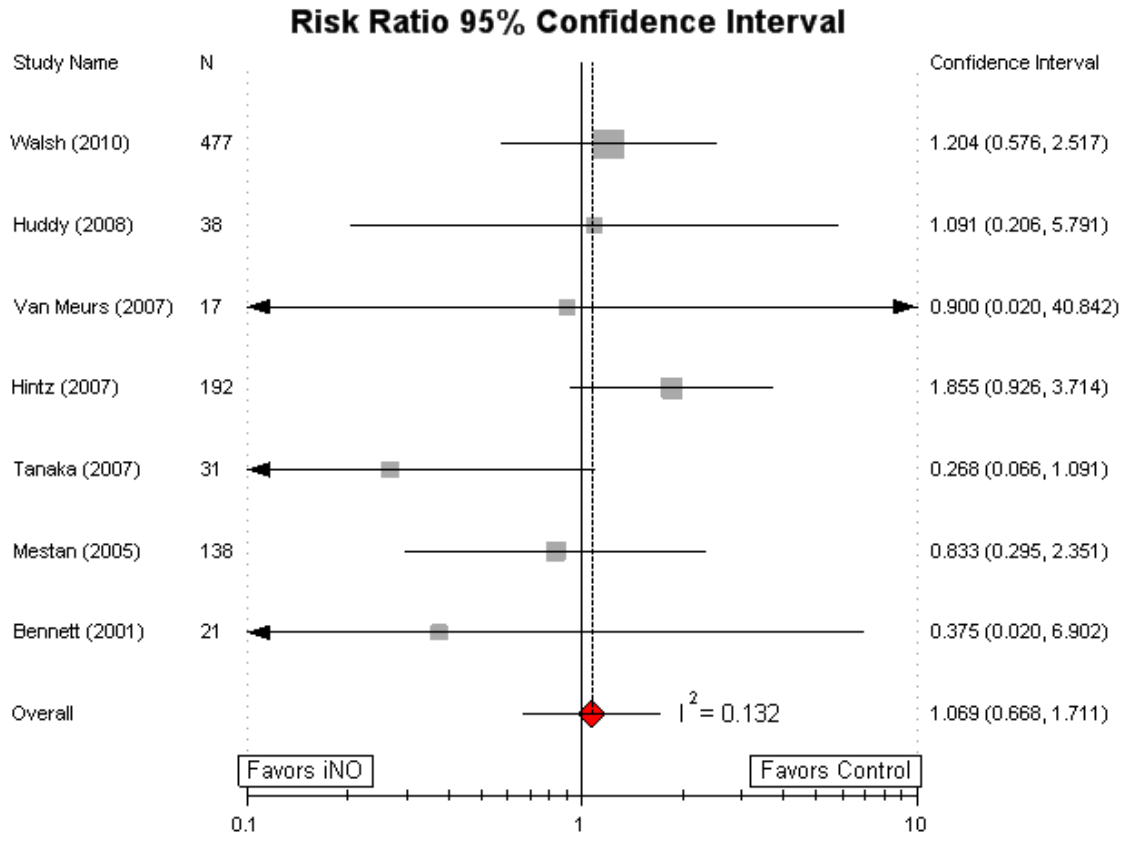

Figure 11. Meta-analysis of cerebral palsy

Cognitive outcomes. There were six RCTs and one cohort study that reported cognitive outcomes. The majority used the Bayley Scales of Infant Development Mental Developmental Index (MDI) for assessment and defined cognitive impairment as MDI < 70, two standard deviations below the mean. The only followup study to report a statistically significant difference in cognitive impairment between the iNO group and controls was the followup of Schreiber, 2003 reported by Mestan, 2005.[56, 58] Their followup rate was 82 percent at two years corrected for degree of prematurity. They found that only 19 percent of the iNO group had a Bayley MDI score more than two standard deviations below the mean compared to 35 percent of controls, p-value = 0.03. This result must be considered in the context of the significantly lower rate of the combined variable of grade 3 IVH, IPH, and PVL in the iNO group compared to controls as reported in Schreiber, 2003 (Appendix E, Evidence Table 12).

Hintz, 2007 evaluated participants with birth weight 400 to 1500 g enrolled in Van Meurs, 2005 at 18 to 22 months of age. Forty-three percent of infants in the iNO group had MDI scores more than two standard deviations below the mean compared to 36 percent of controls, RR 1.2 (0.84, 1.73).[30] Infants in the Van Meurs, 2007 RCT with birth weight above 1500 g were followed to one year corrected for degree of prematurity. In the iNO group, 11 percent had MDI scores more than two standard deviations below the mean, compared to 25 percent of controls, RR 0.44 (0.50, 4.02).[39]

A meta-analysis was performed using these three studies in which cognitive impairment was defined as MDI < 70. This revealed no statistically significantly difference between those treated

with iNO therapy and controls, RR 0.78 (0.39, 1.60) (Figure 12). As in the meta-analysis for the brain injury, there is substantial heterogeneity, reflecting that many of the same infants are included in this meta-analysis. Again, the Van Meurs, 2007[39] and Mestan, 2005[56] (followup of Schreiber, 2003) studies included infants with birth weight above 1500 g with a lower risk for brain injury and subsequent cognitive impairment than the Hintz[30] study (followup of Van Meurs, 2005) that restricted enrollment to those with birth weight of 400 to 1500 g.

In their two year followup of Ballard, 2006, Walsh, 2010 reported cognitive outcomes in terms of normal intelligence, defined as MDI score above 85, one standard deviation below the mean.[34, 57] There was no significant difference in proportion of survivors with MDI above 85; there were 39 percent in the iNO group and 35 percent in the placebo control group. Translating these data into the proportion with cognitive delay, 61 percent in the iNO group and 65 percent in the placebo control group had MDI scores one standard deviation below the mean or lower. They also reported mean MDI scores for each group and found no significant difference: 81 +/- 20 versus 79 +/- 22 (Appendix E, Evidence Table 12). Bennett, 2001 reported the incidence of cognitive delay, defined as MDI < 85 in survivors from Subhedar, 1997 at 30 months of age corrected for prematurity.[76] There was no significant difference in the incidence of cognitive neurodevelopmental delay when comparing those treated with iNO to controls, RR 0.89 (0.37, 1.75).

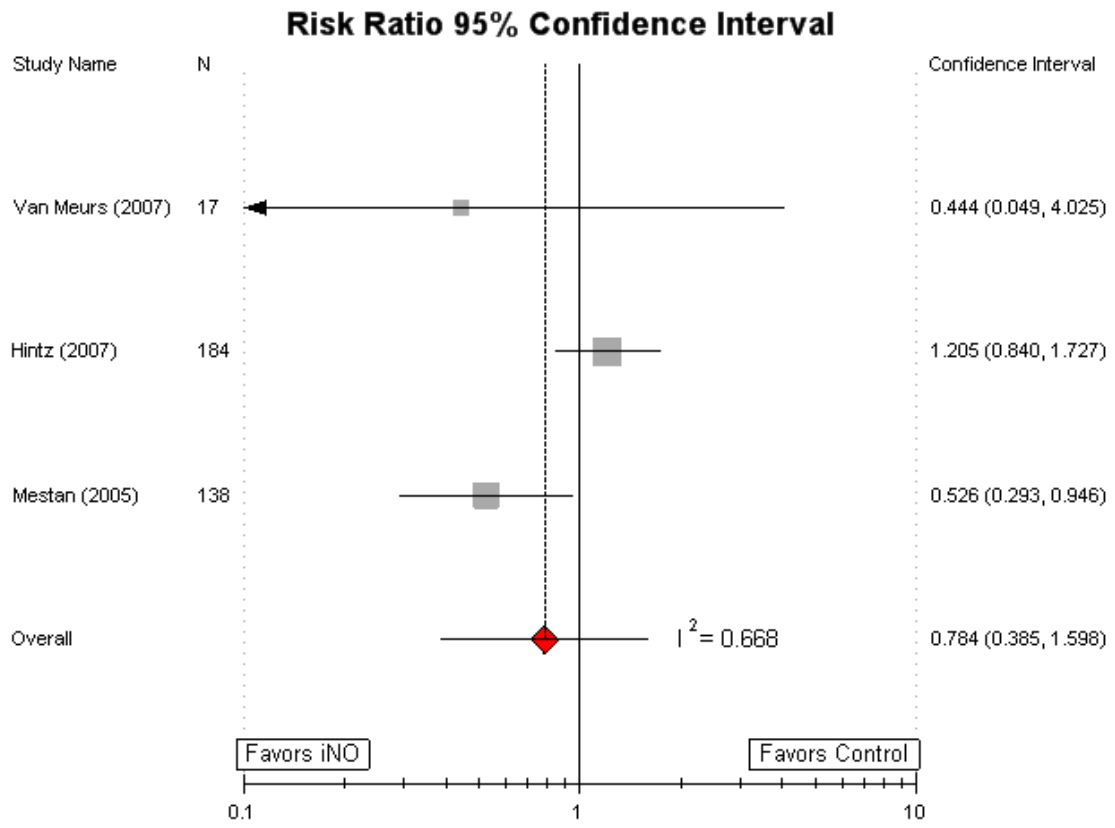

Figure 12. Meta-analysis of cognitive development as measured by the Bayley Scales Mental Developmental Index below 70

To evaluate cognition at four to five years, the Huddy, 2008[35] followup of the Field, 2005 cohort used the British Ability Scales (BAS),[89] which has norms similar to the Bayley and other intelligence tests, with a standardized mean of 100 and a standard deviation value of 15.[35] Three children in the iNO group and one control had severe impairments that precluded using the BAS. There were no statistically significant differences in mean General Conceptual Ability Score (GCAS) between the 19 children in the iNO group and the 15 children in the control group: 91.2 +/- 21.1 versus 81.3 +/- 22.5. They also found no statistically significant differences in the BAS cluster scores for verbal ability, pictorial reasoning, spatial abilities, and the nonverbal composite scores. There were six of 22 children (27 percent) in the iNO group with GCAS scores two or more standard deviations below the mean, compared with six of 16 controls (38 percent) (Appendix E, Evidence Table 12).

Sensory impairment. There were no significant differences between the iNO and control groups in proportion of children with visual impairment or hearing impairment in seven studies (representing six original trials) that report these outcomes. Visual impairments occurred in zero to four percent of children in the iNO group compared to zero to four percent in controls in the six studies that reported this outcome. [63] Our meta-analysis that included trials reporting early childhood blindness revealed no significant difference between those treated with iNO therapy and controls, RR 1.09 (0.52, 2.30) (Figure 13). Hearing impairments occurred in zero to nine percent of children in the iNO group compared to zero to seven percent of controls in the same six followup studies [30, 39, 56, 57, 63, 76] (Appendix E, Evidence Table 13). The pooled risk ratio for hearing loss also showed no significant difference with iNO therapy compared to controls, RR 1.50 (0.69, 3.27) (Figure 14).

Neurodevelopmental impairment. Seven studies reported the proportion of children with neurodevelopmental impairment (NDI), a combined variable that included cognitive, neuromotor, and sensory impairments. Children with moderate to severe CP were included, as were children with severe visual or hearing impairments. All studies defined "cognitive impairment" as two or more standard deviations below the mean score for the assessment tool that was used. Most studies also included children with Psychomotor Developmental Index scores two or more standard deviations below the mean from the Bayley Scales of Infant Development[30, 36, 39, 56, 57, 76] (Appendix E, Evidence Table 14, Table 8).

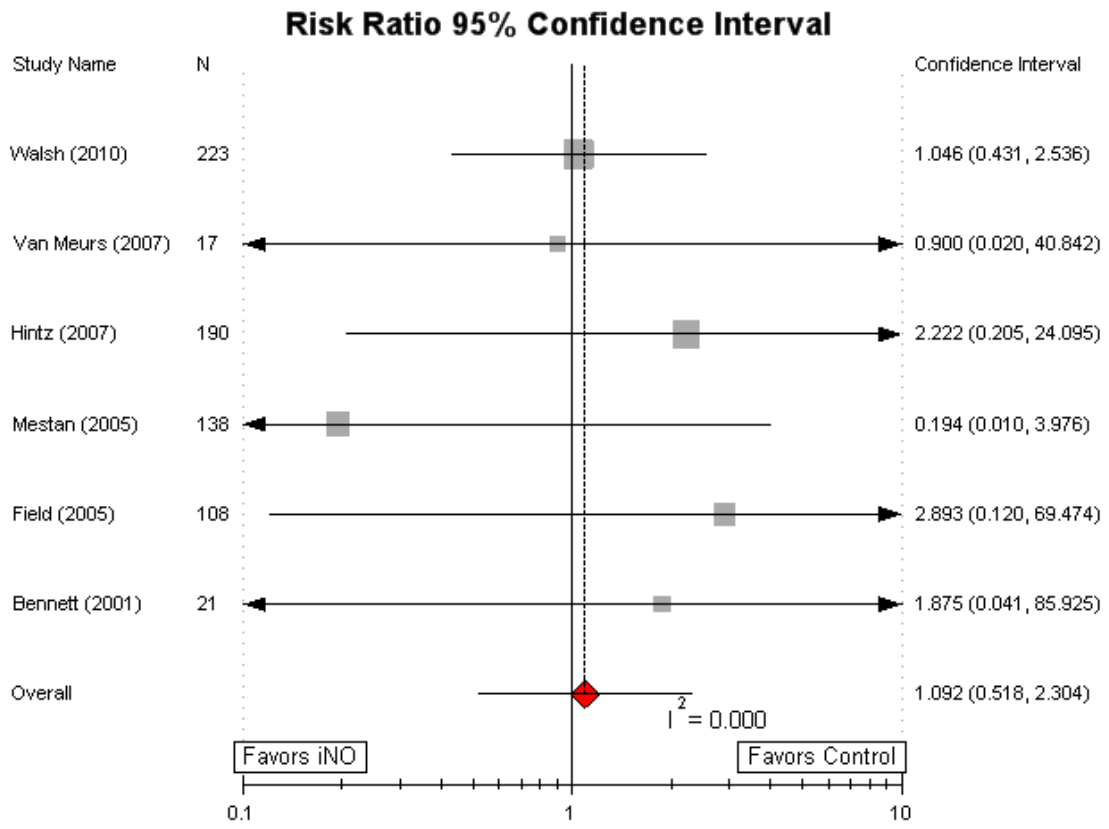

Figure 13. Meta-analysis of visual impairment

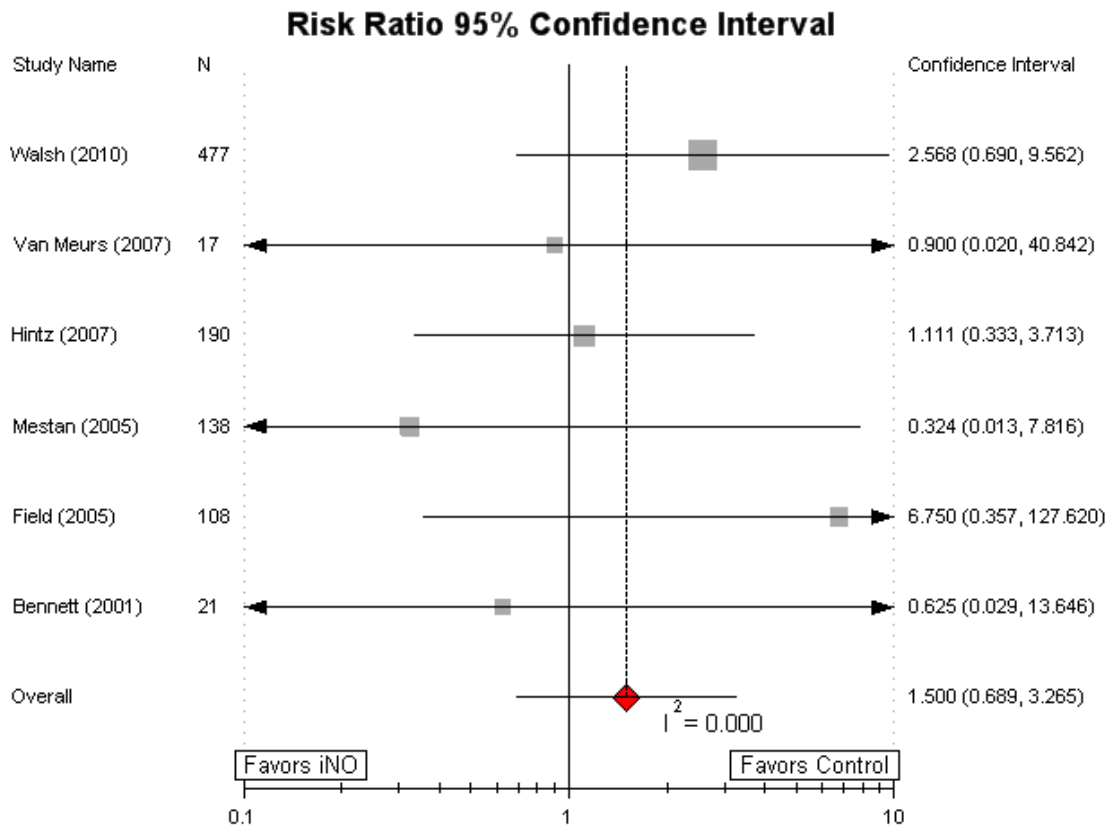

Figure 14. Meta-analysis of hearing impairment

Just as they found statistically significant differences in cognitive impairment, the Mestan, 2005 two year followup study of Schreiber, 2003 found that NDI rates were lower in the iNO group compared to placebo controls: 24 percent versus 46 percent, RR 0.53 (0.33, 0.87), p-value = 0.01. The six other followup studies revealed no significant differences between the two groups.[35, 39, 56-58, 76] In two large RCT two year followup studies, as many as half of the survivors in both the iNO and control groups had NDI: 45 percent versus 49 percent respectively, RR 0.92 (0.75, 1.12) reported by Walsh, 2010 using Ballard, 2006 cohort; and 51 percent versus 47 percent respectively, RR 1.07 (0.8, 1.44) reported by Hintz, 2007 for the Van Meurs, 2005 multicenter RCT.[57, 30] The Van Meurs, 2007 RCT of infants with birth weight above 1500 g reported a lower rate of NDI in both iNO and control groups, with no statistically significant difference between the two groups: 11 percent versus 25 percent, RR 0.44 (0.5, 4.02).[30, 39] Despite the finding in Kinsella, 2006 of a lower rate of grade 3 IVH, IPH or PVL in infants in the iNO group, Watson, 2009 reported no statistically significant differences in the rate of NDI at one year corrected for degree of prematurity in infants in the iNO group compared to controls, 35 percent versus 34 percent.[36, 37] Huddy, 2008 reported no significant differences in four to five year old children from the Field, 2005 cohort, with NDI in 36 percent of children in the iNO group and in 44 percent of controls.[35, 63] Bennett, 2001 reported that for 30 month old children in the Subhedar, 1997 RCT, none of the seven survivors had NDI compared to 36 percent of controls[64, 76] (Appendix E, Evidence Table 14).

Table 8. Studies addressing neurodevelopmental impairment

Author, Year	Age	Definition	Control, n/N (%)	iNO
Walsh, 2010[57]	2 years	MDI or PDI<70, GMLS≥2, blind, deaf	115/234 (49)	109/243 (45)
Watson, 2009[36]	1 year	CP, blind, severe HI, MDI or PDI<70	73/218 (33.5)	84/237 (35.4)
Huddy, 2008[35]	4-5 years	Mod-Sev Disability	7/16 (44)	8/22 (36)
Hintz, 2007[30]	18-22 months	MDI/PDI<70, mod-severe CP, VI	48/102 (47)	45/89 (51)
Van Meurs, 2007[39]	18-22 months	MDI or PDI<70, mod-severe CP, blind, deaf	2/8 (25)	1/9 (11)
Mestan, 2005[56]	2 years	CP, blind, HI, MDI<70	31/68 (46)	17/70 (24)
Bennett, 2001[76]	30 months	MDI or PDI<70, CP, blind, HI	5/14 (36)	0/7 (0)

HI = hearing impairment; VI = visual impairment; GMLS = Palisano gross motor level score; MDI = mental development index; PDI = physical development index; CP = cerebral palsy

Our meta-analysis of trials that measured outcome at 12 to 30 months suggests no statistically significant difference in the proportion of infants with NDI between those given iNO versus the control group (RR 0.91 (0.77, 1.12)) (Figure 15).

Two followup studies reported the rate of children in each group who had no impairment. For the followup of infants from Kinsella, 2006, Watson, 2009 defined "no impairment" to include only those children who had MDI and Bayley Physical Developmental Index (PDI) above 85, and no CP or severe visual or hearing impairment.[36, 37] They found no statistically significant differences in the proportion of children with no impairments at one year corrected for degree of prematurity between the iNO group and controls: 38 percent versus 37 percent. In reporting the 18 to 22 month followup results from Van Meurs, 2005 RCT on preterm infants with birth weight 400 to 1500 g, Hintz, 2007 used a similar definition of "unimpaired": MDI and PDI ≥ 85, no moderate to severe CP and not blind or deaf. [30] They found that 23 percent in the iNO group and 25 percent in placebo controls were unimpaired. The low proportion of survivors with no impairments is an indication of how sick the infants enrolled in the RCTs were. Conversely, there was a higher survival rate among infants with NDI. (Appendix E, Evidence Table 13).

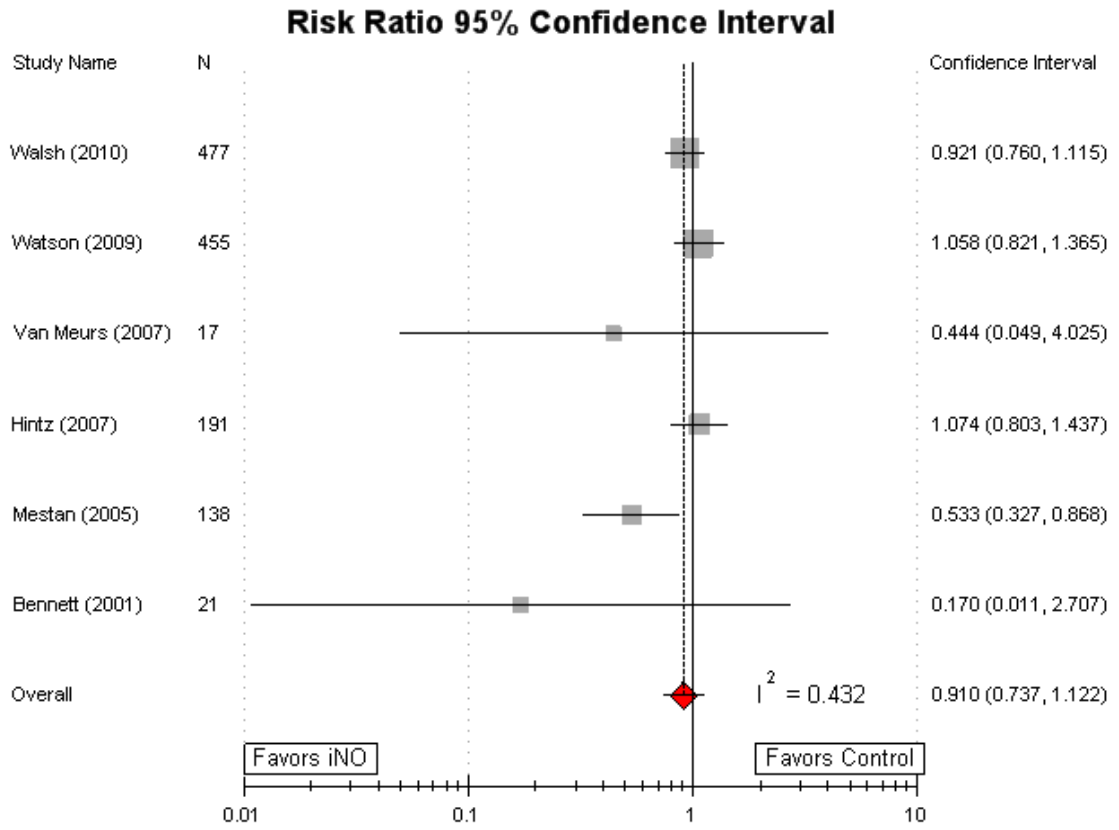

Figure 15. Meta-analysis of studies reporting NDI

Death or neurodevelopmental impairment. None of the four studies that reported the rate of the composite variable, death or NDI, for infants enrolled in four RCTs found any significant differences between the iNO and control groups.[30, 36, 39, 76] Although Kinsella, 2006 reported lower rates of grade 3 IVH, IPH or PVL in infants in the iNO group compared to controls, Watson, 2009 reported no significant differences in the rate of death or NDI at one year corrected for degree of prematurity: 42.4 percent in the iNO group and 44.5 percent in placebo controls.[36] Similarly, in the two Van Meurs RCTs, there were no significant differences between the iNO groups and placebo controls; Hintz, 2007 reported that 78 percent of preterm infants with birth weight 400 to 1500 g in the iNO group died or had NDI compared to 73 percent of controls, RR 1.07 (0.95, 1.19)[30]; while Van Meurs, 2007 reported that 43 percent of preterm infants with birth weight above 1500 g in the iNO group died or had NDI compared to 50 percent of placebo controls, RR 0.86 (0.37, 1.96).[39] In the Bennett, 2001 followup of Subhedar, 1997, 63 percent in the iNO group and 59 percent in the control group died or had NDI at 30 months[64, 76] (Appendix E, Evidence Table 14).

Long term health outcomes.

Seizures. Seizures can accompany complications that occur in the antenatal period or in the NICU, including perinatal asphyxia, hypoxia, hypoglycemia and other electrolyte abnormalities, intraventricular hemorrhage and meningitis. Seizures in premature infants that persist beyond the NICU are usually a result of brain injury and associated with other neurodevelopmental sequelae. Field, 2005[63] included “on anticonvulsants” and “fits in previous four weeks” with neuromotor outcomes at one year corrected age. These outcomes are based on available pediatrician

assessments. In the iNO group, three of the 25 infants, and one of the 18 control infants with available reports were being treated with anticonvulsants. Three infants in the iNO group and none of the 18 control infants had experienced a fit or seizure in the four weeks prior to the assessment. Seizures were included in the General Health domain of the four to five year assessments of infants enrolled in the Field, 2005 RCT performed by Huddy, 2008.[35] Children could be categorized as normal, impaired, or mildly, moderately, or severely disabled with regard to seizures. Of the five children who had seizures in the 12 months prior to assessment (3 of 22 iNO, 2 of 16 controls), three iNO and one control were on regular seizure medications, and considered to be impaired. One iNO child had more than one seizure per month and was classified as mildly disabled (Appendix E, Evidence Table 15).

Growth. There are five RCTs and one cohort study in which growth parameters were included with early childhood outcomes. Cheung, 1998 evaluated the 10 survivors from a cohort of 24 infants who received rescue iNO therapy for severe hypoxemic respiratory failure. One or more anthropometric measures (weight, length, head circumference) of four of the 10 (40 percent) infants evaluated at 13 to 40 months were below the third percentile on a standard growth curve when plotted at their corrected age.[72] In the followup of survivors from the Van Meurs, 2005 RCT at 18 to 22 months,[30] Hintz, 2007 measured weight and head circumference. When comparing the infants who had received iNO to controls, there was no difference in the measures of weight and head circumference, or percentage of infants with weight or head circumference below the fifth percentile for corrected age, based on CDC growth charts[90] (Appendix E, Evidence Table 15).

Infants enrolled in the Field, 2005 trial had growth parameters reported at one year corrected age, [63] and four to five years chronologic age. [35] At one year, there were pediatrician reports on 25 infants who had received iNO, and 18 controls.[63] Infants were categorized by the number of standard deviations their length and weight were from a standardized height and weight.[91] There was no reported analysis to determine whether this distribution was different between the two groups. The actual measure of head circumference was reported. The mean head circumference was similar in the two groups, within one standard deviation: iNO 45.5 cm (1.8), control 45.2 cm (1.6). In the followup study by Huddy, 2008, weight, length, and head circumference were measured in 22 participants from the iNO group and 15 controls at four to five year of age.[35] There were no differences in the standardized mean values[91] for any of the three parameters between the iNO and control groups. It was noted that values were lower in both groups than those of normal population. Walsh, 2010[57] and Mestan, 2005[56] both evaluated infants at two years of age corrected for prematurity from Ballard 2006 multicenter RCT, and Schreiber 2003 single center RCT, respectively. In the former, there were no significant differences in measures of weight, length or head circumference. Mestan, 2005[56] reported the measures and generated z-scores using the CDC growth charts,[90] which revealed that both the iNO and control groups were smaller than the reference population for all measures. Unlike the others who reported growth measures, Mestan, 2005[56] found that those in the iNO group were significantly heavier than participants in the control group (median weights 11.7 kg versus 10.8 kg, p-value = 0.04; z-scores -0.49 versus -1.07, p-value = 0.02); and measures of length and head circumference were not different (Appendix E, Evidence Table 15). Participants lost to followup had a higher birth weight and greater gestational age at delivery, which could influence followup weight if they were not equally distributed among the iNO and control groups.

Oral feeding. Successful oral feeding requires the coordination of basic reflexes, more complicated motor skills, and effective breathing. Infants must coordinate these efficiently in

order to take in enough to support the energy expenditure required for this task, as well as growth. Any of the required skills can be adversely affected by premature birth and associated complications. Lung disease can increase the required energy expenditure that is necessary for maintenance and catch up growth. Only Field, 2005[63] reported oral feeding and did so as a secondary outcome measure. Reports from pediatricians revealed that three of 25 infants who received iNO had a stoma for feeding. Of these infants, only one was limited to feeding through the stoma only; two infants also took some pureed feeds orally. One infant who did not receive iNO (of 18) was limited to liquid feeds through a tube but did not have a surgical ostomy placed for feeding. Five iNO infants and four controls could only manage pureed foods. The remainder (17 iNO and 13 control infants) could also manage eating lumps (Appendix E, Evidence Table 15).

Pulmonary and other health outcomes. There were two cohort studies and four randomized controlled trials that reported pulmonary outcomes beyond NICU hospitalization. The reported markers of pulmonary health varied among studies and included the use of supplemental oxygen or respiratory medications, asthma or wheezing, respiratory disability, feeding tube, and recurrent aspiration.

The safety and efficacy study by Clark, 2002[71] included infants $\leq$1250 grams birth weight, on mean airway pressure of $\geq$ 7cm H20 and FiO2 $\geq$ 40 percent at 10 to 30 days of age. The focus of the study was safety and short term efficacy. However, records of 25 of the 29 survivors were available at six months of age and revealed that 10 of the infants continued to require supplemental oxygen (40 percent) (Appendix E, Evidence Table 15).

Cheung, 1998 reported on the ten survivors from the cohort of 24 infants who received iNO as rescue therapy for severe hypoxemic respiratory failure. Eight were diagnosed with bronchopulmonary dysplasia; all had supplemental oxygen discontinued by 10 months corrected age. Other pulmonary issues reported at followup that occurred in the range of 13 to 40 months corrected age include recurrent aspiration pneumonia (1/10), and chronic lung disease requiring bronchodilator therapy on a regular basis (1/10). Four of the 10 children had recurrent wheezing episodes and used bronchodilator therapy intermittently[72] (Appendix E, Evidence Table 15).

Hibbs, 2007 reported the pulmonary outcomes at one year of 85 percent of the survivors enrolled in Ballard, 2006. [34, 44] The control group had a greater prevalence of reported pulmonary morbidity at one year of age when compared to the iNO group, based on respiratory symptoms (56.4 percent versus 49.6 percent ; OR 0.70 (0.48–1.03)), use of diuretics (28.4 percent versus 18.6 percent; OR 0.54 (0.34, 0.85)), systemic (17.7 percent versus 11 percent; OR 0.56 (0.32, 0.97)), and inhaled steroids (32.4 percent versus 19.8 percent; OR 0.50 (0.32, 0.77)), inhaled bronchodilators (54.1 percent versus 40.1 percent; OR 0.53 (0.36, 0.78)), and supplemental oxygen (9.4 percent versus 3.0 percent; OR 0.30 (0.13, 0.73)) at time of followup. Similarly, a greater percentage of the control infants had received supplemental home oxygen at some time since NICU discharge when compared to infants who had received iNO (49.5 percent versus 38.4 percent; OR 0.65 (0.44, 0.95)). However, there was no difference between the two groups in the percent who were rehospitalized for respiratory complications, or for any reason (21.9 percent versus 22.6 percent; OR 1.03 (0.65, 1.62)) (Appendix E, Evidence Table 15).

Field, 2005[63] reported respiratory outcomes from assessments by pediatricians in the first year of life for 25 of 55 who had received iNO and 18 of 53 infants who had not. Three iNO infants required respiratory support day or night, and three required supplemental oxygen. Ten used bronchodilators since discharge, and five used steroids. Respiratory symptoms in the three months prior to assessment included coughing at night (8 infants) and wheezing day or night (13

infants). Nine iNO infants had respiratory signs and symptoms on exam by the pediatrician. Two control infants required respiratory support day or night, and one required supplemental oxygen. Seven had used bronchodilators since discharge and five had used steroids. Respiratory symptoms in the three months prior to assessment included coughing at night (5 infants) and wheezing day or night (11 infants). Four control infants had respiratory signs and symptoms on exam by the pediatrician (Appendix E, Evidence Table 15).

Watson, 2009[36] assessed the outcomes of premature infants with respiratory failure who were randomized to receive iNO versus standard therapy. One year outcomes for these infants focused on health resource utilization and neurodevelopment. Use of supplemental oxygen at home was not a primary outcome variable but was reported as: 1) percentage of infants using supplemental oxygen prior to one year corrected age; 2) percentage on oxygen at one year of age; 3) duration of supplemental home oxygen. There were no significant differences in any of these measures by study arm when the entire group was evaluated. However, when stratified into birth weight categories, the smallest infants (500 to 749 g) who did not receive iNO had an advantage; fewer required supplemental oxygen at one year corrected age (4 percent versus 11.7 percent, p-value < 0.04).

Our meta-analysis including the trials of Field, 2005 and Hibbs, 2007, showed a statistically significant lower risk for those receiving iNO therapy compared to controls in the need for bronchodilator, RR 0.75 (0.62, 0.91), and steroid therapy, RR 0.62 (0.46, 0.85), but not in wheezing, RR 1.14 (0.56, 2.32).

Respiratory health was one of the domains assessed at four to five year followup by Huddy, 2008.[35] Twenty of 22 iNO infants and 15 of 16 control infants were reported to have no respiratory disability. The remaining infants in each group (2 iNO, 1 control) had mild respiratory disability (Appendix E, Evidence Table 15).

Conclusion

Our search identified twelve articles that included outcomes into early childhood. Six randomized controlled trials provided the baseline population for nine followup studies. Only Field, 2005 includes any post NICU followup among primary outcome measures, and this study included just over half of the planned sample size for this outcome. We also identified three cohort studies addressing long term outcomes. The two prospective cohort studies do not include controls for comparison. The controls in the retrospective cohort study are chosen from an earlier time period when practice standards other than just iNO use may have differed. Therefore, evidence to definitively answer any facet of this key question is not adequate.

Few individual studies and none of the meta-analyses revealed a significant association between neonatal iNO exposure and any neurodevelopmental outcome up to five years of age. For CP the two studies that did show associations conflicted in the direction of association. Tanaka, 2007 reports a decreased incidence of CP in the iNO group and Hintz reports an increase in CP in the iNO group. Both studies also had design or statistics issues that limit interpretation of the results. Mestan, 2005 reported a lower incidence of MDI < 70, NDI and the composite variable, death or NDI in those treated with iNO from Schreiber, 2003. This provides consistency, as the latter found a lower rate of CLD or death, and significant perinatal brain injury in the iNO treated infants. Of the studies that report growth parameters, Mestan, 2005 also reported the only difference in any anthropometric measure; the iNO treated infants were heavier at the time of followup. This set of results provides an incentive to pursue additional randomized

controlled trials of iNO in premature infants with primary outcomes, such as neurodevelopment, that extend into early childhood.

Of the studies that reported pulmonary outcomes after NICU discharge, only Hibbs, 2008[44] found significant associations that favor iNO use in the NICU; iNO treated infants from Ballard, 2006 were less likely to use bronchodilators and steroids at one year of age corrected for prematurity than controls. Field, 2005 provided the only other comparable data for meta-analyses. This study increased total sample in the meta-analyses by only 10 percent and the addition of this study to the meta-analysis did not have any significant influence on the results. Meta-analyses found statistically significantly lower use of bronchodilators and steroids in the iNO treated infants at followup. Ballard, 2006 treated infants with iNO or study gas at a later chronological age than most RCTs (at 7 to 21 days) and for the longest duration, a minimum of 24 days. This is compelling evidence, but it is not sufficient to recommend routine use of iNO for protection against chronic respiratory illnesses of childhood. It does, however, warrant directing focus to additional RCTs of iNO use in premature infants in the NICU and considering that the timing of initiation and duration of therapy may play an important role in outcome. Design of future studies should focus on early childhood outcomes, with definitive and objective outcome measures.

Key Question 4. Does the effect of iNO therapy on BPD and/or death or neurodevelopmental impairment vary across subpopulations of premature infants?

Major Findings

- There is insufficient evidence to determine whether the effect of iNO therapy on mortality, BPD, or motor impairment differs by the birth weight of the treated infants.
- There is insufficient evidence to evaluate the relationship between iNO therapy and infant sex, race/ethnic group, gestational age, or socioeconomic status.
- There are no published data available to evaluate the association between iNO therapy and, antenatal steroids, chorioamnionitis, multiple birth, or growth restriction.
- There is insufficient evidence concerning the relationship between iNO therapy and the severity of illness.
- There is insufficient evidence that iNO therapy improves outcome of infants suffering respiratory failure from pulmonary hypoplasia, respiratory distress syndrome or pulmonary hypertension.
- There is no consistent pattern of infants that respond to iNO therapy and those that do not.

Detailed Analysis

Six randomized controlled trials,[34, 37, 40, 58, 63, 62] four with long term followup,[30, 36, 56, 57] and seven other studies[38, 68, 69, 70, 73, 74, 77] addressed one or more subpopulations of interest in this Key Question (Table 9).

Four RCTs investigated whether iNO therapy has a differential effect by birth weight[37, 40, 58, 34]; three of the trials[34, 37, 40] reported long term followup.[30, 36, 57] Birth weight subgroup analyses

were planned *a priori* in two trials[34, 37, 58] and were done post hoc for the other two trials.[40, 58] Three trials enrolled infants at ≤ three days of age,[40, 58, 92] while the fourth RCT enrolled infants at seven to 21 days of age. [34]

Only small numbers of trials have addressed the effect of iNO therapy on other subpopulations including the severity of infant illness, as measured by the oxygenation index (OI)[40, 58, 63] or respiratory severity score,[34] race,[34, 37, 57, 62] sex,[34, 57, 62] gestational age, [62] pulmonary hypertension,[38] and pulmonary hypoplasia.[69, 77]

Descriptions of studies that evaluate iNO therapy in subgroups of infants by demographic characteristics are reviewed first below. Studies that evaluated iNO therapy by severity of illness indicators and causes for respiratory failure follow (Appendix E, Evidence Tables 3 and 4; Table 9).

Birth weight. The evidence for the effect of iNO is presented in standard birth weight groupings: < 750 g, 750 to 999 g, 1000 to 1250 g, ≤ 1000 g, > 1000 g, and others. For individual studies, the birth weight stratum may vary slightly from the category heading. For instance, results for a study using the stratum ≤ 750 g are included under the heading < 750 g. Ballard, 2006[34] is an exception as infants were categorized into birth weight groups of 500 to 799 g and 800 to 1250 g. This trial has been reviewed in the birth weight category of < 750 grams and 1000 to 1250 grams birth weight

Birth weight < 750 g. In two trials,[30, 71] including one with 384 infants with birth weight between 500 g and 749 g, there was no difference in mortality in the NICU,[37] or survival without chronic lung disease[58] between those treated with iNO and controls. In followup to a third trial,[40] mortality at 18 to 22 months was significantly higher in the iNO group compared with the controls (73 percent versus 56 percent; p-value = 0.01).[30] A fourth trial, Ballard 2006[34], reported no significant difference between infants treated with iNO and controls in survival without CLD at 36 wks PMA (RR 1.26 (0.98, 1.62)) or death (RR 1.02 (0.96, 1.08)), among infants with birth weight of 500 to 799 g[80] (Appendix E, Evidence Table 16).

No difference was reported in the incidence of BPD at 36 weeks PMA between groups for the three trials that reported the outcome.[34, 37, 40] At one year corrected age, Watson 2009[36] reported more infants treated with iNO in Kinsella, 2006 [37] remained on oxygen compared with control infants (11.7 percent versus 4 percent, p-value = 0.04). (Appendix E, Evidence Tables 16).

Table 9. Summary of outcomes for RCTs addressing KQ4

Subanalysis	Outcome	Number of Studies	Total sample size
Birth weight < 750 g	Death	3[30]	573
	BPD at 36 weeks PMA	5[34, 36, 37, 40, 44]	1464
	Death or BPD	4[37,34, 36, 58]	1355
	Survival without BPD	2[34, 58]	601
	NDI	2[30, 36]	254
	Death or NDI	1[30]	94
Birth weight 750-999 g	Death	2[37, 40]	388
	BPD at 36 weeks PMA	1[37, 40]	380
	Death or BPD	2[36, 37, 40]	865
	Survival without BPD	1[58]	57
	NDI	2[36, 37, 40]	384
	Death or NDI	1[36]	273
Birth weight <1000 g	Death	1[30, 40]	316
	BPD at 36 weeks PMA	1[40]	155
	Death or BPD	1[40]	316
Birth weight 1000-1250 g	Death	1[36, 37]	129
	BPD at 36 weeks PMA	1[37]	129
	Death or BPD	2[36, 37]	251
	NDI	1[36]	77
Other Birth weight categories	Death	3[34,*58,†40,‡30]	343
	BPD at 36 weeks PMA	3[34,§58,†40‡]	343
	Death or BPD	1[40‡]	104
	Survival without BPD	2[34,§58†]	239
	Survival with BPD	2[34,§58†]	239
Gestational age	Survival without BPD	1[62]	795
Sex	Survival without BPD	1[62]	795
Race	Survival without BPD	1[34]	582
	Death, ICH, and PVL	1[37]	793
Socioeconomic status	NDI	1[57]	396
OI	Risk of Death	1[40, 63]	108
	BPD and Death or BPD	3[40, 58, 63]	726
	NDI	1[56]	138
	Death or disability	1[63]	108
Respiratory severity score	Survival w/o BPD	1[34]	582
	NDI	1[57]	477
RDS	BPD at 36 weeks PMA	1[63]	108
	Death or NDI	1[63]	108
Pulmonary hypoplasia	Death	2[69, 77]	30
	BPD at 36 weeks PMA	2[69, 77]	25
	Death or BPD	1[77]	12
	NDI	1[77]	4
Pulmonary HTN	Cerebral Palsy	1[38]	31
Responders vs. nonresponders	Death	3[68, 70, 73, 74]	169
	BPD, ventilator dependant survivors	1[70, 74]	105
	Survival to discharge	1[73]	41

* Birth weight 500-799g
† Birth weight 1000-1500g
‡Birth weight >1000g
§Birth weight 800-1250g

BPD = Bronchopulmonary Dysplasia; PMA = Post menstrual age; NDI = Neurodevelopmental impairment; IVH = Intraventricular hemorrhage; ICH: Intracranial Hemorrhage; PVL = Periventricular leukomalacia; CP = Cerebral palsy

No meta-analyses were conducted for this Key Question because of the differences in the definitions of subgroups across studies and the reported outcomes measured.

Similar rates of the composite outcome death or BPD at 36 weeks PMA were reported for iNO treated infants and controls in all three studies that reported this outcome. [34, 37, 58] In one followup study, the combined outcome of death or an oxygen requirement to one year of age occurred in 37 percent of infants in each group[36] (Appendix E, Evidence Tables 16).

Inhaled nitric oxide therapy did not improve neurodevelopmental outcome in this birth weight category. Neurodevelopmental impairment (NDI) was similar between iNO treated infants and controls when measured by Hintz 2007 at 18 to 22 months corrected age (NDI defined as including any of the following: moderate to severe CP, blind, deaf, MDI < 70, or PDI < 70),[36] by Walsh, 2010 at 24 months corrected age (NDI defined as moderate or severe CP, bilateral blindness, bilateral hearing loss requiring amplification, or score <70 on the Bayley Scales MDI or PDI) (RR 0.85 (0.67, 1.08))[57], and by Watson 2009 at one year of age corrected for gestational age at birth (NDI defined as including any of CP, blindness, severe hearing loss, MDI < 70 or PDI < 70). [30] In two followup studies[30, 36] the composite outcome death or NDI was similar between the groups. The composite death or moderate to severe CP occurred more frequently in the iNO treated infants than controls (81 percent versus 62 percent, p-value = 0.0039), in one study. [30] (Appendix E, Evidence Table 16).

Birth weight 750 to 999 g. No differences were reported between iNO and control infants in this subgroup with respect to mortality, BPD, the combined outcome of death or BPD, neurodevelopmental impairment (NDI),[37, 40] or survival without BPD[58] in the three studies. Watson, 2009 reported that iNO treated infants had lower rates of death or NDI at one year compared with controls (32.1 percent versus 44.4 percent, p-value=0.04), as well as a decreased rate of the combined outcome of death, on oxygen, or NDI at one year corrected age (32.9 percent versus 45.1 percent, p-value = 0.04)[36] (Appendix E, Evidence Table 16).

Birth weight <1000 g. Only one study examined this birth weight subgroup, using post hoc analyses. The iNO treated infants had a higher mortality rate than the control group (62 percent versus 48 percent, RR 1.28 (1.06, 1.54)), but they also had a higher rate of severe (Grade 3 or 4) IVH (43 percent versus 33 percent, RR 1.40 (1.03, 1.88)). No difference was found in the incidence of BPD, or the composite outcome death or BPD[40] (Appendix E, Evidence Table 16).

At followup to 18 to 22 months corrected age, the iNO group had a higher rate of death (98/152, 64 percent) than the control group (79/152, 52 percent; p-value=0.04). Those treated with iNO also had a 22 percent greater rate of death or moderate to severe CP at 74 percent (111/151) compared to 59 percent (89/152) in the control group (RR 1.22 (1.05, 1.43) p-value = 0.01) [30] (Appendix E, Evidence Table 16).

Birth weight 1000 to 1250 g. The largest RCT that described birth weight subgroups and outcomes is Kinsella, 2006.[37] For this higher birth weight stratum, Kinsella reported a significant reduction in the combined outcome of death or BPD for the iNO treated infants (38.5 percent versus 64.1 percent, RR 0.60 (0.42, 0.86)), as well as a lower rate of BPD alone (29.8 percent versus 59.6 percent, RR 0.50 (0.32, 0.79)), although there was no difference in death alone. In followup at one year corrected age, there were no significant differences in the incidence of NDI, death, subjects on oxygen, or any composite outcomes[36] (Appendix E, Evidence Table 16).

In the Ballard, 2006 RCT,[34] which stratified infants across the wider birth weight category of 800 to 1250 g, there was no significant difference for iNO treated infants compared with controls for death (RR 1.00 (0.95, 1.06)) or survival without BPD at 36 wks PMA (RR 1.25 (0.88, 1.79)).[80] There was also no significant difference between iNO treated infants and controls for

BPD alone (51.5 percent versus 61.5percent) nor death or survival with BPD (54.6 percent versus 64.8 percent).[80] In followup at two years corrected age,[57] there was no difference between groups in the incidence of NDI (RR 1.07 (0.76, 1.50)).

Other birth weight groups including infants larger than 1250 g. No differences were reported for any outcome in studies that reported birth weights of 1000 to 1500 g[40, 58] or >1500 g.[58] However, in post hoc analyses for the subgroup of infants with birth weight > 1000g, Van Meurs, 2005[40] found a lower rate of the composite outcome of death or BPD for the iNO treated group compared to controls (50 percent versus 69 percent, p-value = 0.03; RR 0.72 (0.54, 0.96)), but no difference in death or BPD alone (Appendix E, Evidence Table 16).

We determined that meta-analyses of trials reporting outcomes by birth weight subgroups would not be performed due to the differences in definitions of birth weight categories, the marked variability in iNO administration and differences in outcomes reported in these few trials.

Gestational age. Mercier, 2010[62] assessed the relationship between iNO and gestational age at birth in infants born at less than 29 weeks. A similar incidence in survival without BPD at 36 weeks PMA was reported for infants treated with iNO therapy and controls resulting in a risk ratio for those with gestational age <26 weeks of RR 1.14 (0.71, 1.82), and for those with gestational age ≥26 weeks of RR 0.94 (0.64, 1.38) (Appendix E, Evidence Table 16).

Sex. Two RCTs commented on the association of iNO therapy and an infant's sex. In post hoc analysis, Ballard, 2006[34] stated that there was no difference in the response to iNO according to sex, but no data were shown. In the two year followup to Ballard, 2006, Walsh, 2010 reported there was no interaction between treatment with iNO and infant sex for the composite outcome NDI.[57]

Mercier, 2010[62] also showed no treatment effect by sex with similar relative risks of survival without BPD at 36 weeks PMA among girls treated with iNO compared with controls, RR 1.18 (0.76, 1.83), and boys treated with iNO compared with controls, RR 0.85 (0.58, 1.26) (Appendix E, Evidence Table 16).

Race/ethnicity. Kinsella, 2006[37] performed post hoc analyses and found no significant effect of race or ethnic group on the composite outcome of death, ICH or PVL following iNO treatment. In a post hoc analysis by Ballard, 2006[34] the effect of iNO did not differ significantly according to race or ethnicity (p-value = 0.06).[75] The risk ratios for survival without BPD at 36 weeks PMA by individual race follow: whites RR 1.06 (0.76, 1.47), blacks RR 1.72 (1.20, 2.47), Hispanics RR 1.66 (1.06, 2.59), and other 0.54 (0.25, 1.14).[80] Walsh 2010, in two year followup to the Ballard, 2006 trial, found no significant interaction between iNO treatment and race, white infants versus non-white infants, in NDI .[57] Mercier 2010[62] reported no difference between those receiving iNO and controls in survival without BPD for black infants, RR 1.49 (0.61, 3.65), or non-black infants, RR 0.94 (0.69, 1.28). (Appendix E, Evidence Table 16). None of the studies reporting on race/ethnicity were powered to address these subgroups.

Socioeconomic status. In the only study to consider socioeconomic indicators of outcome, Walsh, 2010 reported no statistically different risk of NDI at two year followup for infants treated with iNO and controls when mothers had less than a high school education, RR 0.77 (0.46, 1.30), compared to those that had a high school education or greater, RR 0.92 (0.72, 1.17)[57]; no data was provided in the original trial[34] (Appendix E, Evidence Table 16).

Other subgroups. There were no trials that specified outcomes by subgroups of exposure to antenatal steroids, chorioamnionitis, multiple births, and small for gestational age.

Description of trials based on severity of illness.

Oxygenation index. Three RCTs used the oxygenation index (OI, OI = mean airway pressure in cm H_2O x fraction of inspired O_2 x 100)/postductal arterial partial pressure of O_2 (PaO_2) in mm Hg) as a surrogate measure of severity of illness.

The study of Van Meurs, 2005[40] required an OI $\geq$ 10 on two consecutive arterial blood gases (ABGs) for study entry. Following the first interim analysis, due to a higher than expected mortality rate in both treatment and control arms, the respiratory criteria for study entry were revised to an OI $\geq$ five followed by an OI $\geq$ 7.5. In infants with birth weight 401 to 1500 g, the mean OI (SD) at randomization was 23$\pm$17 for the iNO treated infants and 22 $\pm$ 17 for the controls. Post hoc analysis indicated no interaction between iNO treatment and OI stratum. The risk of death, BPD, and death or BPD were similar between the iNO treatment and control groups for those with a median OI $\leq$ 17 and for those with OI > 17 at the time of randomization. Severe IVH or PVL rates were similar between groups within the OI strata[40] (Appendix E, Evidence Table 16).

Field, 2005 reported on a total cohort of 108 subjects with a notably high severity of illness as assessed by OI. At study entry, the iNO treated group had a median (IQR) OI of 32.9 (22.2, 49.8), and 55 percent had an OI > 30 as compared to the control group median OI 31.9 (17.4, 51.8), and 53 percent with an OI > 30. When primary outcomes were stratified by OI < 30 or $\geq$ 30, there were no significant differences in death or severe disability (defined as no/minimal head control or inability to sit unsupported or no/minimal responses to visual stimuli) (RR 0.99 (0.76, 1.28), p-value = 0.62); death or supplemental O_2 at expected date of delivery (RR 0.83 (0.68, 1.02), p-value = 0.87); or death or supplemental O_2 at 36 weeks PMA (RR 0.98 (0.87, 1.12), p-value = 0.81) in the iNO group compared to controls[63] (Appendix E, Evidence Table 16).

In Schreiber, 2003,[58] a post hoc analysis was performed, stratified by OI as a measure of severity of illness. For the group of iNO treated infants with OI < 6.94 (median), there was a significantly decreased risk of the composite outcome death or survival with CLD compared with the placebo group (36 percent versus 67.4 percent; RR 0.53 (0.35, 0.81)). There was no significant difference for the subgroup with OI $\geq$ 6.94. Mestan, 2009[56] reported the neurodevelopmental outcomes at a corrected age of two years for the cohort of survivors (N = 138). In a post hoc analysis, in comparison with the placebo group the iNO treated group with initial OI < 6.94 had no significant difference in abnormal neurodevelopmental outcome (defined as either disability (CP, bilateral blindness, or bilateral hearing loss) or delay (MDI < 70 or PDI <70), RR 0.52 (0.26, 1.01), but for the iNO treated infants with initial OI $\geq$ 6.94 there was 62 percent lower risk for abnormal neurodevelopmental outcome, RR 0.38 (0.16, 0.93) (Appendix E, Evidence Table 16).

We opted not to undertake a meta-analysis since these three RCTs had such a wide disparity in the OI criteria used, rendering them much less clinically comparable. The relatively low median OI in the Schreiber trial[58] reflects a population of infants presumably less critically ill than those in the Van Meurs trial[40] with a median OI of 17, and markedly less critically ill then those infants in the Field trial[63] with more than half having an OI > 30. The Mestan study is the only one to report neurodevelopmental outcomes by OI.

Respiratory severity score. In Ballard, 2006,[34] a simplified respiratory severity score was used, calculated as the mean airway pressure x FiO_2, since actual PaO_2 (needed to calculate the OI) was often not available. At study entry, the median severity score was 3.5 for both iNO treated and control groups, and was noted to be equivalent to an OI in the range of five to nine.

In post hoc analyses, there was no interaction between the severity score at study entry and treatment for the outcome survival without CLD at 36 weeks PMA.[34, 80] Followup at two years corrected age showed no difference in NDI between iNO treated and control infants if the respiratory severity score was < 3.5, RR 0.93 (0.69, 1.26) or ≥ 3.5, RR 0.93 (0.72, 1.19)[57] (Appendix E, Evidence Table 16).

Other measures of severity of illness. We found no trials that studied the effect of iNO therapy by subgroups defined by oxygen requirement alone.

Description of trials based on causes of respiratory failure.

Respiratory distress syndrome. In Field, 2005, the primary outcome measures were stratified by principal diagnoses, defined as acute preterm lung disease (presenting immediately after birth and randomized at ≤ 3 days of age), chronic preterm lung disease (presenting immediately after birth and randomized for continuing problems after 3 days of age), and other (developed lung disease after recovering from an initial respiratory problem). There were no differences between iNO treated infants and controls in death or supplemental O_2 at 36 weeks PMA, RR 0.98 (0.87, 1.11); death or supplemental O_2 at the expected date of delivery, RR 0.83 (0.68, 1.01); or death or severe disability, RR 0.99 (0.76, 1.28) [63] (Appendix E, Evidence Table 16).

Pulmonary hypoplasia. In very low birth weight preterm infants, pulmonary hypoplasia can occur following maternal preterm premature rupture of membranes (PPROM) > five days with subsequent oligohydramnios, and may further be complicated by persistent pulmonary hypertension. Two groups of investigators conducted retrospective analyses of infants with suspected pulmonary hypoplasia. In a subset analysis of infants with suspected pulmonary hypoplasia from the two Van Meurs trials, Chock, 2009[77] compared six infants exposed to iNO with six controls; the infants were similar at baseline. There was no statistically significant difference between iNO treated infants and controls in death (33 percent versus 67 percent, p-value = 0.57), BPD at 36 weeks PMA in the seven survivors (2/5 (40 percent) versus 2/2 (100 percent), p-value = 0.43)), or death or BPD (50 percent versus 100 percent, RR 0.50 (0.22, 1.11)). At 18 to 22 months followup, none of the four surviving iNO treated infants assessed had NDI (defined as moderate to severe CP, blindness, or deafness); the two survivors from the placebo group were lost to followup, and thus no comparisons were made. Uga, 2004[69] compared eight infants treated with iNO to 10 controls. All eight infants treated with iNO survived to 28 days compared to 5/10 control infants (p-value < 0.05). The groups had similar rates of BPD (undefined) (Appendix E, Evidence Table 16).

A meta-analysis was not performed for these two retrospective cohort studies with very limited numbers of infants enrolled, and widely different time points for death, i.e., prior to discharge home or within 365 days in hospitalized infants[77] versus seven and 28 days.[69]

Pulmonary hypertension. In persistent pulmonary hypertension of the newborn (PPHN), the pulmonary vascular resistance remains elevated in the newborn period, and it is the primary U.S. FDA approved indication for iNO in the term and near term infant population. In a retrospective case control study of 31 singleton preterm infants at median 25 weeks gestational age (IQR 24 – 28 weeks) with clinical pulmonary hypertension confirmed by echocardiography, Tanaka, 2007 reported that at three years of age 2/9 (22.2 percent) infants with CP had been treated with iNO compared to 14/22 (63.6 percent) infants without CP[38] (Appendix E, Evidence Table 16).

iNO responders compared to nonresponders. Four studies reported primary outcomes by the presence or absence of response to iNO therapy. Yadav, 1999 reported results from a retrospective study of iNO given to 41 preterm infants with a mean OI of 40 on maximal medical therapies. Response to an initial 10 ppm iNO was defined as a decrease in OI by ≥ 10 at one hour

of treatment. The 26 responders and 15 nonresponders were similar with respect to birth weight, gestational age, and OI at the start of treatment. Death was reported as 11/26 (42 percent) for responders but 14/15 (93 percent) for nonresponders. In a multivariable model, early response to iNO was associated with survival to discharge (p-value = 0.01)[73] (Appendix E, Evidence Table16).

Banks, 1999 studied iNO usage in severe BPD in 16 ventilator dependent preterm infants more than a month old (range 1 to 7 months). In this open label non controlled trial, iNO was administered at 20 ppm for the first 72 hours, then titrated slowly (median duration 27 days) for responders or discontinued in 24 hrs for nonresponders. Non response was defined as a 10 percent increase in oxygen requirement, a $PaCO_2$ of 70 mm Hg on baseline ventilator settings, worsening chest x ray, or a methemoglobin of > five percent within 72 hours of starting iNO therapy. Mortality for the overall cohort was 44 percent (7/16). For iNO responders, 4/11 (36 percent) died over the range of 11 days to five months, while in the nonresponder group 3/5 (60 percent) died and the two survivors remained ventilator dependent[70] (Appendix E, Evidence Table 16).

Kumar, 2007 performed a retrospective chart review of preterm infants < 37 weeks gestational age at birth with pulmonary hypertension treated with iNO. Pulmonary hypertension was diagnosed by echocardiography within the first four weeks of life; iNO treatment at doses of 5 to 15 ppm was at the discretion of the clinical team after an infant failed standard medical management. Within the gestational age range of interest in this evidence report, ≤ 34 weeks gestation, response to iNO was least likely to occur in the most immature infants: only 1/6 (16 percent) of infants < 29 weeks responded to iNO, defined as an increase in postductal PaO_2 of 20 mm Hg or greater within 30 minutes without any change in inspired oxygen, while 5/6 (83 percent) of infants 29 to 31 weeks gestation, and 5/6 (83 percent) of infants 32 to 34 weeks gestation responded to iNO[68] (Appendix E, Evidence Table 16). Mortality was significantly higher for the non responders (6/8, 75 percent) compared to iNO responders (4/15, 26 percent) ($p < 0.04$) (Appendix E, Evidence Table 16).

In a pilot study of the European iNO Registry, Dewhurst 2010,[74] reported the outcome for 44 preterm infants <34 weeks gestational age at birth. Infants with congenital heart disease were excluded. Infants were treated with a median starting dose of iNO of 20 ppm (range 3.3 to 25 ppm), and a median maintenance dose of 10 ppm (range 0.7 to 25 ppm). Response to iNO was defined as a 15 percent reduction in the baseline OI within 30 to 60 minutes of starting therapy; 26 infants responded and eight did not. Infants that responded to iNO were younger than non responders (median (IQR) gestational age at birth, 26 (25 to 29) weeks versus 29 (27 to 30) weeks, p-value = 0.043) and had a significantly higher baseline oxygen requirement (median (IQR) $Fi0_2$ 1.0 (0.9, 1.0) responders versus 0.8 (0.5, 1.0) non responders; p-value = 0.021). Birth weight, age at starting iNO, starting dose, and baseline OI were similar between responders and non responders. There was no difference in mortality: 12 of the 21 responders for whom complete data were available died; 5/8 non responders died (Appendix E, Evidence Table 16).

No meta-analysis for the iNO responder versus non responder studies was undertaken due to the wide variations in iNO dosage and timing, as well as the variability and incomplete description of the diagnoses underlying the respiratory failure in these preterm cohorts.

Conclusions

For the question of whether iNO therapy has an effect on the major outcomes of interest (death and/or BPD or neurodevelopmental impairment) across various subpopulations of premature infants, we reviewed 17 studies which included six original RCTs,[34, 37, 40, 58, 63, 74] with four followup studies,[30, 36, 56, 57, 77] and seven other studies,[38, 68, 69, 73, 70, 74, 77] As noted in the conclusion of Key Question 1, some of the studies that reported no significant differences in rates of death, BPD at 36 weeks PMA, or the composite outcome death or BPD at 36 weeks PMA for the overall cohort did find statistically significant subgroup differences. For example, two studies[37, 40] report decreased rates of one or more of the major outcomes among infants with birth weight > 1000 grams.[36, 56] The lack of consistency in defining or subdividing certain subgroups, (e.g., by birth weight, or oxygenation index) hampered the ability to answer this Key Question. In addition, many of the subgroup analyses performed were by post hoc analyses (e.g., birth weight, race), increasing the need for cautious interpretation of results. Some of the specific subpopulations of interest had little or no outcomes related data at all. Based on the current body of evidence, no definitive and generalizable conclusions may be made about iNO treatment in specific subpopulations. Future research is needed to examine the role of iNO treatment in these and alternative subgroups, so as to more clearly define populations of preterm infants which may benefit most from this therapy.

Key Question 5. Does the effect of iNO therapy on BPD and/or death or neurodevelopmental impairment vary by timing of initiation, mode of delivery, dose and duration, or concurrent therapies?

Major Findings

- There is insufficient evidence to determine if initiating iNO therapy for acute respiratory distress at ≤ three days reduces the risk of death or bronchopulmonary dysplasia (BPD) at 36 weeks PMA, or death and neurodevelopmental disability at one year of age, corrected for gestational age at birth.
- In infants with developing BPD, there is insufficient evidence to determine if treatment with iNO during the second week after birth improves survival without BPD compared with treatment during the third week after birth.
- There is insufficient evidence to determine the effect of delivery of iNO by high frequency ventilation on either death or BPD, or neurodevelopmental outcome compared with conventional ventilation.
- There is insufficient evidence to support an optimal dose of iNO or duration of exposure to improve outcome or prevent harm.
- There is insufficient evidence to determine the effect of iNO with concurrent therapy.

Detailed Analysis

Fourteen RCTs reported in 21 papers addressed this key question. Two trials investigated the timing of the initiation of iNO therapy,[34, 63] and two the mode of drug delivery, conventional or high frequency ventilation.[40, 58] The dose of iNO varied considerably among the 14 studies. To examine the effect of dose on the primary outcomes, studies were categorized into those that administered iNO at only 5 ppm,[37, 59, 62] those that delivered a maximum dose of 10 ppm,[39, 40, 58, 61, 67] and those that gave 20 ppm or titrated the dose to the patients' response.[34, 60, 63-66] Duration of iNO exposure also varied considerably among the 14 studies, from three to four days[64] to a minimum of 24 days.[34] As the majority of the studies administered iNO therapy until extubation, the evidence for the effect of duration of exposure of iNO on the primary outcomes of BPD and/or death or neurodevelopmental impairment could not be evaluated. Only two studies explicitly considered concurrent therapies, specifically systemic steroids, on the effect of iNO treatment.[64, 76]

All trials reported death or survival, although the time of ascertainment of the outcomes varied across studies. If death or survival was reported at multiple endpoints in either the original study or in a long term followup publication (e.g., before NICU discharge, and at one year of age, corrected for gestational age at birth), the data are included in this evidence report. Seven of the randomized trials have reported long term followup.[30, 35, 36, 56, 57, 76, 78] The followup studies have varying definitions of neurodevelopmental impairment (NDI), and use different measures of developmental progress, making direct comparison difficult. For questions concerning some subgroups (timing of initiation of iNO therapy, and mode of iNO delivery) the analyses are post hoc, therefore the results must be considered exploratory, as infants were neither randomly assigned to the subgroup, nor was the study powered to consider the variable (Appendix E, Evidence Tables 3 and 4; Table 10). The differences in treatment protocols in studies reporting on subgroups of infants may make pooled estimates of the effect of iNO therapy spurious, so meta-analyses were performed only with RCTs using similar dosing regimens.

Timing: Early versus late iNO administration. Two populations of preterm infants have been treated with iNO, those with early acute respiratory distress (immediately after birth), and those with evolving BPD. Early treatment generally begins within the first three days after birth in an effort to improve oxygenation in infants with acute hypoxemia, as in respiratory distress syndrome (RDS) or pneumonia. Late treatment may begin any time after three days, with evidence of progressive respiratory failure. Theoretically, late treatment avoids exposing an infant to iNO who would otherwise have resolving RDS during the first week. The goal of both strategies is to prevent the development of BPD and all its sequelae. Although the age at initiation of iNO therapy was available for all trials, aggregating studies into meaningful categories was problematic; RCTs started iNO therapy at < 48 hours, < 72 hours, < 96 hrs, four to 120 hours, < seven days, seven to 21 days, and < 28 days of age. Some trials also had varying additional entry criteria concerning severity of illness, further complicating the ability to combine studies into clinically meaningful groups. Because of this variability we did not conduct meta-analyses; instead we report the results of two RCTs that specifically considered the timing of the initiation of iNO therapy, both in post hoc analyses (Appendix E, Evidence Table 17).

Table 10. Summary of outcomes for RCTs addressing KQ5

Subanalysis	Outcome	Number of Studies	Total sample size
Timing: Early vs. late iNO administration	Death	1[34]	582
	Death or BPD	1[63]	108
	Death or Severe Disability	1[63]	108
	Survival without BPD	1[34]	582
Mode of drug delivery	Death	2[30, 40]	838
	Death or BPD	1[58]	207
	Death or CP	1[30]	399
	Motor Developmental Impairment	1[30 58]	184
	NDI	2[40, 58]	627
Dose of iNO, 5 ppm	Death	3[37, 59, 62]	1666
	BPD at 36 weeks	3[37, 59, 62]	1563
	Death or BPD	3[37, 59, 62]	1661
	NDI	1[36]	455
Dose of iNO, 10 ppm	Death	5[39, 40, 58, 61, 67]	839
	BPD at 36 weeks	4[39, 40, 56, 58, 67]	696
	Death or BPD	4[39, 40, 58, 67]	694
Dose of iNO 20 ppm	Death	6[34, 60, 63-66]	962
	BPD at 36 weeks	5[34, 60, 63-65]	55
	Death or BPD	4[34, 60, 63, 64]	774
	NDI	7[30, 35, 56, 57, 63 ,64, 76]	977
iNO with concurrent therapies	Death	2[64, 76]	84
	BPD at 36 weeks	2[64,76]	84
	Death or BPD	2[64,76]	84

BPD = Bronchopulmonary dysplasia; iNO = Inhaled nitric oxide; NDI = Neurodevelopmental impairment; CP = Cerebral palsy

In a small sample, Field, 2005[63] found a similar risk of death or BPD at 36 weeks PMA in infants treated with iNO within three days of birth (25/38, 66 percent) and those treated at four to 28 days (12/17, 71 percent; RR 0.98 (0.87, 1.11)). There was an advantage to early iNO administration when death or BPD was measured at the expected date of delivery (61 percent versus 94 percent when iNO was initiated at 4 to 28 days), but the difference was attenuated after adjustment for diagnosis (acute lung disease beginning at birth and treated at ≤ three days, chronic lung disease with respiratory distress at birth and continuing at four to 24 days; and other respiratory distress after recovery from an initial respiratory problem), and severity of illness (OI ≤ 30 versus > 30), RR 0.83 (0.69, 1.01). The time of initiation of iNO had no effect on death or severe disability, defined as no/minimal head control or the inability to sit unsupported or no/minimal response to visual stimuli, at one year of age corrected for gestational age at birth (RR 0.99 (0.76, 1.28)). No data were provided on the median time that iNO therapy was initiated in the early or late group, but the median (IQR) age of initiation for all infants receiving iNO therapy in the study was 1 (0, 6) days, making it unlikely that the groups were very different (Appendix E, Evidence Table 17).

In a large sample of nearly 600 infants with developing BPD, Ballard, 2006[34] reported a similar incidence of death at 36 weeks PMA between the iNO and placebo groups for those entering treatment at seven to 14 days (10.7 percent iNO versus 11.3 percent placebo), or those entering treatment at 15 to 21 days (6.6 percent iNO versus 5.8 percent placebo) [34] However, the likelihood of survival without BPD increased for infants beginning treatment at 7 to 14 days (RR 1.91 (1.31, 2.78)), a result that was not observed in those beginning treatment later, at 15 to 21

days (RR 0.99 (0.77, 1.28)).[34] This result may have been observed because of damage already done to the developing lung before late enrollment (Appendix E, Evidence Table 17).

In both of these studies analyses were conducted post hoc, so neither study was powered to find a statistically significant difference between the groups (Appendix E, Evidence Table 17).

Mode of drug delivery. Two randomized controlled trials, Van Meurs, 2005[40] and Schreiber, 2003[58] reported outcomes for infants treated with iNO and conventional mechanical ventilation compared with those treated with iNO and high frequency ventilation. Patients were randomly assigned to ventilation strategy in one trial,[58] but in the other, analyses were done post hoc. [40] Both studies reported neurodevelopmental followup to 18 to 24 months of age, corrected for gestational age at birth. [30, 56] Patients in the two trials differed by birth weight inclusion criteria (401 to 1500 grams, [40] ≤ 2000 grams [58]) (Appendix E, Evidence Table 17).

Schreiber, 2003[58] found no difference in the combined outcome of death or BPD at 36 weeks PMA between infants randomized to treatment with iNO and conventional ventilation (RR 0.61 (0.41, 0.90)) compared with placebo and those randomized to iNO and high frequency ventilation (RR 0.92 (0.67, 1.26)) compared to placebo. Among survivors, the risk of abnormal neurodevelopmental outcome, defined as disability (CP, bilateral blindness, or bilateral hearing loss) or developmental delay (a score of <70 on the Bayley Scales of Infant Development II, but no disability) was not statistically different between high frequency ventilation and conventional ventilation, RR 0.92 (0.58, 1.46) [56] (Appendix E, Evidence Table 17).

In post hoc analysis, Van Meurs, 2005[40] reported that iNO delivered by conventional mechanical ventilation was associated with a 46 percent increase in the risk of death before discharge to home or within 365 days of birth among infants still hospitalized compared with placebo (RR 1.46 (1.10, 1.92)). The risk remained elevated at 18 to 22 months of age (RR 1.37 (1.05, 1.79)).[30] There was no increase in death, at either time, among infants treated with iNO delivered by high frequency ventilation compared to placebo. The risk of developing BPD at 36 weeks PMA was similar if iNO was delivered by conventional ventilation (RR 0.90 (0.65, 1.24)), or high frequency ventilation (RR 0.89 (0.72, 1.10)) (Appendix E, Evidence Table 17). Motor development was impaired at 18 to 22 months of age, in those treated with iNO and conventional ventilation (CP RR 1.29 (1.03, 1.60)), and there was an increased risk of death or moderate to severe CP (moderate CP was defined as the ability to sit independently or with support but cannot independently ambulate; severe CP was defined as unable to sit or walk even with support), RR 1.29 (1.03, 1.60)[30] (Appendix E, Evidence Table 17). The risk of disability, defined as moderate/severe CP, bilateral blindness, deafness, or MDI or PDI < 70, was not affected by mode of iNO delivery, nor was the combined outcome of death or disability (high frequency ventilation RR 0.97 (0.70, 1.35); conventional ventilation RR 1.07 (0.64, 1.80)[30] (Appendix E, Evidence Table 17).

Although treatment with iNO and conventional ventilation was associated with some measures of adverse outcome, the estimates of harm are the result of post hoc analyses and so must be considered cautiously (Appendix E, Evidence Table 17). We did not perform a meta-analysis for mode of delivery as only one study prospectively randomized infants to conventional versus high frequency ventilation and the other generated comparisons by post hoc analyses.

No data are available on other methods of iNO delivery, such as high or low flow nasal cannula, or continuous positive airway pressure.

Dose of iNO. The initial dose of iNO varied from 5 ppm to 20 ppm among the 14 randomized trials. Data in preterm animal models of RDS indicates improvement in oxygenation in this range.[93] Fear of adverse side effects, specifically bleeding with resulting IVH, resulted in

limitation of iNO exposure in some studies (Appendix E, Evidence Table 17). For this review, studies were grouped as follows: dose restricted to 5 ppm; dose restricted to 10 ppm; dose titrated to response with a maximum of dose 20 ppm to 40 ppm, or dose given as 20 ppm. The effect of iNO doses on the primary outcomes are reviewed below. Meta-analyses were conducted with trials that reported death in the NICU at 36 weeks PMA or later; trials that reported death at seven days or 28 days were excluded. Separate meta-analyses were done that excluded Ballard 2006, because it was the only RCT that delivered iNO for a prolonged period of time (minimum 24 days); the results did not differ from what is reported.

Death. When the dose of iNO was restricted to 5 ppm there was no difference in death at 36 weeks PMA in two trials with 800 infants enrolled in each, RR 0.79 (0.61, 1.03) [37] and RR 1.34 (0.92, 1.95) [62], or in death prior to hospital discharge, RR 0.90 (0.58, 1.40), in one trial with 80 infants[59] (Appendix E, Evidence Table 17). The pooled estimate of the risk of death showed no significant differences in treatment with this dose of iNO, RR 0.97 (0.70, 1.35) (Figure 16).

The risk of death was similar in infants that received iNO therapy at a maximum dose of 10 ppm compared with those receiving placebo in five randomized controlled trials[39, 40, 58, 61, 67] (Appendix E, Evidence Table 17). In the two studies by Van Meurs the risk of death before discharge home or within 365 days for those still hospitalized was not improved with iNO therapy in infants weighing 401 to 1500 grams birth weight, RR 1.16 (0.96, 1.39),[40] or those with birth weight greater than 1500 grams, RR 1.34 (0.45, 4.00) [39] (Appendix E, Evidence Table 17). Three other studies found no significant decrease in death in the NICU (RR 0.68 (0.38, 1.20))[58]; 20 percent iNO versus 30 percent placebo, p-value = 0.494 [67], or at 28 days (41 percent iNO versus 31 percent placebo, no significant difference)[61] (Appendix E, Evidence Table 17). Meta-analysis of the four studies that reported death in the NICU at 36 weeks PMA or later confirmed no statistically significant difference in death for infants treated with 10 ppm iNO compared to controls, RR 1.00 (0.73, 1.38) (Figure 16).

No study found a difference in death between infants that were treated with iNO at 20 ppm or iNO titrated to response and those given standard care, regardless of whether the outcome was measured at seven days,[66] during NICU hospitalization,[60, 64, 65] at 36 weeks PMA,[34] 40 weeks PMA,[34] 44 weeks PMA,[34] at one year of age corrected for gestational age at birth[63], or four to five years of age [35] (Appendix E, Evidence Table 17). The pooled estimate of the relative risk of death at 36 weeks PMA or later during NICU hospitalization showed no statistically significant difference between infants given iNO therapy delivered at 20 ppm or titrated to response and controls, RR 0.91 (0.63, 1.30) (Figure 16).

The RR is similar across each dose category, with little heterogeneity, suggesting that the effect of iNO on the outcome of death does not vary by dose.

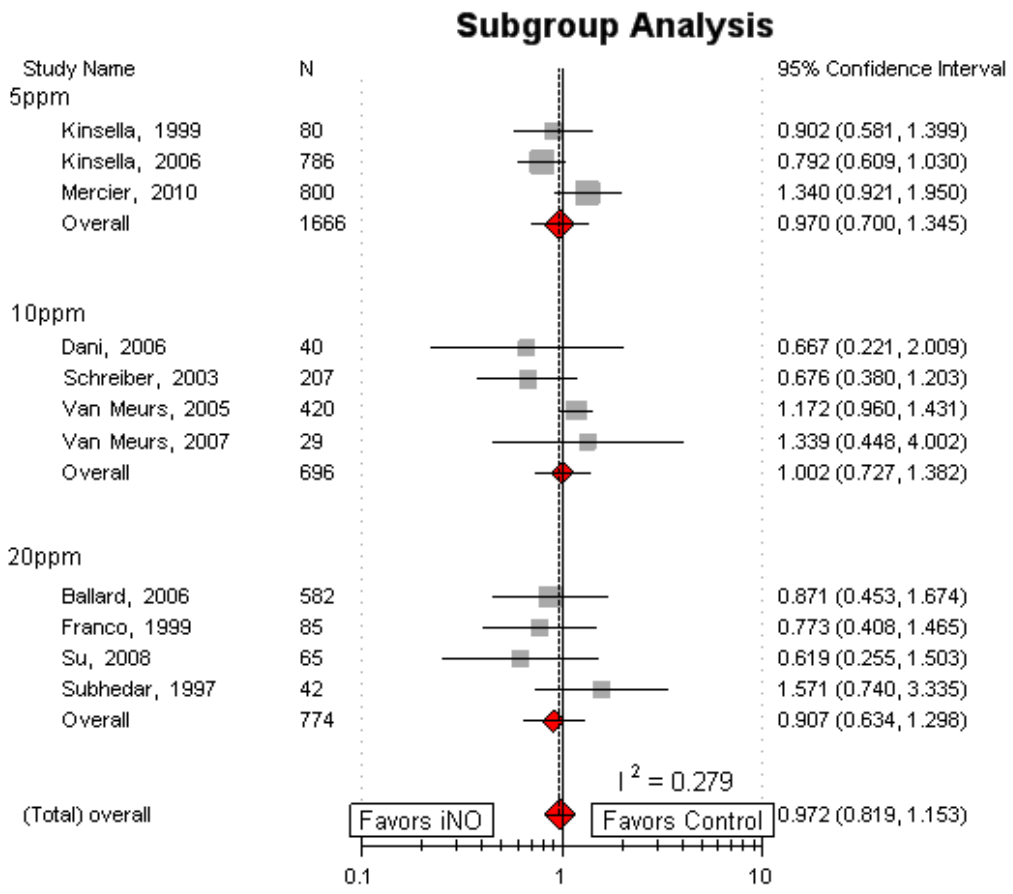

Figure 16. Meta-analysis for dose-stratified death, including only studies that reported death in the NICU at 36 weeks PMA or later

BPD at 36 weeks PMA. Bronchopulmonary dysplasia developed as frequently in those treated with 5ppm iNO as those treated with standard therapy when measured at 36 weeks PMA [37, 59, 62] and when measured prior to hospital discharge [59] (Appendix E, Evidence Table 17) The pooled estimate of the risk of BPD for the three trials that reported the outcome at 36 weeks PMA was RR 0.94 (0.87, 1.02) (Figure 17).

The risk of BPD at 36 weeks PMA was mixed when iNO was given at a maximum dose of 10 ppm. The largest trial, conducted by Van Meurs 2005, with more than 420 infants, reported a 24 percent decrease in the risk of BPD compared to controls, RR 0.76 (0.58, 0.98).[40] Three other trials, with a combined enrollment of 276 infants, reported no significant difference between infants treated with iNO and controls[39, 40, 58, 67] (Appendix E, Evidence Table 17). A meta-analysis with all four RCTs found a 25 percent reduction in the risk of BPD at 36 weeks for infants treated with iNO at 10 ppm compared to controls, RR 0.75 (0.61, 0.91) (Figure 17).

BPD at 36 weeks PMA was common, affecting one third to one half of all infants; the rate was not different between infants treated with 20 ppm or iNO titrated to response and those receiving standard care in the four RCT that used this dosing strategy. [34, 63, 64, 65] The rate of BPD was also similar between the groups when defined as an oxygen requirement measured at 40

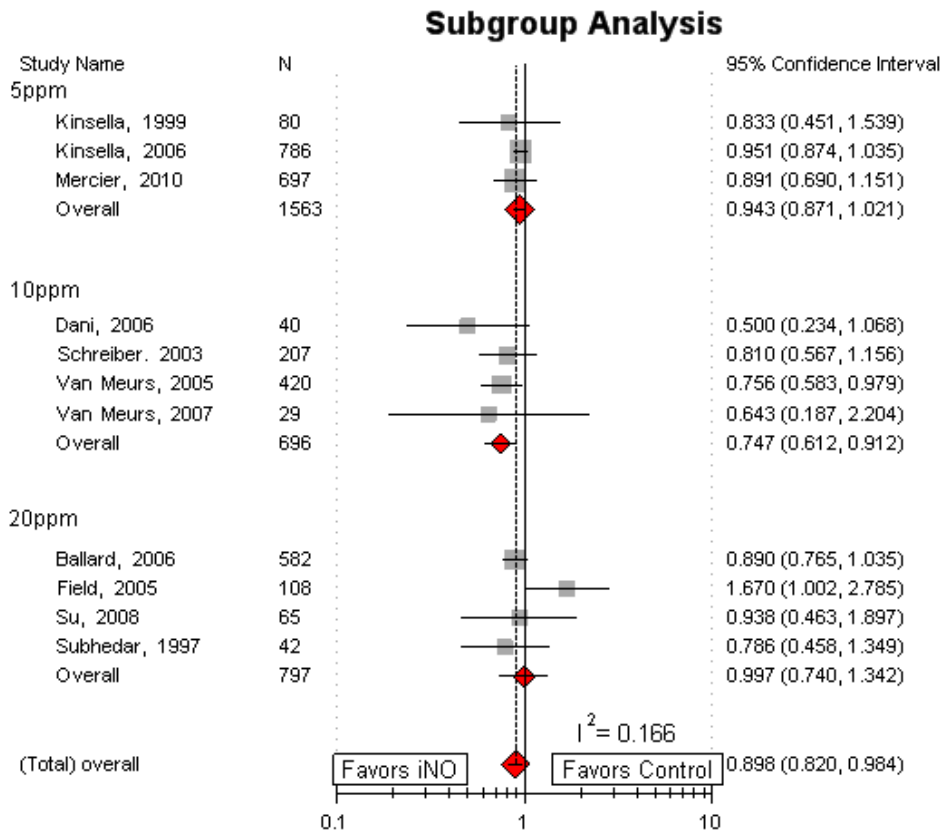

Figure 17: Meta-analysis for dose-stratified BPD at 36 weeks PMA

weeks PMA (22 percent iNO versus 29 percent placebo)[34], 44 weeks PMA (9 percent iNO versus 12 percent placebo),[34] and at one year, corrected for gestational age at birth (15 percent iNO versus 6 percent placebo)[60] (Appendix E, Evidence Table 17). A meta-analysis confirmed no significant difference in the risk of BPD at 36 weeks with iNO therapy at this dose, RR 1.00 (0.74, 1.34) (Figure 17).

Death or BPD. There was no reduction in the composite outcome of death or BPD with 5ppm iNO compared with controls, when measured at 36 weeks PMA, [37, 62] or prior to hospital discharge [59] (Appendix E, Evidence Table 17). Meta-analysis with these three trials resulted in a RR 0.94 (0.88, 1.01) (Figure 18).

Evidence concerning the risk of death or BPD was mixed among the trials that gave 10 ppm iNO (Appendix E, Evidence Table 17). In the largest trial,[40] with more than 200 patients in each arm, the RR of death or BPD at 36 weeks PMA in the iNO group was 0.97 (0.88, 1.07). A similar lack of benefit was found in a small trial of infants with birth weight > 1500 g when death was measured before hospital discharge or at 365 days for infants still hospitalized (RR 0.83 (0.43 1.62)).[39] However, two other studies reported iNO was associated with a decreased risk of death or BPD at 36 weeks PMA. In Schreiber, 2003,[58] with more than 100 infants in each arm, the risk of death or BPD was decreased 23 percent in the iNO treated group (RR 0.77 (0.60, 0.98)),and in a small study with 20 infants in each group, Dani, 2006[67] reported an 89 percent decrease in risk (OR 0.11 (0.02, 0.61)) among the iNO treated group (Figure 18).

The opposite direction of the effect of iNO therapy at 10 ppm in the two largest trials may be accounted for by the degree of illness of infants at study entry. Infants in the study of Schreiber, 2003[58] had a substantially lower oxygenation index at study entry (OI median (IQR) 7.3 (4.1, 12.3) iNO group versus 6.8 (4.4, 12.7) control group) than infants in the study of Van Meurs, 2005[40] (OI mean (SD), 23 (17) iNO group versus 22 (17) placebo group) (see discussion of OI under Key Question 4) (Appendix E, Evidence Table 17). A meta-analysis revealed no significant difference in the risk of the combined outcome of death or BPD at 36 weeks PMA for infants treated with iNO at 10 ppm compared to controls, RR 0.81 (0.64, 1.03) (Figure 18).

In the four studies[34, 60, 63, 64] that dosed iNO at 20 ppm or titrated to response, 50 percent to 100 percent of infants in each arm died or had BPD at 36 weeks PMA (Appendix E, Evidence Table 17). The pooled relative risk, RR 0.94 (0.84, 1.06), confirmed no difference to iNO treatment under these treatment protocols (Figure 18).

Neurodevelopmental impairment. In a followup study of Kinsella, 2006, Watson 2009[36] reported the rate of neurodevelopmental impairment (CP, severe hearing loss, blindness, or MDI or PDI < 70) at one year of age, corrected for gestational age at birth, was similar in the infants that received iNO at 5 ppm (35.4 percent) and those that received standard therapy (33.5 percent) groups (Appendix E, Evidence Table 17).

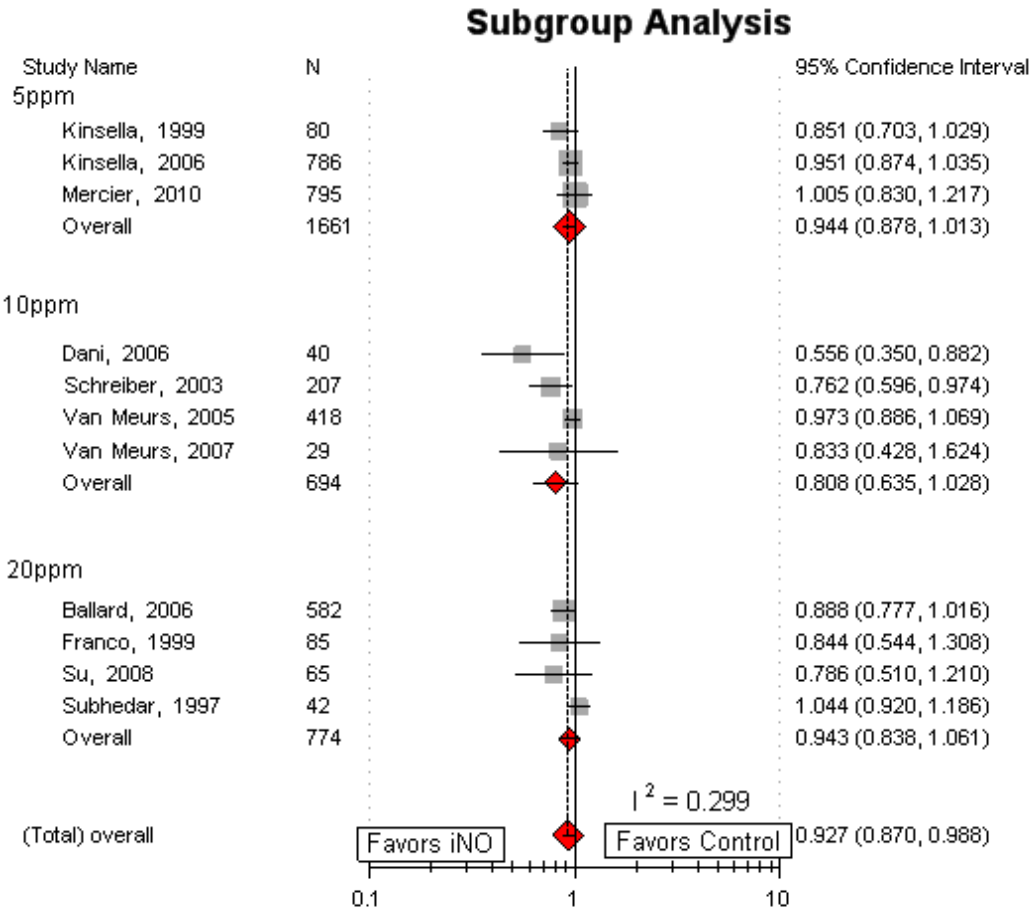

Figure 18: Meta-analysis for dose-stratified death or BPD.

Only two of the studies giving iNO at 10 ppm evaluated long term neurodevelopmental outcome and they found opposite effects. [40, 58] Reporting the followup of Van Meurs, 2005, Hintz, 2007,[30] found no improvement in the combined outcome of death or neurodevelopmental impairment, defined as moderate to severe CP, blindness, deafness or an MDI or PDI < 70, at 18 to 22 months of age for infants treated with iNO compared to placebo, RR 1.07 (0.95, 1.19), or in death or moderate to severe CP, RR 1.17 (0.99, 1.38). Moderate to severe CP was increased in the iNO group (20 percent versus 11 percent), a difference that was not significant in univariate analysis, but reached significance in multivariable models after adjustment for infant characteristics at study entry in one model, RR 2.01 (1.01, 3.98), and infant characteristics and NICU morbidities in another model, RR 2.41 (1.01, 5.75). In both models the confidence intervals are wide (Appendix E, Evidence Table 17).

However, Mestan, 2005,[56] reporting on the outcome of survivors at two years of age of the Schreiber, 2003 study, described a 47 percent decrease in the risk of cognitive impairment, defined as an a MDI < 70 (RR 0.53 (0.29, 0.94)), but no effect on motor impairment, defined as a PDI < 70 (RR 0.73 (0.33, 1.61)). Fewer infants treated with iNO had neurodevelopmental impairment, a composite variable including CP, blindness, hearing loss, and developmental delay, than infants treated with placebo (24 percent versus 46 percent respectively, p-value = 0.01). This difference in the composite outcome was the result of fewer infants with cognitive impairment in the iNO group as there was no difference between the groups in the rate of CP, vision or hearing loss (Appendix E, Evidence Table 17).

Three of the RCTs that gave iNO at 20 ppm or titrated the dose based on response reported long term developmental followup.[35, 57, 76] Walsh, 2010[57] found no improvement in function at two years of age among infants treated with iNO in the study of Ballard, 2006.[34] Rates of CP, cognitive delay, vision impairment, and hearing impairment were similar between the groups. In 30 month followup of infants enrolled in the Subhedar, 1997,[64] and Bennett, 2001[76] studies similar rates of neurodevelopmental delay (MDI or PDI < 85), severe disability (defined as MDI or PDI < 70, or hearing loss or blindness), or death and severe disability were found between iNO treated infants and those receiving standard care. Huddy, 2008[35] found no difference at four to five years of age between the groups enrolled in the study of Field, 2005[63] in the rates of CP, cognitive delay, vision, and hearing impairment, combined moderate to severe disability, or in those free of impairment (23 percent iNO versus 19 percent placebo) (Appendix E, Evidence Table 17).

No meta-analyses were conducted for dose of iNO and neurodevelopmental impairment as the definition of impairment varied significantly between studies.

In summary, a meta-analysis of studies of 10 ppm dose of iNO found a statistically significantly reduction in BPD at 36 weeks PMA but meta-analyses found no statistically significant effect on death, or the combined outcome of death or BPD compared to control. The finding of a statistically significant effect at 10 ppm may be spurious as there is no clinical rationale for why that dose would be different from the others.[34, 63-66] Results for neurodevelopmental impairment at this dose were inconsistent. There was no statistically significant different between iNO and control at doses of 5 ppm, 20 ppm or titrating the dose to the patients' response. [37]

iNO with concurrent therapies. Two studies directly addressed the effect of iNO with concurrent therapies. In a factorial design, Subhedar, 1997[64] randomized 20 infants to treatment with iNO and dexamethasone and compared their outcome to 22 infants randomized to dexamethasone alone. Dexamethasone was given intravenously every 12 hours for six days at

0.5 mg/kg/dose for six doses, and 0.25 mg/kg/dose for the remaining six doses. All infants were less than 32 weeks gestational age at birth (Appendix E, Evidence Table 17). There was no difference between groups in the risk of death (RR 1.57 (0.76, 3.38)); BPD at 36 weeks PMA, defined as an oxygen requirement beyond 36 weeks PMA and an abnormal chest radiograph (RR 0.79 (0.44, 1.33)); the combined outcome of death or BPD at 36 weeks PMA (RR 1.05 (0.84, 1.25)); or BPD in survivors (RR 1.07 (0.71, 1.37)) (Appendix E, Evidence Table 17).

In a post hoc analysis, Ballard, 2006 [34] reported that there were no significant differences in response to iNO by exposure to postnatal corticosteroids, though data were not shown. In two year followup, Walsh 2010[57] found that there was no interaction between iNO treatment and postnatal dexamethasone therapy given > three days after study enrollment compared with dexamethasone given ≤ three days from enrollment in a multivariable model of NDI.

Conclusion

Only two of the 14 randomized controlled trials that reported death, BPD, death or BPD, or neurodevelopmental impairment planned *a priori* to evaluate infants by subgroups,[58, 64] so the evidence to answer this Key Question is not optimal. There is insufficient evidence to support treatment with iNO for acute lung disease within the first three days after birth. The one trial that compared infants treated at ≤ three days with those treated at four to 28 days found no difference between the groups. Given that none of the 14 RCTs reviewed in Key Question 1 found a significant difference in mortality or survival between those treated with iNO controls, many of which initiated therapy at less than three days, it is likely that early treatment is not beneficial. However, the duration of exposure to iNO varied in the trials and has yet to be systematically studied. For infants with developing BPD, earlier treatment (7 to 14 days) may prove to be more beneficial than later treatment (15 to 21 days) as shown by improved survival without BPD in the Ballard 2006 trial; an RCT with this primary hypothesis needs to be done. It is not surprising that delivery of iNO by high frequency ventilation conferred no convincing benefit, as high frequency ventilation alone has not been shown to reduce mortality, BPD, or improve neurodevelopmental impairment in preterm infants compared to conventional ventilation in systematic review.[94] The optimal dose of iNO has yet to be determined. Our meta-analysis found a statistically significant effect for 10 ppm for BPD at 36 weeks PMA, but this may be a spurious finding. A similar effect was not seen for death or the composite outcome of death or BPD. Dose may be[34, 37, 63-66] less important than the duration of iNO exposure, but data are insufficient to make that determination. The effect of concurrent therapies other than postnatal dexamethasone and iNO administration has not been studied in preterm infants.

Chapter 4. Discussion

The most prevalent finding of this report is the lack of effectiveness of iNO in improving survival or decreasing pulmonary morbidity or neurodevelopmental impairment for preterm infants who receive respiratory support. A systematic review of the evidence and meta-analyses revealed no significant difference between preterm infants ≤ 34 weeks gestational age treated with iNO and control infants in the risk for mortality, BPD at 36 weeks PMA, short term risks (PDA, sepsis, NEC, treated ROP, pulmonary hemorrhage, or air leak), brain injury, motor or cognitive impairment, sensory impairments, growth or many other health outcomes.

The most important positive finding of this review is a meta-analysis of pooled data from 11 RCTs that reported the composite outcome of death or BPD at 36 weeks PMA which found a small (7 percent) but statistically significant reduction in the risk with iNO therapy. Power calculations for sample size determination were performed *a priori* for death or BPD or its complement, survival without BPD, in eight of the 11 (73%) trials in the meta-analysis. It has been suggested that the study by Ballard, 2006[34] should not be included in meta-analyses as it had a very different study design as well as the lowest mortality rates when compared to the other RCTs. In a sensitivity analysis, removing Ballard, 2006 from this meta-analysis did not change the effect estimate (RR 0.93) but did result in wider confidence interval that included 1. We feel that the meta-analysis with all 11 trials provides a more complete picture of the available evidence, considering the effect of iNO as a continuum of exposure

By analyzing reported outcomes from the 14 RCTs and, where appropriate, other cohort studies, we tried to glean as much evidence as possible of how exposure to iNO influences preterm outcomes. Some statistically significant differences were reported for a few individual RCTs included in this review. Two large trials[37, 58] reported a statistically significant reduction of brain injury in favor of iNO, and raised hopes that iNO may be neuroprotective. One followup study of a RCT found a statistically significant reduction in cognitive and neurodevelopmental impairment.[56] One large multicenter trial was stopped early for concern that the iNO group had a higher rate of brain injury,[40] and on followup at two years, found a statistically significant increase in the rate of CP with iNO compared to the control group. In contrast, a smaller trial in preterm infants with pulmonary hypertension found a reduction in CP rate with iNO[38] None of our meta-analyses of these variables found statistically significant effects of iNO exposure, but variability in definitions of outcome variables hindered our ability to aggregate all of the available data and perform meaningful meta-analyses.

Once iNO was found to be an effective treatment for full term and late preterm infants with hypoxemic respiratory failure,[4] attention turned to using it in more immature preterm infants. Some of the earlier and smaller studies of iNO in preterm infants focused on immediate physiological response to iNO (i.e., improvement in oxygenation index, arterial-alveolar oxygenation ratio, changes in echocardiographic estimates of pulmonary artery pressure) and toxicities, including methemoglobinemia, and pulmonary and intracranial hemorrhages.[59-61, 64-67, 72] Some early studies started with the iNO dose recommended for full term infants, 20 ppm,[64, 66, 72] whereas other early studies started at 5 to 10 ppm, and some increased to 20-40 ppm if there was no response.[60, 63, 65] The majority of the earlier RCTs began weaning iNO within two to six hours.[60, 61, 64-67] An alternative approach views iNO as a potential growth promoter of the lung and its underlying vascular bed, requiring a longer duration of treatment. Since 2003, four well conducted multicenter RCTs and one single center RCT have published their outcomes for 200 or more infants randomized to receive iNO or placebo gas for one or more weeks.[34, 37, 40, 58, 62]

Barrington and Finer conducted a systematic review of the evidence for efficacy and toxicities of iNO in preterm infants born before 35 weeks gestation, updated in 2007.[31] They grouped 11 RCTs into categories based on inclusion criteria: 1) the early routine use of iNO (i.e., RCTs that treated preterm infants on mechanical ventilation in the first three days after birth) found a marginally significant reduction in death or BPD, RR 0.91 (95 percent CI 0.84, 0.99), and, in severe IVH, IPH or PVL, RR 0.70 (CI 0.53, 0.91); 2) early rescue treatment based on oxygenation inclusion criteria found no significant differences in death or BPD but a trend toward increased risk of severe IVH; and 3) enrollment based on increased risk of BPD at four or more days after birth, and there were no statistically significant effects of iNO on mortality or BPD or increase progression of IVH. They were able to report on neurodevelopmental outcomes from only two RCTs.[56, 76]

The strength of the evidence was graded for all outcomes included in each key question and the results are presented below (Tables 11 to 15). A summary of the meta-analyses completed, by key question and outcome, is provided in Table 16.

Our review differs from the Barrington and Finer Cochrane review[31] in that there have been three more RCTs published: 1) a small Asian RCT of 65 infants with severe respiratory distress syndrome (Su, 2008[65]), 2) a report of the 29 infants born below 34 weeks gestation but with birth weight above 1500 g from the NICHD Neonatal Research Network (Van Meurs, 2007),[39] and 3) a large multicenter trial of 800 infants with gestational ages of 24 to 28 weeks.[62] In addition, we were charged with a broader mission: to review the data regarding a number of short term risks, long term pulmonary and neurodevelopmental outcomes, outcomes among subpopulations, and the effects of iNO dose, timing, duration, and concurrent therapies on outcomes. By using a broader definition to include outcome at one year corrected for degree of prematurity, and finding more recent outcome studies, including one with outcomes at four to five years, we were able to review long term outcomes for eight RCTs.[30, 35, 36, 39, 44, 56, 57, 76] The Barrington and Finer Cochrane systematic review[31] makes a valid point that the studies of iNO in preterm infants vary substantially in their eligibility criteria. The RCTs also vary widely in dose, method, and duration of administration of iNO. But the focus of studying effects of iNO on preterm infants has evolved from immediate pulmonary or cardiovascular effects, to how it may influence the growth and maturation of the developing lung and its cardiovascular support. To provide another perspective, we chose to view the variation in respiratory disease severity, iNO dose, method, and duration of iNO administration as varying degrees of iNO exposure on a continuum of degree of organ maturation, as measured by postmenstrual age. Postmenstrual age is the sum of gestational age at birth and chronological age, and is currently the best measure of preterm maturation that we have. We view brain injury and neurodevelopmental outcomes also in terms of degree of maturation (i.e., PMA) when exposed to iNO. The heterogeneity of our meta-analyses for the composite brain injury variable and for cognitive impairment could be explained by the effect of iNO in the two trials that included preterm infants with birth weights over 1500 g (Schreiber, 2003 and Van Meurs, 2007).[39, 58] The bigger infants are more likely to be the more mature infants, and may benefit more from iNO effects on pulmonary blood flow because they are better able to autoregulate their cerebral blood flow.

Table 11. Strength of evidence for articles addressing Key Question 1

Outcome	Number of Studies; Subjects	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Strength of Evidence
Death/Survival	14; 4754	RCT/ fair	Consistent	Direct	Imprecise	Moderate
Death or BPD	12; 3301	RCT/ fair	Inconsistent	Direct	Imprecise	Low
BPD at 36 Weeks	12; 2665	RCT/ fair	Consistent	Direct	Imprecise	Moderate
BPD, other measures	11; 3315	RCT/ fair	Inconsistent	Indirect	Imprecise	Low

BPD = bronchopulmonary dysplasia

Table 12. Strength of evidence for articles addressing Key Question 2

Outcome	Number of Studies; Subjects	Risk of Bias Design; Quality	Consistency	Directness	Precision	Strength of Evidence
Pulmonary Hemorrhage	7; 2085	RCT/ fair	Consistent	Direct	Imprecise	Moderate
Air leak or Pneumothorax	10; 2361	RCT/ fair	Consistent	Direct	Imprecise	Moderate
Methemoglobinemia	12; 3190	RCT/ fair	Consistent	Direct	Imprecise	Moderate
Brain Injury	13; 2936	RCT/ good	Unknown	Direct	Imprecise	Low
PDA	11; 2870	RCT/ fair	Consistent	Direct	Imprecise	Moderate
Sepsis	8; 2958	RCT/poor	Consistent	Indirect	Imprecise	Low
NEC	8; 2683	RCT/ fair	Consistent	Direct	Imprecise	Moderate
ROP	8; 2025	RCT/fair	Consistent	Direct	Imprecise	Moderate

PDA = patent ductus arteriosus; NEC = necrotizing enterocolitis; ROP = severe retinopathy of prematurity

Table 13. Strength of evidence for articles addressing Key Question 3

Outcome	Number of Studies; Subjects	Risk of Bias Design; Quality	Consistency	Directness	Precision	Strength of Evidence
Death and Survival	9; 2635	RCT/ fair	Consistent	Direct	Imprecise	Moderate
Cerebral palsy	6; 914	RCT/ fair	Inconsistent	Direct	Imprecise	Low
	1; 9	Cohort/fair				
Sensory Impairment	7; 951	RCT/ poor	Consistent	Direct	Imprecise	Moderate
Cognitive Outcomes	5; 896	RCT/ poor	Inconsistent	Direct	Imprecise	Low
Neurodevelopmental Impairment	7; 1315	RCT/ good	Inconsistent	Direct	Imprecise	Low
Death or Neurodevelopmental Impairment	4; 1236	RCT/ good	Consistent	Direct	Imprecise	Moderate
Growth	5; 968	RCT/ fair	Consistent	Direct	Imprecise	Low
	1; 10	Cohort/poor	Unknown	Direct	Unknown	Insufficient
Pulmonary and other health outcomes	4; 1329	RCT/poor	Inconsistent	Direct	Imprecise	Low
	2; 35	Cohort/poor				
Oral feeding	1; 108	RCT/ poor	Unknown	Direct	Unknown	Insufficient

Table 14. Strength of Evidence for articles being addressed by Key Question 4

Outcome	Number of Studies; Subjects	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Strength of Evidence
Death	6; 1444	RCT/ fair	Consistent	Direct	Imprecise	Moderate
	2; 57	Cohort/ poor				
Death or BPD	6; 1529	RCT/ fair	Inconsistent	Direct	Imprecise	Low
Death or NDI	3; 851	RCT/ fair	Consistent	Direct	Imprecise	Low
BPD at 36 weeks	4; 1321	RCT/ good	Consistent	Direct	Imprecise	Moderate
BPD not defined	1; 18	Cohort/fair	Unknown	Indirect	Imprecise	Low
Severe BPD, Mechanical vent (survivors)	1; 16	Cohort/fair	Unknown	Direct	Imprecise	Low
On O2 at 1 year	1: 502	RCT/Good	Inconsistent	Direct	Imprecise	Low
Survival without BPD	2; 790	RCT/ fair	Consistent	Direct	Imprecise	Moderate
Survival to discharge	1; 41	Cohort/ poor	Unknown	Direct	Imprecise	Low
Survival > 28 days	1; 18	Cohort/fair	Unknown	Direct	Imprecise	Low
Survival with BPD	1; 208	RCT/good	Unknown	Direct	Imprecise	Low
Cerebral palsy	1; 31	Cohort/ fair	Unknown	Direct	Imprecise	Low
Neuro-developmental Index-related outcomes	5; 1442	RCT/ good	Inconsistent	Direct	Imprecise	Low
Severe IVH (3-4) or PVL	1; 420	RCT/ good	Unknown	Direct	Imprecise	Low

Table 14. Strength of Evidence for articles being addressed by Key Question 4 (continued)
BPD = bronchopulmonary dyplasia; NDI = neurodevelopmental impairment; IVH = intraventricular hemorrhage; PVL = periventricular leukomalacia

Table 15. Strength of Evidence for articles being addressed by Key Question 5

Outcomes	Number of Studies; Subjects	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Strength of Evidence
Death	14; 2693	RCT/ fair	Consistent	Direct	Imprecise	Low
Death or BPD	11; 2365	RCT/ fair	Inconsistent	Direct	Imprecise	Low
Death or cerebral palsy	1; 420	RCT/good	Inconsistent	Direct	Imprecise	Low
Survival without BPD	2; 734	RCT/ good	Consistent	Direct	Imprecise	Moderate
BPD at 36 weeks	11; 1690	RCT/ fair	Consistent	Direct	Imprecise	Moderate
Cerebral palsy	1; 420	RCT/good	Inconsistent	Direct	Imprecise	Low
NDI	5; 1034	RCT/ fair	Consistent	Direct	Imprecise	Low
Severe Disability	1; 420	RCT/good	Inconsistent	Direct	Imprecise	Low

Table 16. Summary of meta-analyses

Key Question	Outcome	Studies, N	Studies included in the meta-analysis	GRADE	RR (95% CI)
1	Survival/Death	14	11	Moderate	0.97 (0.82, 1.15)
	Survival/Death 2*	14	10	Moderate	0.98 (0.81, 1.17)
	BPD at 36 weeks PMA	12	8	Moderate	0.93 (0.86, 1.003)
	Death or BPD at 36 weeks PMA	12	11	Low	0.93 (0.87, 0.99)
	Death or BPD at 36 weeks PMA*	12	10	Low	0.93 (0.87, 1.00)
2	Brain injury	13	5	Low	0.86 (0.56, 1.29)
	PDA	11	9	Moderate	1.01 (0.86, 1.19)
	Sepsis	8	8	Low	1.05 (0.95, 1.18)
	NEC	8	7	Moderate	1.23 (0.94, 1.26)
	ROP	8	8	Moderate	1.01 (0.82. 1.24)
	Pulmonary hemorrhage	7	4	Moderate	0.89 (0.60, 1.33)
	Air leak	10	7	Moderate	0.95 (0.71, 1.28)
3	Survival/Death	9	7	Moderate	1.02 (0.86, 1.20)
	Cerebral palsy	7	7	Low	1.07 (0.67, 1.71)
	PDI < 70	4	4	Low	0.95 (0.66, 1.36)
	MDI < 70	3	3	Low	0.78 (0.39, 1.60)
	Sensory impairment (visual)	7	6	Moderate	1.09 (0.52, 2.034
	Sensory impairment (hearing)	7	6	Moderate	1.50 (0.69, 3.27)
	NDI	7	6	Low	0.91 (0.74, 1.12)
4	NO META-ANALYSES				

Table 16. Summary of meta-analyses (continued)

Key Question	Outcome	Studies, N	Studies included in the meta-analysis	GRADE	RR (95% CI)
5	Dose stratified death	14	11	Low	0.97 (0.82, 1.15)
	5 ppm iNO	3	3		0.97 (0.70, 1.35)
	10 ppm iNO	5	4		1.00 (0.73, 1.38)
	20 ppm iNO	6	4		0.91 (0.63, 1.30)
	BPD at 36 weeks PMA	13	11	Moderate	0.90 (0.82, 0.98)
	5 ppm iNO	3	3		0.94 (0.87, 1.02)
	10 ppm iNO	5	4		0.75 (0.61, 0.91)
	20 ppm iNO	5	4		0.99 (0.74, 1.34)
	Death or BPD at 36 weeks PMA	11	11	Low	0.93 (0.87, 0.99)
	5 ppm iNO	3	3		0.94 (0.88, 1.01)
	10 ppm iNO	4	4		0.08 (0.64, 1.03)
	20 ppm iNO	4	4		0.94 (0.84, 1.06)

*Analysis does not include the Ballard, 2006[34] data

RR = Risk ratio; CI = confidence interval; BPD = bronchopulmonary dysplasia; PMA = post menstrual age; PDA = patent ductus arteriosis; NEC = Necrotizing enterocolitis, ROP = retinopathy of prematurity, treated; PDI = physical development index; MDI = mental development index; ppm = parts per million

A recent individual patient data meta-analysis has been presented,[95] but has not yet been published. A synthesis of data on short term outcomes on 3298 preterm infants (< 37 weeks) from 11 trials found no statistically significant differences in death or CLD, RR 0.96 (0.92, 1.01) or in severe neurological abnormalities on neuroimaging, RR 1.12 (0.98, 1.28).[95] They concluded that there was a lack of evidence to support the "indiscriminate" use of iNO in treating preterm infants with respiratory failure.

The driving force behind the studies of iNO in preterm infants who receive respiratory support is the search for an effective treatment that improves survival and pulmonary health without increasing the risk of adverse short and long term outcomes. As many as one third to one half of the preterm infants enrolled in the studies discussed in this report died in the NICU. Most of the survivors had residual chronic lung disease (BPD) that significantly prolonged their hospitalization and influenced their quality of life after discharge home from the NICU. In the two studies that reported it, only 20 to 40 percent of survivors in both the iNO and control groups had normal neurodevelopmental outcomes at one to two years.[30, 35, 36] As cohort studies and RCTs of iNO in preterm infants born at or before 34 weeks gestation were being conducted, off label use of iNO in this population dramatically increased. One publication reported a six fold increase in its use between 2000 and 2008 in a large multisite pediatric group.[47]

Whether the small statistically significant reduction of death or BPD we found on meta-analysis is clinically meaningful depends on one's point of view. When compared to the evidence amassed for the efficacy iNO in treating full term infants and preterm infants born after 34 weeks gestation with respiratory failure, a reduction of death or BPD by less than 10% is very weak. But many parents would grasp at even that small a difference in their sick preterm infant's chances in surviving without BPD or NDI. We agree with Barrington and Finer in their 2007 Cochrane review [31] and Askie, 2010 (abstract)[96] that current evidence does not support the routine use of iNO to treat preterm infants. We do not conclude, however, that we should abandon the possibility that iNO may someday become a component of a treatment strategy for some preterm infants receiving respiratory support. Several factors contribute to our

recommendation to continue the study of iNO: 1) our finding a small but statistically significant difference in death or BPD at 36 weeks PMA, the common primary outcome variable of 73 percent of RCT conducted to date; 2) the statistically significant finding of a diminished need for chronic pulmonary medication at one year corrected age, suggesting less severe lung disease in those treated with iNO, and 3) no studies have been powered to detect meaningful differences in infant functional outcome or quality of life with iNO treatment compared to standard therapy.

Treatment of preterm infants born at or below 34 weeks gestation with iNO should occur only in the context of rigorously conducted RCTs that have the power to detect meaningful long term outcomes. Strategies for treatment need to consider how different preterm infants are from full term infants. Their immature organs are not prepared to support extrauterine life, persistent pulmonary hypertension is not as much of a problem early in the disease process, they lack important natural defenses (e.g., surfactant, cortisol, immune responses), and their response to organ injury seems to vary depending on degree of maturation. Studies of iNO therapy to date have enrolled and treated infants based on gestational age and chronological age, both imperfect measures of maturity. Degree of lung and brain maturation seems to be a very important variable, and treatment should be viewed in terms of postmenstrual age, a construct that better reflects organ maturation. Consideration of postmenstrual age at the time of initiation and duration of iNO therapy may help select subgroups of infants most like to benefit from the therapy. Funded, ongoing basic research into the mechanisms by which iNO may influence the developing lung can provide insight into how to design future clinical trials. Evaluating the effect of iNO on brain injury requires neuroimaging before treatment, as well as on serial studies. BPD at 36 weeks PMA and evidence of brain injury are important mediators. Prolonged hospitalizations, use of supplemental oxygen and pulmonary medications after NICU discharge, prevalence of reactive airway disease and recurrent hospitalizations (as reported by Ballard, 2006[34] and Hibbs, 2007[44]) are more important indicators of pulmonary function and health. [44] Neurodevelopmental outcomes and functional abilities in childhood are far more important outcomes than evidence of brain injury on neuroimaging studies. Careful assessment of the few statistically significant but inconsistent differences with iNO exposure, combined with ongoing basic science and clinical research on the developing lung and brain, their response to and recovery from injury can provide insights that lead to testable hypotheses for future randomized controlled trials.

Chapter 5. Future Research

Future studies on the efficacy of iNO therapy for preterm infants that require respiratory support should have strong conceptual frameworks that test hypotheses on the mechanism by which iNO therapy improves pulmonary or neurodevelopmental outcomes. Such research should measure biomarkers of this mechanism of action, beyond improvement in oxygenation and neuroimaging. Inhaled NO has been given to infants as prophylaxis to prevent the development of BPD, as rescue therapy for respiratory failure, and as treatment in those with evolving BPD. Future studies should postulate and test hypotheses concerning the role of iNO in improving outcomes for any of these conditions or groups of preterm infants.

Bronchopulmonary dysplasia at 36 weeks PMA and intraventricular hemorrhage, intraparenchymal hemorrhage, and periventricular leaukomalacia are useful intermediate variables and should be thought of in that context. Although neuroimaging of brain injury can monitor for safety, the more important outcomes for future RCTs are neurodevelopmental outcomes and function in childhood. Standardized tools that measure childhood quality of life and functional outcomes would assess the long term impact of iNO on health and development. Considerations of the frequency of pulmonary rehospitalization, chronic and episodic pulmonary medication, and missed school days would provide a broader context in which to view the efficacy of iNO. Studies should be powered to assess pulmonary, neurodevelopmental, and health outcomes at two to five years or more. Measuring such outcomes will require substantial investment by funders. What follows are considerations for future research.

Other Future Research Needs

Patients

- RCTs must be adequately powered to assess the effect of iNO on subgroups of preterm infants, such as those of varying birth weight.
- Special care must be taken if infants born at the limit of viability are included in randomized controlled trials. These infants do not yet have alveoli (gas exchange occurs through their terminal bronchioles) and their brains do not yet have gyri or sulci. They are most vulnerable to organ injury, which may be most evident on long term followup. Every effort must be taken to obtain pulmonary, neurodevelopmental and health followup for all infants in this category.
- There may be a value to viewing the use of iNO in terms of postmenstrual age, which is a better measure of degree of maturation and takes into account both gestational age and chronologic age in developing preterm infants.

Intervention

- Since the goal is to support pulmonary and brain development in the NICU, courses of iNO given for weeks, not days, should be studied.

- Mode of ventilation should be considered in randomization schemes for trials restricted to infants < 1500 grams, those at highest risk for death, BPD, and neurodevelopmental impairment, to adequately address the question concerning mode of delivery.
- As many of the smallest preterm infants are managed with CPAP or high flow nasal cannula alone, without intubation, information concerning iNO delivery with these devices is needed.

Outcomes

- Future RCTs should require neuroimaging by standardized protocols before trial enrollment, to detect the occurrence and progression of brain injury during iNO treatment.
- Studies should be powered to assess long term neurodevelopmental, pulmonary, and other health outcomes.
- Outcomes should focus on functional status and quality of life, as well as neurodevelopmental disabilities.
- Studies are needed to provide information on resource utilization such as rehospitalizations, medications, physicians' visits. Future focus should be on the real pulmonary problems of prolonged hospitalizations, use of supplemental oxygen, and pulmonary medications after NICU discharge, prevalence of reactive airway disease, and recurrent hospitalizations.
- Consideration should be given to assess longer term childhood outcomes (e.g., pulmonary function tests, school performances).
- Cost benefit analyses should be conducted with multicenter RCTs of iNO.

References and Included Studies

1. Institute of Medicine. Preterm Birth: Causes, Consequences, and Prevention 2005 Richard E. Behrman and Adrienne Stith Butler, Editors The National Academies Press Washington, D.C.
2. Berman W Jr, Katz R, Yabek SM, Dillon T, Fripp RR, Papile LA. Long-term follow-up of bronchopulmonary dysplasia. J Pediatr 1986; 109(1):45-50.
3. Heron M, Sutton PD, Xu J, Ventura SJ, Strobino DM, Guyer B. Annual summary of vital statistics: 2007. Pediatrics 2010; 125(1):4-15.
4. Finer NN, Barrington KJ. Nitric oxide for respiratory failure in infants born at or near term. Cochrane Database Syst Rev 2006; (4):CD000399.
5. Palmer RM, Ferrige AG, Moncada S. Nitric oxide release accounts for the biological activity of endothelium-derived relaxing factor. Nature 1987; 327(6122):524-6.
6. Bin-Nun A, Schreiber MD. Role of iNO in the modulation of pulmonary vascular resistance. J Perinatol 2008; 28 Suppl 3:S84-92.
7. Kinsella JP, Abman SH. Inhaled nitric oxide: current and future uses in neonates. Semin Perinatol 2000; 24(6):387-95.
8. Kinsella JP, Ivy DD, Abman SH. Inhaled nitric oxide improves gas exchange and lowers pulmonary vascular resistance in severe experimental hyaline membrane disease. Pediatr Res 1994; 36(3):402-8.
9. Cornfield DN, Abman SH. Inhalational nitric oxide in pulmonary parenchymal and vascular disease. J Lab Clin Med 1996; 127(6):530-9.
10. Gianetti J, Bevilacqua S, De Caterina R. Inhaled nitric oxide: more than a selective pulmonary vasodilator. Eur J Clin Invest 2002; 32(8):628-35.
11. Edwards AD. The pharmacology of inhaled nitric oxide. Arch Dis Child Fetal Neonatal Ed 1995; 72(2):F127-30.
12. Miller SS, Rhine WD. Inhaled nitric oxide in the treatment of preterm infants. Early Hum Dev 2008; 84(11):703-7.
13. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails Last accessed June 14, 2010.
14. Kinsella JP, Abman SH. Clinical approach to inhaled nitric oxide therapy in the newborn with hypoxemia. J. Pediatr. 2000; 136(6):717-26.
15. Kinsella JP, Neish SR, Dunbar Ivy D, Shaffer E, Abman SH. Clinical responses to prolonged treatment of persistent pulmonary hypertension of the newborn with low doses of inhaled nitric oxide. J. Pediatr. 1993; 123(1):103-8.
16. Macrae DJ, Field D, Mercier JC et al. Inhaled nitric oxide therapy in neonates and children: reaching a European consensus. Intensive Care Med 2004; 30(3):372-80.
17. Ballard PL, Gonzales LW, Godinez RI et al. Surfactant composition and function in a primate model of infant chronic lung disease: effects of inhaled nitric oxide. Pediatr Res 2006; 59(1):157-62.
18. McCurnin DC, Pierce RA, Chang LY et al. Inhaled NO improves early pulmonary function and modifies lung growth and elastin deposition in a baboon model of neonatal chronic lung disease. Am J Physiol Lung Cell Mol Physiol 2005; 288(3):L450-9.
19. Cotton RB, Sundell HW, Zeldin DC et al. Inhaled nitric oxide attenuates hyperoxic lung injury in lambs. Pediatr. Res. 2006; 59(1):142-6.
20. Kinsella JP, Parker TA, Galan H, Sheridan BC, Halbower AC, Abman SH. Effects of inhaled nitric oxide on pulmonary edema and lung neutrophil accumulation in severe experimental hyaline membrane disease. Pediatr Res 1997; 41(4 Pt 1):457-63.
21. Tang JR, Markham NE, Lin YJ et al. Inhaled nitric oxide attenuates pulmonary hypertension and improves lung growth in infant rats after neonatal treatment with a VEGF receptor inhibitor. Am J Physiol Lung Cell Mol Physiol 2004; 287(2):L344-51.
22. Lin YJ, Markham NE, Balasubramaniam V et al. Inhaled nitric oxide enhances distal lung growth after exposure to hyperoxia in neonatal rats. Pediatr Res 2005; 58(1):22-9.
23. Weinberger B, Laskin DL, Heck DE, Laskin JD. The toxicology of inhaled nitric oxide. Toxicol Sci 2001; 59(1):5-16.
24. Frank L, Groseclose EE. Preparation for birth into an O2-rich environment: the antioxidant enzymes in the developing rabbit lung. Pediatr Res 1984; 18(3):240-4.
25. Gaston B, Drazen JM, Loscalzo J, Stamler JS. The biology of nitrogen oxides in the airways. Am J Respir Crit Care Med 1994; 149(2 Pt 1):538-51.
26. Centers for Disease Control. Recommendations for occupational safety and health standards. Morbid Mortal Wkly 1988; report 37(supplement 7, 21).
27. Gries A, Herr A, Motsch J et al. Randomized, placebo-controlled, blinded and cross-matched study on the antiplatelet effect of inhaled nitric oxide in healthy volunteers. Thromb Haemost 2000; 83(2):309-15.
28. Albert J, Norman M, Wallen NH, Frostell C, Hjemdahl P. Inhaled nitric oxide does not influence bleeding time or platelet function in healthy volunteers. Eur J Clin Invest 1999; 29(11):953-9.
29. Roberts JD, Polaner DM, Lang P, Zapol WM. Inhaled nitric oxide in persistent pulmonary hypertension of the newborn. Lancet 1992; 340(8823):818-9.
30. Hintz SR, Van Meurs KP, Perritt R et al. Neurodevelopmental outcomes of premature infants with severe respiratory failure enrolled in a randomized controlled trial of inhaled nitric oxide. J Pediatr 2007; 151(1):16-22, 22.e1-3.
31. Barrington Keith J, Finer Neil. Inhaled nitric oxide for respiratory failure in preterm infants. Barrington Keith J, Finer Neil. Inhaled Nitric Oxide for Respiratory Failure in Preterm Infants. Cochrane Database of Systematic Reviews: Reviews 2007 Issue 3 John Wiley & Sons, Ltd Chichester, UK DOI: 10.1002/14651858.CD000509.Pub3 2007; (3).

32. Hoehn T, Krause MF, Buhrer C. Meta-analysis of inhaled nitric oxide in premature infants: An update. Klin. Padiatr. 2006; 218(2):57-61.
33. Steinhorn RH, Porta NF. Use of inhaled nitric oxide in the preterm infant. Curr Opin Pediatr 2007; 19(2):137-41.
34. Ballard RA, Truog WE, Cnaan A et al. Inhaled nitric oxide in preterm infants undergoing mechanical ventilation. New Engl. J. Med. 2006; 355(4):343-53.
35. Huddy CL, Bennett CC, Hardy P et al. The INNOVO multicentre randomised controlled trial: neonatal ventilation with inhaled nitric oxide versus ventilatory support without nitric oxide for severe respiratory failure in preterm infants: follow up at 4-5 years. Arch Dis Child Fetal Neonatal Ed 2008; 93(6):F430-5.
36. Watson RS, Clermont G, Kinsella JP et al. Clinical and economic effects of iNO in premature newborns with respiratory failure at 1 year. Pediatrics 2009; 124(5):1333-43.
37. Kinsella JP, Cutter GR, Walsh WF et al. Early inhaled nitric oxide therapy in premature newborns with respiratory failure. N Engl J Med 2006; 355(4):354-64.
38. Tanaka Y, Hayashi T, Kitajima H, Sumi K, Fujimura M. Inhaled nitric oxide therapy decreases the risk of cerebral palsy in preterm infants with persistent pulmonary hypertension of the newborn. Pediatrics 2007; 119(6):1159-64.
39. Van Meurs KP, Hintz SR, Ehrenkranz RA et al. Inhaled nitric oxide in infants >1500 g and <34 weeks gestation with severe respiratory failure. J Perinatol 2007; 27(6):347-52.
40. Van Meurs KP, Wright LL, Ehrenkranz RA et al. Inhaled nitric oxide for premature infants with severe respiratory failure. N Engl J Med 2005; 353(1):13-22.
41. Ambalavanan N, Van Meurs KP, Perritt R et al. Predictors of death or bronchopulmonary dysplasia in preterm infants with respiratory failure. J Perinatol 2008; 28(6):420-6.
42. Bruckner TA, Carlo WA, Ambalavanan N, Gould JB. Neonatal mortality among low birth weight infants during the initial months of the academic year. J Perinatol 2008; 28(10):691-5.
43. Hoo A-F, Beardsmore CS, Castle RA et al. Respiratory function during infancy in survivors of the INNOVO trial. Pediatr. Pulmonol. 2009; 44(2):155-61.
44. Hibbs AM, Walsh MC, Martin RJ et al. One-year respiratory outcomes of preterm infants enrolled in the Nitric Oxide (to prevent) Chronic Lung Disease trial. J Pediatr. 2008;153(4):525-9.
45. Kinsella, JP, Cutter, WF, Gerstman, DR, et al. Outcomes of Premature Infants Enrolled in the Early Inhaled Nitric Oxide for the Prevention of Chronic Lung Disease Trial. PASA Abstract, E-PAS2009:2155.6, 2009.
46. Keller, RL, Walsh E, Vittinghoff E, et al. Response to inhaled nitric oxide (iNO) and neurodevelopmental impairment (NDI) in NO CLD. PASA Abstract, E-PAS2009:2155.7, 2009
47. Clark RH, Ursprung RL, Walker MW, Ellsbury DL, Spitzer AR. The changing pattern of inhaled nitric oxide use in the neonatal intensive care unit. J Perinatol 2010.
48. Berlin JA. Does blinding of readers affect the results of meta-analyses? University of Pennsylvania Meta-analysis Blinding Study Group. Lancet 1997; 350(9072):185-6.
49. The Cochrane Collaboration. Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2. updated September 2009. Higgins JPT, Green S. The Cochrane Collaboration, 2009.
50. Wells GA , Shea B, O'Connell D, Peterson J., Welch V., Losos M., Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. Department of Epidemiology and Community Medicine, University of Ottawa, Canada. http://www.lri.ca/programs/ceu/oxford.htm
51. Atkins D, Best D, Briss PA et al. Grading quality of evidence and strength of recommendations. BMJ 2004; 328(7454):1490.
52. Owens DK, Lohr KN, Atkins D et al. AHRQ series paper 5: grading the strength of a body of evidence when comparing medical interventions--agency for healthcare research and quality and the effective health-care program. J Clin Epidemiol 2010; 63(5):513-23.
53. Wallace BC, Schmid CH, Lau J, Trikalinos TA. Meta-Analyst: software for meta-analysis of binary, continuous and diagnostic data. BMC Med Res Methodol 2009; 9(80).
54. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986; 7(3):177-88.
55. Schlesselman J, Stolley P. Case-control studies. Design, conduct, analysis. New York: Oxford University Press; 1982.
56. Mestan KK, Marks JD, Hecox K, Huo D, Schreiber MD. Neurodevelopmental outcomes of premature infants treated with inhaled nitric oxide. N Engl J Med 2005; 353(1):23-32.
57. Walsh MC, Hibbs AM, Martin CR et al. Two year neurodevelopmental outcomes of ventilated preterm infants treated with inhaled nitric oxide. J Pediatr 2010; 156(4):556-61.e1.
58. Schreiber MD, Gin-Mestan K, Marks JD, Huo D, Lee G, Srisuparp P. Inhaled Nitric Oxide in Premature Infants with the Respiratory Distress Syndrome. New Engl. J. Med. 2003; 349(22):2099-107.
59. Kinsella JP, Walsh WF, Bose CL et al. Inhaled nitric oxide in premature neonates with severe hypoxaemic respiratory failure: A randomised controlled trial. Lancet 1999; 354(9184):1061-5.
60. Franco-Belgium Collaborative NO Trial Group. Early compared with delayed inhaled nitric oxide in moderately hypoxaemic neonates with respiratory failure: a randomised controlled trial. The Franco-Belgium Collaborative NO Trial Group. Lancet 1999; 354(9184):1066-71.
61. Hascoet JM, Fresson J, Claris O et al. The safety and efficacy of nitric oxide therapy in premature infants. J. Pediatr. 2005; 146(3):318-23.

62. Mercier JC, Hummler H, Durrmeyer X et al. Inhaled nitric oxide for prevention of bronchopulmonary dysplasia in premature babies (EUNO): a randomised controlled trial. Lancet 2010;376(9738):346-54
63. Field D, Elbourne D, Truesdale A et al. Neonatal Ventilation With Inhaled Nitric Oxide Versus Ventilatory Support Without Inhaled Nitric Oxide for Preterm Infants With Severe Respiratory Failure: the INNOVO multicentre randomised controlled trial (ISRCTN 17821339). Pediatrics 2005; 115(4):926-36.
64. Subhedar NV, Ryan SW, Shaw NJ. Open randomised controlled trial of inhaled nitric oxide and early dexamethasone in high risk preterm infants. Arch Dis Child Fetal Neonatal Ed 1997; 77(3):F185-90.
65. Su PH, Chen JY. Inhaled nitric oxide in the management of preterm infants with severe respiratory failure. J Perinatol 2008; 28(2):112-6.
66. Srisuparp P, Heitschmidt M, Schreiber MD. Inhaled nitric oxide therapy in premature infants with mild to moderate respiratory distress syndrome. J Med Assoc Thai 2002; 85 Suppl 2:S469-78.
67. Dani C, Bertini G, Pezzati M, Filippi L, Cecchi A, Rubaltelli FF. Inhaled nitric oxide in very preterm infants with severe respiratory distress syndrome. Acta Paediatr 2006; 95(9):1116-23.
68. Kumar VH, Hutchison AA, Lakshminrusimha S, Morin FC 3rd, Wynn RJ, Ryan RM. Characteristics of pulmonary hypertension in preterm neonates. J Perinatol 2007; 27(4):214-9.
69. Uga N, Ishii T, Kawase Y, Arai H, Tada H. Nitric oxide inhalation therapy in very low-birthweight infants with hypoplastic lung due to oligohydramnios. Pediatr. Int. 2004; 46(1):10-4.
70. Banks BA, Seri I, Ischiropoulos H, Merrill J, Rychik J, Ballard RA. Changes in oxygenation with inhaled nitric oxide in severe bronchopulmonary dysplasia. Pediatrics 1999; 103(3):610-8.
71. Clark PL, Ekekezie II, Kaftan HA, Castor CA, Truog WE. Safety and efficacy of nitric oxide in chronic lung disease. Arch Dis Child Fetal Neonatal Ed 2002; 86(1):F41-5.
72. Cheung P-Y, Peliowski A, Robertson CMT. The outcome of very low birth weight neonates ((less-than or equal to)1500 g) rescued by inhaled nitric oxide: Neurodevelopment in early childhood. J. Pediatr. 1998; 133(6):735-9.
73. Yadav M, Emmerson AJ. Inhaled nitric oxide in premature neonates. Lancet 1999; 354(9196):2162-3.
74. Dewhurst C, Ibrahim H, Gothberg S, Jonsson B, Subhedar N. Use of inhaled nitric oxide in the new born period: Results from the European inhaled nitric oxide registry. Acta Paediatr. 2010; 99(6):854-60.
75. Ballard RA. Inhaled nitric oxide in preterm infants--correction. N Engl J Med 2007; 357(14):1444-5.
76. Bennett AJ, Shaw NJ, Gregg JE, Subhedar NV. Neurodevelopmental outcome in high-risk preterm infants treated with inhaled nitric oxide. Acta Paediatr 2001; 90(5):573-6.
77. Chock VY, Van Meurs KP, Hintz SR et al. Inhaled nitric oxide for preterm premature rupture of membranes, oligohydramnios, and pulmonary hypoplasia. Am J Perinatol 2009; 26(4):317-22.
78. Hamon I, Fresson J, Nicolas MB, Buchweiller MC, Franck P, Hascoet JM. Early inhaled nitric oxide improves oxidative balance in very preterm infants. Pediatr Res 2005; 57(5 Pt 1):637-43.
79. McAdams RM, Garza-Cox S, Yoder BA. Early-onset neonatal pneumococcal sepsis syndrome. Pediatr Crit Care Med 2005; 6(5):595-7.
80. Ballard RA. Inhaled nitric oxide in preterm infants--correction. N Engl J Med 2007; 357(14):1444-5.
81. Ryan SW, Nycyk J, Shaw BN. Prediction of chronic neonatal lung disease on day 4 of life. Eur J Pediatr 1996; 155(8):668-71.
82. Northway WH Jr, Rosan RC, Porter DY. Pulmonary disease following respirator therapy of hyaline-membrane disease: bronchopulmonary dysplasia. N Engl J Med 1967; 276:357-68.
83. Van Marter LJ. Epidemiology of bronchopulmonary dysplasia. Semin Fetal Neonatal Med 2009; 14(6):358-66.
84. Walsh MC, Wilson-Costello D, Zadell A, Newman N, Fanaroff A. Safety, reliability, and validity of a physiologic definition of bronchopulmonary dysplasia. J Perinatol 2003; 23:451-6.
85. Tennakoon J, Koh TH, Alcock G. Pyloric stenosis in a newborn baby with polycystic kidneys. J Perinatol 2007; 27(2):125-6.
86. Institute of Medicine, Committee on Understanding Premature Birth and Assuring Healthy Outcomes, Board on Health Sciences Policy. Preterm Birth: Causes, Consequences and Prevention. Behrman RE, Stith Butler A (Eds)Washington, DC: National Academies Press; 2007.
87. Papile LA, Burnstein J, Burnstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants less than 1500 gm. J Pediatr 1978; 92:529-34.
88. Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. Dev Med Child Neurol 1997; 39(4):214-23.
89. Elliot CD, Smith P, McCulloch K. British ability scales second edition (BAS II). Windsor: NFER-Nelson, 1996.
90. Kuczmarski RJ, Ogden CL, Grummer-Strawn LM et al. CDC growth charts: United States. Advance data from vital and health statistics; no. 314. Hyattsville, MD: National Center for Health Statistics 2000.
91. Da Costa DE, Nair AK, Pai MG, Al Khusaiby SM. Steroids in full term infants with respiratory failure and pulmonary hypertension due to meconium aspiration syndrome. Eur. J. Pediatr. 2001; 160(3):150-3.
92. Groenendaal F, Lammers H, Smit D, Nikkels PG. Nitrotyrosine in brain tissue of neonates after perinatal asphyxia. Arch Dis Child Fetal Neonatal Ed 2006; 91(6):F429-33.
93. Skimming JW, DeMarco VG, Cassin S. The effects of nitric oxide inhalation on the pulmonary circulation of preterm lambs. Pediatr Res 1995; 37(1):35-40.

94. Cools F, Henderson-Smart DJ, Offringa M, Askie LM. Elective high frequency oscillatory ventilation versus conventional ventilation for acute pulmonary dysfunction in preterm infants. Cochrane Database Syst Rev. 2009 Jul 8;(3):CD000104.
95. Askie L, Ballard R, Cutter G, et al. Inhaled Nitric Oxide in Preterm Infants: An Individual Patient Data Meta-Analysis. PASA Abstract, E-PAS2010: 1172.7,2010.
96. Askie LM, Ballard RA, Cutter G et al. Inhaled Nitric Oxide in preterm infants: a systematic review and individual patient data meta-analysis. BMC Pediatr 2010; 10:15.

Appendix A: List of Acronyms

Acronym	Definition
AHRQ	Agency for Healthcare Research and Quality
ArtrCath	Arterial catheter
BPD	Bronchopulmonary dysplasia
BSID	Bayley scale of infant development
BW	Birth weight
CMV	Conventional mechanical ventilation
Congen	Congenital anomaly/malformation
CP	Cerebral palsy
CPAP	Continuous Positive Airway Pressure
DQ	Developmental quotient
Dshunting	Ductal Shunting
ECMO	Extracorporeal membrane oxygenation
EDC	Estimated date of confinement
F/U	Follow- up
FDA	Food and Drug Administration
FiO2	Fraction of Inspired Oxygen
g	grams
GA	Gestational age
GCAS	General conceptual ability
HFFI	High-frequency flow interruption
HFOV	High-frequency oscillatory ventilation
HFV	High-frequency ventilation
HRF	Hypoxemic respiratory failure
iNO	inhaled Nitric Oxide
intrprncyml	Intraparenchymal lesion
IPH	intraparenchymal hemorrhage
IQR	Inter-quartile range
IVH	Intraventricular Hemorrhage
JHU	Johns Hopkins University
KG	Kilograms
MAP	Mean airway pressure
MDI	Mental developmental index
mmHg	millimeters of mercury
NDI	Neurodevelopmental impairment
NEC	Necrotizing enterocolitis
NICU	Neonatal intensive care unit
NIH	National Institutes of Health
NO	Nitric oxide
NO_2	Nitrogen dioxide
OI	Oxygenation Index
Oligho	Oligohydramnios
OMAR	Office of Medical Applications of Research
PDA	Patent Ductus Arteriosis
PDI	Physical developmental index
PMA	post menstrual age
PPHN	Persistent Pulmonary Hypertension of the Newborn
ppm	parts per million
Pulmhyp	Pulmonary hypoplasia
PVL	Periventricular leukomalacia
RCT	Randomized controlled trial
RDS	Respiratory distress syndrome
Respfail	Respiratory failure
ROP	Retinopathy of Prematurity
RX	treatment
SD	Standard deviation
Vent Support	Ventilation Support

APPENDIX B: Detailed Electronic Database Search Strategies

MEDLINE Strategy

Terms	Returns
(("nitric oxide"[tiab] OR "nitric oxide"[mh] OR iNO[tiab]) AND ("infant, newborn"[mh] OR premature[tiab] OR preterm[tiab] OR prematurity[tiab])) NOT (Animal[mh] NOT Human[mh])	1747

EMBASE Strategy

(('nitric oxide':ab,ti OR 'nitric oxide'/exp OR 'ino':ab,ti) AND ('newborn'/exp OR 'newborn':ab,ti OR 'prematurity'/exp OR 'premature':ab,ti OR 'prematurity':ab,ti OR 'preterm':ab,ti)) NOT ([animals]/lim NOT [humans]/lim)	2464

The Cochrane Central Register of Controlled Trials (CENTRAL)

((((nitric oxide):ti,ab,kw OR (iNO):ti,ab,kw) AND ((infant):ti,ab,kw OR (newborn):ti,ab,kw OR (premature):ti,ab,kw OR (preterm):ti,ab,kw)) NOT ((animals) NOT (humans)))	260

Psycinfo Strategy

(TX "nitric oxide" or TX "iNO") and (TX "infant, newborn" or TX "premature" or TX "preterm" or TX prematurity)	13

Refid: 12, Skateboards: Are they really perilous? A retrospective study froma district hospital. RethnamU, Yesupalan RS, Sinha A.

Submit Form and go to [ ] or Skip to Next

ALL Outcomes

1. **Study Arm** (Glossary)

- ArmA (control)
- ArmB
- ArmC
- ArmD
- ArmE
- ArmF
- ArmG
- ArmH

Clear Response

2. **If this is arm contains subgroups, indicate and define the subgroups below:**

- Subgroup 1 (Define)
- Subgroup 2 (Define)
- Subgroup 3 (Define)
- Subgroup 4 (Define)
- Subgroup 5 (Define)
- Subgroup 6 (Define)
- Subgroup 7 (Define)
- Subgroup 8 (Define)
- Subgroup 9 (Define)
- Subgroup 10 (Define)

Clear Response

3. **If this arm has a single follow-up time, indicate the follow up time below:**

- Follow-up time

Death

4. Measured at:

- Time post birth OR actual follow-up time (specify units)
- iNO dosage
- N
- Indentify comparison for significance values (ex: ArmA vs. ArmB)
- ----------
- *Significance values adjusted for* ***gestational age***
- *Significance values adjusted for* ***birth weight***
- *Significance values adjusted for* ***race***
- *Significance values adjusted for* ***prenatal steroids***
- *Significance values adjusted for* ***other***
- *Significance values adjusted for* ***other***

5. Death

- n
- %n
- p-value
- RR (95% CI)
- HR (95% CI)
- OR (95% CI)
- Max adj. p-value
- Max adj. RR (95% CI)
- Max adj. HR (95% CI)
- Max adj. OR (95% CI)

6. Death or BPD

- n
- %n
- p-value
- RR (95% CI)
- HR (95% CI)
- OR (95% CI)
- Max adj. p-value
- Max adj. RR (95% CI)
- Max adj. HR (95% CI)
- Max adj. OR (95% CI)

7. Measured at:		8. Death		9. Death or BPD	
☐ Time post birth OR actual follow-up time (specify units)		☐ n		☐ n	
☐ iNO dosage		☐ %n		☐ %n	
☐ N		☐ p-value		☐ p-value	
☐ Indentify comparison for significance values (ex: ArmA vs. ArmB)		☐ RR (95% CI)		☐ RR (95% CI)	
☐ *Significance values adjusted for* ***gestational age***		☐ HR (95% CI)		☐ HR (95% CI)	
☐ *Significance values adjusted for* ***birth weight***		☐ OR (95% CI)		☐ OR (95% CI)	
☐ *Significance values adjusted for* ***race***		☐ Max. Adj. p-value		☐ Max. Adj. p-value	
☐ *Significance values adjusted for* ***prenatal steroids***		☐ Max. Adj. RR (95% CI)		☐ Max. Adj. RR (95% CI)	
☐ *Significance values adjusted for* ***other***		☐ Max. Adj. HR (95% CI)		☐ Max. Adj. HR (95% CI)	
☐ *Significance values adjusted for* ***other***		☐ Max. Adj. OR (95% CI)		☐ Max. Adj. OR (95% CI)	

10. Measured at:		11. Death		12. Death or BPD	
☐ Time post birth OR actual follow-up time (specify units)		☐ n		☐ n	
☐ iNO dosage		☐ %n		☐ %n	
☐ N		☐ p-value		☐ p-value	
☐ Indentify comparison for significance values (ex: ArmA vs. ArmB)		☐ RR (95% CI)		☐ RR (95% CI)	
☐ *Significance values adjusted for* ***gestational age***		☐ HR (95% CI)		☐ HR (95% CI)	
☐ *Significance values adjusted for* ***birth weight***		☐ OR (95% CI)		☐ OR (95% CI)	
☐ *Significance values adjusted for* ***race***		☐ Max. Adj. p-value		☐ Max. Adj. p-value	
☐ *Significance values adjusted for* ***prenatal steroids***		☐ Max. Adj. RR (95% CI)		☐ Max. Adj. RR (95% CI)	
☐ *Significance values adjusted for* ***other***		☐ Max. Adj. HR (95% CI)		☐ Max. Adj. HR (95% CI)	
☐ *Significance values adjusted for* ***other***		☐ Max. Adj. OR (95% CI)		☐ Max. Adj. OR (95% CI)	

13. Measured at:		14. Death		15. Death or BPD	
☐ Time post birth OR actual follow-up time (specify units)		☐ n		☐ n	
☐ iNO dosage		☐ %n		☐ %n	
☐ N		☐ p-value		☐ p-value	
☐ Indentify comparison for significance values (ex: ArmA vs. ArmB)		☐ RR (95% CI)		☐ RR (95% CI)	
☐ *Significance values adjusted for* ***gestational age***		☐ HR (95% CI)		☐ HR (95% CI)	
☐ *Significance values adjusted for* ***birth weight***		☐ OR (95% CI)		☐ OR (95% CI)	
☐ *Significance values adjusted for* ***race***		☐ Max. adj. p-value		☐ Max. adj. p-value	
☐ *Significance values adjusted for* ***prenatal steroids***		☐ Max. adj. RR (95% CI)		☐ Max. adj. RR (95% CI)	
☐ *Significance values adjusted for* ***other***		☐ Max. adj. HR (95% CI)		☐ Max. adj. HR (95% CI)	
☐ *Significance values adjusted for* ***other***		☐ Max. adj. OR (95% CI)		☐ Max. adj. OR (95% CI)	

Survival

16. Measured at:		17. Survival to childhood at time of Follow-up		18. Survival WITH BPD		19. Survival WITHOUT BPD	
☐ Time post birth OR actual follow-up time (specify units)		☐ n		☐ n		☐ n	
☐ iNO dosage		☐ %n		☐ %n		☐ %n	
☐ N		☐ p-value		☐ p-value		☐ p-value	
☐ Indentify comparison for significance values (ex: ArmA vs. ArmB)		☐ RR (95% CI)		☐ RR (95% CI)		☐ RR (95% CI)	
☐ *Significance values adjusted for* ***gestational age***		☐ RR (95% CI)		☐ HR (95% CI)		☐ HR (95% CI)	
☐ *Significance values adjusted for* ***birth weight***		☐ OR (95% CI)		☐ OR (95% CI)		☐ OR (95% CI)	
☐ *Significance values adjusted for* ***race***		☐ Max. Adj. p-value		☐ Max. adj. p-value		☐ Max. adj. p-value	
☐ *Significance values adjusted for* ***prenatal steroids***		☐ Max. Adj. RR (95% CI)		☐ Max. adj. RR (95% CI)		☐ Max. adj. RR (95% CI)	
☐ *Significance values adjusted for* ***other***		☐ Max. Adj. HR (95% CI)		☐ Max. adj. HR (95% CI)		☐ Max. adj. HR (95% CI)	
☐ *Significance values adjusted for* ***other***		☐ Max. Adj. OR (95% CI)		☐ Max. adj. OR (95% CI)		☐ Max. adj. OR (95% CI)	

20. Measured at:		21. Survival to childhood at time of Follow-up		22. Survival WITH BPD		23. Survival WITHOUT BPD	
☐ Time post birth OR actual follow-up time (specify units)		☐ n		☐ n		☐ n	
☐ iNO dosage		☐ %n		☐ %n		☐ %n	
☐ N		☐ p-value		☐ p-value		☐ p-value	
☐ Indentify comparison for significance values (ex: ArmA vs. ArmB)		☐ RR (95% CI)		☐ RR (95% CI)		☐ RR (95% CI)	
☐ *Significance values adjusted for* ***gestational age***		☐ HR (95% CI)		☐ HR (95% CI)		☐ HR (95% CI)	
☐ *Significance values adjusted for* ***birth weight***		☐ OR (95% CI)		☐ OR (95% CI)		☐ OR (95% CI)	
☐ *Significance values adjusted for* ***race***		☐ Max. adj. p-value		☐ Max. adj. p-value		☐ Max. adj. p-value	
☐ *Significance values adjusted for* ***prenatal steroids***		☐ Max. adj. RR (95% CI)		☐ Max. adj. RR (95% CI)		☐ Max. adj. RR (95% CI)	
☐ *Significance values adjusted for* ***other***		☐ Max. adj. HR (95% CI)		☐ Max. adj. HR (95% CI)		☐ Max. adj. HR (95% CI)	
☐ *Significance values adjusted for* ***other***		☐ Max. adj. OR (95% CI)		☐ Max. adj. OR (95% CI)		☐ Max. adj. OR (95% CI)	

24. Measured at:		25. Survival to childhood at time of Follow-up		26. Survival WITH BPD		27. Survival WITHOUT BPD	
Time post birth OR actual follow-up time (specify units)		n		n		n	
iNO dosage		%n		%n		%n	
N		p-value		p-value		p-value	
Indentify comparison for significance values (ex: ArmA vs. ArmB)		RR (95% CI)		RR (95% CI)		RR (95% CI)	
Significance values adjusted for ***gestational age***		HR (95% CI)		HR (95% CI)		HR (95% CI)	
Significance values adjusted for ***birth weight***		OR (95% CI)		OR (95% CI)		OR (95% CI)	
Significance values adjusted for ***race***		Max. adj. p-value		Max. adj. p-value		Max. adj. p-value	
Significance values adjusted for ***prenatal steroids***		Max. adj. RR (95% CI)		Max. adj. RR (95% CI)		Max. adj. RR (95% CI)	
Significance values adjusted for ***other***		Max. adj. HR (95% CI)		Max. adj. HR (95% CI)		Max. adj. HR (95% CI)	
Significance values adjusted for ***other***		Max. adj. OR (95% CI)		Max. adj. OR (95% CI)		Max. adj. OR (95% CI)	

28. Measured at:		29. Survival to childhood at time of Follow-up		30. Survival WITH BPD		31. Survival WITHOUT BPD	
Time post birth OR actual follow-up time (specify units)		n		n		n	
iNO dosage		%n		%n		%n	
N		p-value		p-value		p-value	
Indentify comparison for significance values (ex: ArmA vs. ArmB)		RR (95% CI)		RR (95% CI)		RR (95% CI)	
Significance values adjusted for ***gestational age***		HR (95% CI)		HR (95% CI)		HR (95% CI)	
Significance values adjusted for ***birth weight***		OR (95% CI)		OR (95% CI)		OR (95% CI)	
Significance values adjusted for ***race***		Max. adj. p-value		Max. adj. p-value		Max. adj. p-value	
Significance values adjusted for ***prenatal steroids***		Max. adj. RR (95% CI)		Max. adj. RR (95% CI)		Max. adj. RR (95% CI)	
Significance values adjusted for ***other***		Max. adj. HR (95% CI)		Max. adj. HR (95% CI)		Max. adj. HR (95% CI)	
Significance values adjusted for ***other***		Max. adj. OR (95% CI)		Max. adj. OR (95% CI)		Max. adj. OR (95% CI)	

Cardiac/Infectious Disease/Gastrointestinal outcomes

Patent Ductus Arteriosus (PDA)

32. Measured at:

- ☐ Time post birth OR actual follow-up time (specify units) ☐
- ☐ iNO dosage ☐
- ☐ N ☐
- ☐ Indentify comparison for significance values (ex: ArmA vs. ArmB) ☐
- ☐ *Significance values adjusted for **gestational age***
- ☐ *Significance values adjusted for **birth weight***
- ☐ *Significance values adjusted for **race***
- ☐ *Significance values adjusted for **prenatal steroids***
- ☐ *Significance values adjusted for **other*** ☐
- ☐ *Significance values adjusted for **other*** ☐

33. PDA requiring medical treatment

- ☐ n ☐
- ☐ %n ☐
- ☐ p-value ☐
- ☐ RR (95% CI) ☐
- ☐ HR (95% CI) ☐
- ☐ OR (95% CI) ☐
- ☐ Max adj. p-value ☐
- ☐ Max adj. RR (95% CI) ☐
- ☐ Max adj. HR (95% CI) ☐
- ☐ Max adj. OR (95% CI) ☐

34. PDA requiring surgical treatment

- ☐ n ☐
- ☐ %n ☐
- ☐ p-value ☐
- ☐ RR (95% CI) ☐
- ☐ HR (95% CI) ☐
- ☐ OR (95% CI) ☐
- ☐ Max adj. p-value ☐
- ☐ Max adj. RR (95% CI) ☐
- ☐ Max adj. HR (95% CI) ☐
- ☐ Max adj. OR (95% CI) ☐

35. Not Defined by two above

- ☐ Define ☐
- ☐ n ☐
- ☐ %n ☐
- ☐ p-value ☐
- ☐ RR (95% CI) ☐
- ☐ HR (95% CI) ☐
- ☐ OR (95% CI) ☐
- ☐ Max adj. p-value ☐
- ☐ Max adj. RR (95% CI) ☐
- ☐ Max adj. HR (95% CI) ☐
- ☐ Max adj. OR (95% CI)

36. Measured at:

- ☐ Time post birth OR actual follow-up time (specify units) ☐
- ☐ iNO dosage ☐
- ☐ N ☐
- ☐ Indentify comparison for significance values (ex: ArmA vs. ArmB) ☐
- ☐ *Significance values adjusted for **gestational age***
- ☐ *Significance values adjusted for **birth weight***

37. PDA requiring medical treatment

- ☐ n ☐
- ☐ %n ☐
- ☐ p-value ☐
- ☐ RR (95% CI) ☐
- ☐ HR (95% CI) ☐
- ☐ OR (95% CI) ☐

38. PDA requiring surgical treatment

- ☐ n ☐
- ☐ %n ☐
- ☐ p-value ☐
- ☐ RR (95% CI) ☐
- ☐ HR (95% CI) ☐
- ☐ OR (95% CI) ☐

39. Not Defined by two above

- ☐ Define ☐
- ☐ n ☐
- ☐ %n ☐
- ☐ p-value ☐
- ☐ RR (95% CI) ☐
- ☐ HR (95% CI) ☐

☐ *Significance values adjusted for **race***		☐ Max adj. p-value		☐ Max adj. p-value		☐ OR (95% CI)	
☐ *Significance values adjusted for **prenatal steroids***		☐ Max adj. RR (95% CI)		☐ Max adj. RR (95% CI)		☐ Max adj. p-value	
☐ *Significance values adjusted for **other***		☐ Max adj. HR (95% CI)		☐ Max adj. HR (95% CI)		☐ Max adj. RR (95% CI)	
☐ *Significance values adjusted for **other***		☐ Max adj. OR (95% CI)		☐ Max adj. OR (95% CI)		☐ Max adj. HR (95% CI)	
						☐ Max adj. OR (95% CI)	

Methemoglobinemia

40. Measured at:		41. >4%		42. >8%	
☐ Time post birth OR actual follow-up time (specify units)		☐ n		☐ n	
☐ iNO dosage		☐ %n		☐ %n	
☐ N		☐ p-value		☐ p-value	
☐ Indentify comparison for significance values (ex: ArmA vs. ArmB)		☐ RR (95% CI)		☐ RR (95% CI)	
☐ *Significance values adjusted for **gestational age***		☐ HR (95% CI)		☐ HR (95% CI)	
☐ *Significance values adjusted for **birth weight***		☐ OR (95% CI)		☐ OR (95% CI)	
☐ *Significance values adjusted for **race***		☐ Max. adj. p-value		☐ Max adj. p-value	
☐ *Significance values adjusted for **prenatal steroids***		☐ Max. adj. RR (95% CI)		☐ Max adj. RR (95% CI)	
☐ *Significance values adjusted for **other***		☐ Max. adj. HR (95% CI)		☐ Max adj. HR (95% CI)	
☐ *Significance values adjusted for **other***		☐ Max. adj. OR (95% CI)		☐ Max adj. OR (95% CI)	

43. Measured at:		44. >4%		45. >8%	
☐ Time post birth OR actual follow-up time (specify units)		☐ n		☐ n	
☐ iNO dosage		☐ %n		☐ %n	
☐ N		☐ p-value		☐ p-value	
☐ Indentify comparison for significance values (ex: ArmA vs. ArmB)		☐ RR (95% CI)		☐ RR (95% CI)	
☐ *Significance values adjusted for **gestational age***		☐ HR (95% CI)		☐ HR (95% CI)	
☐ *Significance values adjusted for **birth weight***		☐ OR (95% CI)		☐ OR (95% CI)	
☐ *Significance values adjusted for **race***		☐ Max. adj. p-value		☐ Max. adj. p-value	
☐ *Significance values adjusted for **prenatal steroids***		☐ Max. adj. RR (95% CI)		☐ Max. adj. RR (95% CI)	
☐ *Significance values adjusted for **other***		☐ Max. adj. HR (95% CI)		☐ Max. adj. HR (95% CI)	
☐ *Significance values adjusted for **other***		☐ Max. adj. OR (95% CI)		☐ Max. adj. OR (95% CI)	

Sepsis

46. Measured at:

- ☐ Time post birth OR actual follow-up time (specify units) ☐
- ☐ iNO dosage ☐
- ☐ N ☐
- ☐ Indentify comparison for significance values (ex: ArmA vs. ArmB) ☐
- ☐ *Significance values adjusted for* ***gestational age***
- ☐ *Significance values adjusted for* ***birth weight***
- ☐ *Significance values adjusted for* ***race***
- ☐ *Significance values adjusted for* ***prenatal steroids***
- ☐ *Significance values adjusted for* ***other*** ☐
- ☐ *Significance values adjusted for* ***other*** ☐

47. Diagnosed by positive culture

- ☐ n ☐
- ☐ %n ☐
- ☐ p-value ☐
- ☐ RR (95% CI) ☐
- ☐ HR (95% CI) ☐
- ☐ OR (95% CI) ☐
- ☐ Max. adj. p-value ☐
- ☐ Max. adj. RR (95% CI) ☐
- ☐ Max. adj. HR (95% CI) ☐
- ☐ Max. adj. OR (95% CI) ☐

48. Clinical sepsis

- ☐ Define ☐
- ☐ n ☐
- ☐ %n ☐
- ☐ p-value ☐
- ☐ RR (95% CI) ☐
- ☐ HR (95% CI) ☐
- ☐ OR (95% CI) ☐
- ☐ Max. adj. p-value ☐
- ☐ Max. adj. RR (95% CI) ☐
- ☐ Max. adj. HR (95% CI) ☐
- ☐ Max. adj. OR (95% CI) ☐

49. Undefined sepsis

- ☐ n ☐
- ☐ %n ☐
- ☐ p-value ☐
- ☐ RR (95% CI) ☐
- ☐ HR (95% CI) ☐
- ☐ OR (95% CI) ☐
- ☐ Max. adj. p-value ☐
- ☐ Max. adj. RR (95% CI) ☐
- ☐ Max. adj. HR (95% CI) ☐
- ☐ Max. adj. OR (95% CI) ☐

50. Measured at:

- ☐ Time post birth OR actual follow-up time (specify units) ☐
- ☐ iNO dosage ☐
- ☐ N ☐
- ☐ Indentify comparison for significance values (ex: ArmA vs. ArmB) ☐
- ☐ *Significance values adjusted for* ***gestational age***
- ☐ *Significance values adjusted for* ***birth weight***
- ☐ *Significance values adjusted for* ***race***

51. Diagnosed by positive culture

- ☐ n ☐
- ☐ %n ☐
- ☐ p-value ☐
- ☐ RR (95% CI) ☐
- ☐ HR (95% CI) ☐
- ☐ OR (95% CI) ☐
- ☐ Max. adj. p-value ☐

52. Clinical sepsis

- ☐ Define ☐
- ☐ n ☐
- ☐ %n ☐
- ☐ p-value ☐
- ☐ RR (95% CI) ☐
- ☐ HR (95% CI) ☐
- ☐ OR (95% CI) ☐

53. Undefined sepsis

- ☐ n ☐
- ☐ %n ☐
- ☐ p-value ☐
- ☐ RR (95% CI) ☐
- ☐ HR (95% CI) ☐
- ☐ OR (95% CI) ☐
- ☐ Max. adj. p-value ☐

Indentify comparison for significance values (ex: ArmA vs. ArmB)		RR (95% CI)		p-value		RR (95% CI)	
Significance values adjusted for ***gestational age***		HR (95% CI)		RR (95% CI)		HR (95% CI)	
Significance values adjusted for ***birth weight***		OR (95% CI)		HR (95% CI)		OR (95% CI)	
Significance values adjusted for ***race***		Max. adj. p-value		OR (95% CI)		Max. adj. p-value	
Significance values adjusted for ***prenatal steroids***		Max. adj. RR (95% CI)		Max adj. p-value		Max. adj. RR (95% CI)	
Significance values adjusted for ***other***		Max. adj. HR (95% CI)		Max adj. RR (95% CI)		Max. adj. HR (95% CI)	
Significance values adjusted for ***other***		Max. adj. OR (95% CI)		Max adj. HR (95% CI)		Max. adj. OR (95% CI)	
				Max adj. OR (95% CI)			

54. Measured at:		55. Diagnosed by positive culture		56. Clinical sepsis		57. Undefined sepsis	
Time post birth OR actual follow-up time (specify units)		n		Define		n	
iNO dosage		%n		n		%n	
N		p-value		%n		p-value	
Indentify comparison for significance values (ex: ArmA vs. ArmB)		RR (95% CI)		p-value		RR (95% CI)	
Significance values adjusted for ***gestational age***		HR (95% CI)		RR (95% CI)		HR (95% CI)	
Significance values adjusted for ***birth weight***		OR (95% CI)		HR (95% CI)		OR (95% CI)	
Significance values adjusted for ***race***		Max. adj. p-value		OR (95% CI)		Max. adj. p-value	
Significance values adjusted for ***prenatal steroids***		Max. adj. RR (95% CI)		Max. adj. p-value		Max. adj. RR (95% CI)	
Significance values adjusted for ***other***		Max. adj. HR (95% CI)		Max. adj. RR (95% CI)		Max. adj. HR (95% CI)	
Significance values adjusted for ***other***		Max. adj. OR (95% CI)		Max. adj. HR (95% CI)		Max. adj. OR (95% CI)	

Necrotizing Enterocolitis (NEC)

58. Measured at:		59. Requiring medical treatment		60. Requiring surgical treatment		61. Not defined by above 2 criteria	
☐ Time post birth OR actual follow-up time (specify units)		☐ n		☐ n		☐ n	
☐ iNO dosage		☐ %n		☐ %n		☐ %n	
☐ N		☐ p-value		☐ p-value		☐ p-value	
☐ Indentify comparison for significance values (ex: ArmA vs. ArmB)		☐ RR (95% CI)		☐ RR (95% CI)		☐ RR (95% CI)	
☐ *Significance values adjusted for* ***gestational age***		☐ HR (95% CI)		☐ HR (95% CI)		☐ HR (95% CI)	
☐ *Significance values adjusted for* ***birth weight***		☐ OR (95% CI)		☐ OR (95% CI)		☐ OR (95% CI)	
☐ *Significance values adjusted for* ***race***		☐ Max. adj. p-value		☐ Max. adj. p-value		☐ Max. adj. p-value	
☐ *Significance values adjusted for* ***prenatal steroids***		☐ Max. adj. RR (95% CI)		☐ Max. adj. RR (95% CI)		☐ Max. adj. RR (95% CI)	
☐ *Significance values adjusted for* ***other***		☐ Max. adj. HR (95% CI)		☐ Max. adj. HR (95% CI)		☐ Max. adj. HR (95% CI)	
☐ *Significance values adjusted for* ***other***		☐ Max. adj. OR (95% CI)		☐ Max. adj. OR (95% CI)		☐ Max. adj. OR (95% CI)	

62. Measured at:		63. Requiring medical treatment		64. Requiring surgical treatment		65. Not defined by above 2 criteria	
☐ Time post birth OR actual follow-up time (specify units)		☐ n		☐ n		☐ n	
☐ iNO dosage		☐ %n		☐ %n		☐ %n	
☐ N		☐ p-value		☐ p-value		☐ p-value	
☐ Indentify comparison for significance values (ex: ArmA vs. ArmB)		☐ RR (95% CI)		☐ RR (95% CI)		☐ RR (95% CI)	
☐ *Significance values adjusted for* ***gestational age***		☐ HR (95% CI)		☐ HR (95% CI)		☐ HR (95% CI)	
☐ *Significance values adjusted for* ***birth weight***		☐ OR (95% CI)		☐ OR (95% CI)		☐ OR (95% CI)	

Significance values adjusted for ***race***		Max. adj. p-value		Max. adj. p-value		Max. adj. p-value	
Significance values adjusted for ***prenatal steroids***		Max. adj. RR (95% CI)		Max. adj. RR (95% CI)		Max. adj. RR (95% CI)	
Significance values adjusted for ***other***		Max. adj. HR (95% CI)		Max. adj. HR (95% CI)		Max. adj. HR (95% CI)	
Significance values adjusted for ***other***		Max. adj. OR (95% CI)		Max. adj. OR (95% CI)		Max. adj. OR (95% CI)	

Pulmonary Outcomes

Bronchopulmonary Dysplasia (BPD)

66. Measured at:		67. On O_2 at 36 weeks PMA (post-menstrual age)		68. On O_2 at other end point		69. Duration of time on O_2	
Time post birth OR actual follow-up time (specify units)		n		Define Time Point		Days	
iNO dosage		%n		n		Weeks	
N		p-value		%n		Standard Deviation	
Indentify comparison for significance values (ex: ArmA vs. ArmB)		RR (95% CI)		p-value		p-value	
Significance values adjusted for ***gestational age***		HR (95% CI)		RR (95% CI)		RR (95% CI)	
Significance values adjusted for ***birth weight***		OR (95% CI)		HR (95% CI)		HR (95% CI)	
Significance values adjusted for ***race***		Max. adj. p-value		OR (95% CI)		OR (95% CI)	
Significance values adjusted for ***prenatal steroids***		Max. adj. RR (95% CI)		Max. adj. p-value		Max. adj. p-value	
Significance values adjusted for ***other***		Max. adj. HR (95% CI)		Max. adj. RR (95% CI)		Max. adj. RR (95% CI)	
Significance values adjusted for ***other***		Max. adj. OR (95% CI)		Max. adj. HR (95% CI)		Max. adj. HR (95% CI)	
				Max. adj. OR (95% CI)		Max. adj. OR (95% CI)	

70. Measured at:		71. On O_2 at 36 weeks PMA (post-menstrual age)		72. On O_2 at other end point		73. Duration of time on O_2	
Time post birth OR actual follow-up time (specify units)		n		Define Time Point		Days	
iNO dosage		%n		n		Weeks	
N		p-value		%n		Standard Deviation	
Indentify comparison for significance values (ex: ArmA vs. ArmB)		RR (95% CI)		p-value		p-value	
Significance values adjusted for ***gestational age***		HR (95% CI)		RR (95% CI)		RR (95% CI)	
Significance values adjusted for ***birth weight***		OR (95% CI)		HR (95% CI)		HR (95% CI)	
Significance values adjusted for ***race***		Max. adj. p-value		OR (95% CI)		OR (95% CI)	
Significance values adjusted for ***prenatal steroids***		Max. adj. RR (95% CI)		Max. adj. p-value		Max. adj. p-value	
Significance values adjusted for ***other***		Max. adj. HR (95% CI)		Max. adj. RR (95% CI)		Max. adj. RR (95% CI)	
Significance values adjusted for ***other***		Max. adj. OR (95% CI)		Max. adj. HR (95% CI)		Max. adj. HR (95% CI)	
				Max. adj. OR (95% CI)		Max. adj. OR (95% CI)	

Severe Bronchopulmonary Dysplasia--vent dependant BPD

74. Measured at:

- Time post birth OR actual follow-up time (specify units)
- iNO dosage
- N
- Indentify comparison for significance values (ex: ArmA vs. ArmB)
- ***Significance values adjusted for gestational age***
- ***Significance values adjusted for birth weight*** ***Significance values adjusted for birth weight***
- ***Significance values adjusted for race***
- ***Significance values adjusted for prenatal steroids***
- ***Significance values adjusted for other***
- ***Significance values adjusted for other***

75. On O_2 and ventilation–mechanical

- n
- %n
- p-value
- RR (95% CI)
- HR (95% CI)
- OR (95% CI)
- Max. adj. p-value
- Max. adj. RR (95% CI)
- Max. adj. HR (95% CI
- Max. adj. OR (95% CI)

76. On O_2 and ventilation–cannula

- n
- %n
- p-value
- RR (95% CI)
- HR (95% CI)
- OR (95% CI)
- Max. adj. p-value
- Max. adj. RR (95% CI)
- Max. adj. HR (95% CI)
- Max. adj. OR (95% CI)

77. On O_2 and ventilation--other

- Define
- n
- %n
- p-value
- RR (95% CI)
- HR (95% CI)
- OR (95% CI)
- Max. adj. p-value
- Max. adj. RR (95% CI)
- Max. adj. HR (95% CI)
- Max. adj. OR (95% CI)

78. Duration of Ventilation Support

- Days
- Weeks
- Months
- Standard Deviation
- p-value
- RR (95% CI)
- HR (95% CI)
- OR (95% CI)
- Max. adj. p-value
- Max. adj. RR (95% CI)
- Max. adj. HR (95% CI)
- Max. adj. OR (95% CI)

79. Measured at:

- Time post birth OR actual follow-up time (specify units)
- iNO dosage
- N
- Indentify comparison for significance values (ex: ArmA vs. ArmB)
- ***Significance values adjusted for gestational age***
- ***Significance values adjusted for birth weight*** ***Significance values adjusted for birth weight***
- ***Significance values adjusted for race***
- ***Significance values adjusted for prenatal steroids***
- ***Significance values adjusted for other***
- ***Significance values adjusted for other***

80. On O_2 and ventilation–mechanical

- n
- %n
- p-value
- RR (95% CI)
- HR (95% CI)
- OR (95% CI)
- Max. adj. p-value
- Max. adj. RR (95% CI)
- Max. adj. HR (95% CI
- Max. adj. OR (95% CI)

81. On O_2 and ventilation–cannula

- n
- %n
- p-value
- RR (95% CI)
- HR (95% CI)
- OR (95% CI)
- Max. adj. p-value
- Max. adj. RR (95% CI)
- Max. adj. HR (95% CI)
- Max. adj. OR (95% CI)

82. On O_2 and ventilation--other

- Define
- n
- %n
- p-value
- RR (95% CI)
- HR (95% CI)
- OR (95% CI)
- Max. adj. p-value
- Max. adj. RR (95% CI)
- Max. adj. HR (95% CI)
- Max. adj. OR (95% CI)

83. Duration of Ventilation Support

- Days
- Weeks
- Months
- Standard Deviation
- p-value
- RR (95% CI)
- HR (95% CI)
- OR (95% CI)
- Max. adj. p-value
- Max. adj. RR (95% CI)
- Max. adj. HR (95% CI)
- Max. adj. OR (95% CI)

Hospital Discharge / Readmission

84. Measured at:

- Time post birth OR actual follow-up time (specify units)
- iNO dosage
- N
- Indentify comparison for significance values (ex: ArmA vs. ArmB)
- *Significance values adjusted for* ***gestational age***
- *Significance values adjusted for* ***birth weight***
- *Significance values adjusted for* ***race***
- *Significance values adjusted for* ***prenatal steroids***
- *Significance values adjusted for* ***other***
- *Significance values adjusted for* ***other***

85. Hospital discharge

- n
- %n
- p-value
- RR (95% CI)
- HR (95% CI)
- OR (95% CI)
- Max. adj. p-value
- Max. adj. RR (95% CI)
- Max. adj. HR (95% CI)
- Max. adj. OR (95% CI)

86. Rehospitalization for pulmonary disease

- n
- %n
- p-value
- RR (95% CI)
- HR (95% CI)
- OR (95% CI)
- Max. adj. p-value
- Max. adj. RR (95% CI)
- Max. adj. HR (95% CI)
- Max. adj. OR (95% CI)

87. Duration ofhospitalization

- Days
- Weeks
- Months
- Standard Deviation
- p-value
- RR (95% CI)
- HR (95% CI)
- OR (95% CI)
- Max. adj. p-value
- Max. adj. RR (95% CI)
- Max. adj. HR (95% CI)
- Max. adj. OR (95% CI)

88. Measured at:

- Time post birth OR actual follow-up time (specify units)
- iNO dosage
- N
- Indentify comparison for significance values (ex: ArmA vs. ArmB)
- *Significance values adjusted for* ***gestational age***
- *Significance values adjusted for* ***birth weight***
- *Significance values adjusted for* ***race***
- *Significance values adjusted for* ***prenatal steroids***
- *Significance values adjusted for* ***other***
- *Significance values adjusted for* ***other***

89. Hospital discharge

- n
- %n
- p-value
- RR (95% CI)
- HR (95% CI)
- OR (95% CI)
- Max. adj. p-value
- Max. adj. RR (95% CI)
- Max. adj. HR (95% CI)
- Max. adj. OR (95% CI)

90. Rehospitalization for pulmonary disease

- n
- %n
- p-value
- RR (95% CI)
- HR (95% CI)
- OR (95% CI)
- Max. adj. p-value
- Max. adj. RR (95% CI)
- Max. adj. HR (95% CI)
- Max. adj. OR (95% CI)

91. Duration ofhospitalization

- Days
- Weeks
- Months
- Standard Deviation
- p-value
- RR (95% CI)
- HR (95% CI)
- OR (95% CI)
- Max. adj. p-value
- Max. adj. RR (95% CI)
- Max. adj. HR (95% CI)
- Max. adj. OR (95% CI)

92. Measured at:

- ☐ Time post birth OR actual follow-up time (specify units) ☐
- ☐ iNO dosage ☐
- ☐ N ☐
- ☐ Indentify comparison for significance values (ex: ArmA vs. ArmB) ☐
- ☐ *Significance values adjusted for* ***gestational age***
- ☐ *Significance values adjusted for* ***birth weight***
- ☐ *Significance values adjusted for* ***race***
- ☐ *Significance values adjusted for* ***prenatal steroids***
- ☐ *Significance values adjusted for* ***other*** ☐
- ☐ *Significance values adjusted for* ***other*** ☐

93. Hospital discharge

- ☐ n ☐
- ☐ %n ☐
- ☐ p-value ☐
- ☐ RR (95% CI) ☐
- ☐ HR (95% CI) ☐
- ☐ OR (95% CI) ☐
- ☐ Max. adj. p-value ☐
- ☐ Max. adj. RR (95% CI) ☐
- ☐ Max. adj. HR (95% CI) ☐
- ☐ Max. adj. OR (95% CI) ☐

94. Rehospitalization for pulmonary disease

- ☐ n ☐
- ☐ %n ☐
- ☐ p-value ☐
- ☐ RR (95% CI) ☐
- ☐ HR (95% CI) ☐
- ☐ OR (95% CI) ☐
- ☐ Max. adj. p-value ☐
- ☐ Max. adj. RR (95% CI) ☐
- ☐ Max. adj. HR (95% CI) ☐
- ☐ Max. adj. OR (95% CI) ☐

95. Duration ofhospitalization

- ☐ Days ☐
- ☐ Weeks ☐
- ☐ Months ☐
- ☐ Standard Deviation ☐
- ☐ p-value ☐
- ☐ RR (95% CI) ☐
- ☐ HR (95% CI) ☐
- ☐ OR (95% CI) ☐
- ☐ Max. adj. p-value ☐
- ☐ Max. adj. RR (95% CI) ☐
- ☐ Max. adj. HR (95% CI) ☐
- ☐ Max. adj. OR (95% CI) ☐

Pulmonary Function Test (PFT)

96. Measured at:

- ☐ Time post birth OR actual follow-up time (specify units) ☐
- ☐ iNO dosage ☐
- ☐ N ☐
- ☐ Indentify comparison for significance values (ex: ArmA vs. ArmB) ☐
- ☐ *Significance values adjusted for* ***gestational age***
- ☐ *Significance values adjusted for* ***birth weight***
- ☐ *Significance values adjusted for* ***race***

97. V^1_{max}FRC Z-score

- ☐ Z-score ☐
- ☐ n ☐
- ☐ %n ☐
- ☐ p-value ☐
- ☐ RR (95% CI) ☐
- ☐ HR (95% CI) ☐
- ☐ OR (95% CI) ☐

98. Poor pulmonary function

- ☐ Define ☐
- ☐ n ☐
- ☐ %n ☐
- ☐ p-value ☐
- ☐ RR (95% CI) ☐
- ☐ HR (95% CI) ☐
- ☐ OR (95% CI) ☐

- *Significance values adjusted for* ***prenatal steroids***
- *Significance values adjusted for* ***other***
- *Significance values adjusted for* ***other***

- Max. adj. p-value
- Max. adj. RR (95% CI)
- Max. adj. HR (95% CI)
- Max. adj. OR (95% CI)

- Max. adj. p-value
- Max. adj. RR (95% CI)
- Max. adj. HR (95% CI)
- Max. adj. OR (95% CI)

99. Measured at:

- Time post birth OR actual follow-up time (specify units)
- iNO dosage
- N
- Indentify comparison for significance values (ex: ArmA vs. ArmB)
- *Significance values adjusted for* ***gestational age***
- *Significance values adjusted for* ***birth weight***
- *Significance values adjusted for* ***race***
- *Significance values adjusted for* ***prenatal steroids***
- *Significance values adjusted for* ***other***
- *Significance values adjusted for* ***other***

100. V^{1}_{maxFRC} Z-score

- Z-score
- n
- %n
- p-value
- RR (95% CI)
- HR (95% CI)
- OR (95% CI)
- Max. adj. p-value
- Max. adj. RR (95% CI)
- Max. adj. HR (95% CI)
- Max. adj. OR (95% CI)

101. Poor pulmonary function

- Define
- n
- %n
- p-value
- RR (95% CI)
- HR (95% CI)
- OR (95% CI)
- Max. adj. p-value
- Max. adj. RR (95% CI)
- Max. adj. HR (95% CI)
- Max. adj. OR (95% CI)

102. Measured at:

- Time post birth OR actual follow-up time (specify units)
- iNO dosage
- N
- Indentify comparison for significance values (ex: ArmA vs. ArmB)
- *Significance values adjusted for* ***gestational age***
- *Significance values adjusted for* ***birth weight***
- *Significance values adjusted for* ***race***
- *Significance values adjusted for* ***prenatal steroids***
- *Significance values adjusted for* ***other***
- *Significance values adjusted for* ***other***

103. V^{1}_{maxFRC} Z-score

- Z-score
- n
- %n
- p-value
- RR (95% CI)
- HR (95% CI)
- OR (95% CI)
- Max. adj. p-value
- Max. adj. RR (95% CI)
- Max. adj. HR (95% CI)
- Max. adj. OR (95% CI)

104. Poor pulmonary function

- Define
- n
- %n
- p-value
- RR (95% CI)
- HR (95% CI)
- OR (95% CI)
- Max. adj. p-value
- Max. adj. RR (95% CI)
- Max. adj. HR (95% CI)
- Max. adj. OR (95% CI)

105. Measured at:

- Time post birth OR actual follow-up time (specify units)

106. V^{1}_{maxFRC} Z-score

- Z-score

107. Poor pulmonary function

- Define

☐ iNO dosage		☐ n		☐ n	
☐ N		☐ %n		☐ %n	
☐ Indentify comparison for significance values (ex: ArmA vs. ArmB)		☐ p-value		☐ p-value	
☐ *Significance values adjusted for* ***gestational age***		☐ RR (95% CI)		☐ RR (95% CI)	
☐ *Significance values adjusted for* ***birth weight***		☐ HR (95% CI)		☐ HR (95% CI)	
☐ *Significance values adjusted for* ***race***		☐ OR (95% CI)		☐ OR (95% CI)	
☐ *Significance values adjusted for* ***prenatal steroids***		☐ Max. adj. p-value		☐ Max. adj. p-value	
☐ *Significance values adjusted for* ***other***		☐ Max. adj. RR (95% CI)		☐ Max. adj. RR (95% CI)	
☐ *Significance values adjusted for* ***other***		☐ Max. adj. HR (95% CI)		☐ Max. adj. HR (95% CI	
		☐ Max. adj. OR (95% CI)		☐ Max. adj. OR (95% CI)	

Pulmonary Hypertension

108. Measured at:		109. Diagnosed by echocardiogram		110. Diagnosed by cardiac catheterization	
☐ Time post birth OR actual follow-up time (specify units)		☐ n		☐ n	
☐ iNO dosage		☐ %n		☐ %n	
☐ N		☐ p-value		☐ p-value	
☐ Indentify comparison for significance values (ex: ArmA vs. ArmB)		☐ RR (95% CI)		☐ RR (95% CI)	
☐ *Significance values adjusted for* ***gestational age***		☐ HR (95% CI)		☐ HR (95% CI)	
☐ *Significance values adjusted for* ***birth weight***		☐ OR (95% CI)		☐ OR (95% CI)	
☐ *Significance values adjusted for* ***race***		☐ Max. adj. p-value		☐ Max. adj. p-value	
☐ *Significance values adjusted for* ***prenatal steroids***		☐ Max. adj. RR (95% CI)		☐ Max. adj. RR (95% CI)	
☐ *Significance values adjusted for* ***other***		☐ Max. adj. HR (95% CI)		☐ Max. adj. HR (95% CI)	

☐ *Significance values adjusted for* ***other***	☐ Max. adj. OR (95% CI)	☐ Max. adj. OR (95% CI)
111. Measured at:	112. Diagnosed by echocardiogram	113. Diagnosed by cardiac catheterization
☐ Time post birth OR actual follow-up time (specify units)	☐ n	☐ n
☐ iNO dosage	☐ %n	☐ %n
☐ N	☐ p-value	☐ p-value
☐ Indentify comparison for significance values (ex: ArmA vs. ArmB)	☐ RR (95% CI)	☐ RR (95% CI)
☐ *Significance values adjusted for* ***gestational age***	☐ HR (95% CI)	☐ HR (95% CI)
☐ *Significance values adjusted for* ***birth weight***	☐ OR (95% CI)	☐ OR (95% CI)
☐ *Significance values adjusted for* ***race***	☐ Max. adj. p-value	☐ Max. adj. p-value
☐ *Significance values adjusted for* ***prenatal steroids***	☐ Max. adj. RR (95% CI)	☐ Max. adj. RR (95% CI)
☐ *Significance values adjusted for* ***other***	☐ Max. adj. HR (95% CI)	☐ Max. adj. HR (95% CI)
☐ *Significance values adjusted for* ***other***	☐ Max. adj. OR (95% CI)	☐ Max. adj. OR (95% CI)
114. Measured at:	115. Diagnosed by echocardiogram	116. Diagnosed by cardiac catheterization
☐ Time post birth OR actual follow-up time (specify units)	☐ n	☐ n
☐ iNO dosage	☐ %n	☐ %n
☐ N	☐ p-value	☐ p-value
☐ Indentify comparison for significance values (ex: ArmA vs. ArmB)	☐ RR (95% CI)	☐ RR (95% CI)
☐ *Significance values adjusted for* ***gestational age***	☐ HR (95% CI)	☐ HR (95% CI)
☐ *Significance values adjusted for* ***birth weight***	☐ OR (95% CI)	☐ OR (95% CI)

☐ *Significance values adjusted for* ***race***		☐ Max. adj. p-value		☐ Max. adj. p-value	
☐ *Significance values adjusted for* ***prenatal steroids***		☐ Max. adj. RR (95% CI)		☐ Max. adj. RR (95% CI)	
☐ *Significance values adjusted for* ***other***		☐ Max. adj. HR (95% CI)		☐ Max. adj. HR (95% CI)	
☐ *Significance values adjusted for* ***other***		☐ Max. adj. OR (95% CI)		☐ Max. adj. OR (95% CI)	
117. Measured at:		118. Diagnosed by echocardiogram		119. Diagnosed by cardiac catheterization	
☐ Time post birth OR actual follow-up time (specify units)		☐ n		☐ n	
☐ iNO dosage		☐ %n		☐ %n	
☐ N		☐ p-value		☐ p-value	
☐ Indentify comparison for significance values (ex: ArmA vs. ArmB)		☐ RR (95% CI)		☐ RR (95% CI)	
☐ *Significance values adjusted for* ***gestational age***		☐ HR (95% CI)		☐ HR (95% CI)	
☐ *Significance values adjusted for* ***birth weight***		☐ OR (95% CI)		☐ OR (95% CI)	
☐ *Significance values adjusted for* ***race***		☐ Max. adj. p-value		☐ Max. adj. p-value	

Significance values adjusted for ***prenatal steroids***		Max. adj. RR (95% CI)		Max. adj. RR (95% CI)			
Significance values adjusted for ***other***		Max. adj. HR (95% CI)		Max. adj. HR (95% CI)			
Significance values adjusted for ***other***		Max. adj. OR (95% CI)		Max. adj. OR (95% CI)			

Chornic Lung Disease

120. Measured at:		121. Asthma		122. Wheezing		123. Feeding tube	
Time post birth OR actual follow-up time (specify units)		n		n		n	
iNO dosage		%n		%n		%n	
N		p-value		p-value		p-value	
Indentify comparison for significance values (ex: ArmA vs. ArmB)		RR (95% CI)		RR (95% CI)		RR (95% CI)	
Significance values adjusted for ***gestational age***		HR (95% CI)		HR (95% CI)		HR (95% CI)	
Significance values adjusted for ***birth weight***		OR (95% CI)		OR (95% CI)		OR (95% CI)	
Significance values adjusted for ***race***		Max. adj. p-value		Max. adj. p-value		Max. adj. p-value	
Significance values adjusted for ***prenatal steroids***		Max. adj. RR (95% CI)		Max. adj. RR (95% CI)		Max. adj. RR (95% CI)	
Significance values adjusted for ***other***		Max. adj. HR (95% CI)		Max. adj. HR (95% CI)		Max. adj. HR (95% CI)	
Significance values adjusted for ***other***		Max. adj. OR (95% CI)		Max. adj. OR (95% CI)		Max. adj. OR (95% CI)	

124. Measured at:		125. Asthma		126. Wheezing		127. Feeding tube	
Time post birth OR actual follow-up time (specify units)		n		n		n	
iNO dosage		%n		%n		%n	
N		p-value		p-value		p-value	
Indentify comparison for significance values (ex: ArmA vs. ArmB)		RR (95% CI)		RR (95% CI)		RR (95% CI)	
Significance values adjusted for ***gestational age***		HR (95% CI)		HR (95% CI)		HR (95% CI)	
Significance values adjusted for ***birth weight***		OR (95% CI)		OR (95% CI)		OR (95% CI)	

Significance values adjusted for ***race***		Max. adj. p-value		Max. adj. p-value		Max. adj. p-value	
Significance values adjusted for ***prenatal steroids***		Max. adj. RR (95% CI)		Max. adj. RR (95% CI)		Max. adj. RR (95% CI)	
Significance values adjusted for ***other***		Max. adj. HR (95% CI)		Max. adj. HR (95% CI)		Max. adj. HR (95% CI)	
Significance values adjusted for ***other***		Max. adj. OR (95% CI)		Max. adj. OR (95% CI)		Max. adj. OR (95% CI)	
128. Measured at:		129. Asthma		130. Wheezing		131. Feeding tube	
Time post birth OR actual follow-up time (specify units)		n		n		n	
iNO dosage		%n		%n		%n	
N		p-value		p-value		p-value	
Indentify comparison for significance values (ex: ArmA vs. ArmB)		RR (95% CI)		RR (95% CI)		RR (95% CI)	
Significance values adjusted for ***gestational age***		HR (95% CI)		HR (95% CI)		HR (95% CI)	
Significance values adjusted for ***birth weight***		OR (95% CI)		OR (95% CI)		OR (95% CI)	
Significance values adjusted for ***race***		Max. adj. p-value		Max. adj. p-value		Max. adj. p-value	
Significance values adjusted for ***prenatal steroids***		Max. adj. RR (95% CI)		Max. adj. RR (95% CI)		Max. adj. RR (95% CI)	
Significance values adjusted for ***other***		Max. adj. HR (95% CI)		Max. adj. HR (95% CI)		Max. adj. HR (95% CI)	
Significance values adjusted for ***other***		Max. adj. OR (95% CI)		Max. adj. OR (95% CI)		Max. adj. OR (95% CI)	
132. Measured at:		133. Asthma		134. Wheezing		135. Feeding tube	
Time post birth OR actual follow-up time (specify units)		n		n		n	
iNO dosage		%n		%n		%n	
N		p-value		p-value		p-value	
Indentify comparison for significance values (ex: ArmA vs. ArmB)		RR (95% CI)		RR (95% CI)		RR (95% CI)	
Significance values adjusted for ***gestational age***		HR (95% CI)		HR (95% CI)		HR (95% CI)	
Significance values adjusted for ***birth weight***		OR (95% CI)		OR (95% CI)		OR (95% CI)	

Significance values adjusted for ***race***		Max. adj. p-value		Max. adj. p-value		Max. adj. p-value	
Significance values adjusted for ***prenatal steroids***		Max. adj. RR (95% CI)		Max. adj. RR (95% CI)		Max. adj. RR (95% CI)	
Significance values adjusted for ***other***		Max. adj. HR (95% CI)		Max. adj. HR (95% CI)		Max. adj. HR (95% CI)	
Significance values adjusted for ***other***		Max. adj. OR (95% CI)		Max. adj. OR (95% CI)		Max. adj. OR (95% CI)	
132. Measured at:		133. Asthma		134. Wheezing		135. Feeding tube	
Time post birth OR actual follow-up time (specify units)		n		n		n	
iNO dosage		%n		%n		%n	
N		p-value		p-value		p-value	
Indentify comparison for significance values (ex: ArmA vs. ArmB)		RR (95% CI)		RR (95% CI)		RR (95% CI)	
Significance values adjusted for ***gestational age***		HR (95% CI)		HR (95% CI)		HR (95% CI)	
Significance values adjusted for ***birth weight***		OR (95% CI)		OR (95% CI)		OR (95% CI)	
Significance values adjusted for ***race***		Max. adj. p-value		Max. adj. p-value		Max. adj. p-value	
Significance values adjusted for ***prenatal steroids***		Max. adj. RR (95% CI)		Max. adj. RR (95% CI)		Max. adj. RR (95% CI)	
Significance values adjusted for ***other***		Max. adj. HR (95% CI)		Max. adj. HR (95% CI)		Max. adj. HR (95% CI)	
Significance values adjusted for ***other***		Max. adj. OR (95% CI)		Max. adj. OR (95% CI)		Max. adj. OR (95% CI)	

Other Pulmonary Outcomes

136. Measured at:		137. Right heart disease--diagosed by echocardiogram		138. Tracheostomy		139. Pulmonary hemorrhage	
Time post birth OR actual follow-up time (specify units)		n		n		n	
iNO dosage		%n		%n		%n	

Other Pulmonary Outcomes

136. Measured at:		137. Right heart disease--diagosed by echocardiogram		138. Tracheostomy		139. Pulmonary hemorrhage		140. Air leak		141. Other		142. Other	
Time post birth OR actual follow-up time (specify units)		n		n		n		n		Define		Define	
iNO dosage		%n		%n		%n		%n		n		n	

N	p-value	p-value	p-value	p-value	%n	%n
Indentify comparison for significance values (ex: ArmA vs. ArmB)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	p-value	p-value
Significance values adjusted for ***gestational age***	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	RR (95% CI)	RR (95% CI)
Significance values adjusted for ***birth weight***	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	HR (95% CI)	HR (95% CI)
Significance values adjusted for ***race***	Max. adj. p-value	Max. adj. p-value	Max. adj. p-value	Max. adj. p-value	OR (95% CI)	OR (95% CI)
Significance values adjusted for ***prenatal steroids***	Max. adj. RR (95% CI)	Max. adj. RR (95% CI)	Max. adj. RR (95% CI)	Max. adj. RR (95% CI)	Max. adj. p-value	Max. adj. p-value
Significance values adjusted for ***other***	Max. adj. HR (95% CI)	Max. adj. HR (95% CI)	Max. adj. HR (95% CI	Max. adj. HR (95% CI)	Max. adj. RR (95% CI)	Max. adj. RR (95% CI)
Significance values adjusted for ***other***	Max. adj. OR (95% CI)	Max. adj. OR (95% CI)	Max. adj. OR (95% CI)	Max. adj. OR (95% CI)	Max. adj. HR (95% CI)	Max. adj. HR (95% CI)
					Max. adj. OR (95% CI)	Max. adj. OR (95% CI)

143. Measured at:	144. Right heart disease--diagosed by echocardiogram	145. Tracheostomy	146. Pulmonary hemorrhage	147. Air leak	148. Other	149. Other
Time post birth OR actual follow-up time (specify units)	n	n	n	n	Define	Define
iNO dosage	%n	%n	%n	%n	n	n
N	p-value	p-value	p-value	p-value	%n	%n
Indentify comparison for significance values (ex: ArmA vs. ArmB)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	p-value	p-value
Significance values adjusted for ***gestational age***	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	RR (95% CI)	RR (95% CI)
Significance values adjusted for ***birth weight***	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	HR (95% CI)	HR (95% CI)
Significance values adjusted for ***race***	Max. adj. p-value	Max. adj. p-value	Max. adj. p-value	Max. adj. p-value	OR (95% CI)	OR (95% CI)
Significance values adjusted for ***prenatal steroids***	Max. adj. RR (95% CI)	Max. adj. RR (95% CI)	Max. adj. RR (95% CI)	Max. adj. RR (95% CI)	Max. adj. p-value	Max. adj. p-value
Significance values adjusted for ***other***	Max. adj. HR (95% CI)	Max. adj. HR (95% CI)	Max. adj. HR (95% CI)	Max. adj. HR (95% CI)	Max. adj. RR (95% CI)	Max. adj. RR (95% CI)
Significance values adjusted for ***other***	Max. adj. OR (95% CI)	Max. adj. OR (95% CI)	Max. adj. OR (95% CI)	Max. adj. OR (95% CI)	Max. adj. HR (95% CI)	Max. adj. HR (95% CI)
					Max. adj. OR (95% CI)	Max. adj. OR (95% CI)

150. Measured at:	151. Right heart disease--diagosed by echocardiogram	152. Tracheostomy	153. Pulmonary hemorrhage	154. Air leak	155. Other	156. Other
Time post birth OR actual follow-up time (specify units)	n	n	n	n	Define	Define
iNO dosage	%n	%n	%n	%n	n	n
N	p-value	p-value	p-value	p-value	%n	%n
Indentify comparison for significance values (ex: ArmA vs. ArmB)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	p-value	p-value
Significance values adjusted for ***gestational age***	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	RR (95% CI)	RR (95% CI)
Significance values adjusted for ***birth weight***	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	HR (95% CI)	HR (95% CI)
Significance values adjusted for ***race***	Max. adj. p-value	Max. adj. p-value	Max. adj. p-value	Max. adj. p-value	OR (95% CI)	OR (95% CI)
Significance values adjusted for ***prenatal steroids***	Max. adj. RR (95% CI)	Max. adj. RR (95% CI)	Max. adj. RR (95% CI)	Max. adj. RR (95% CI)	Max. adj. p-value	Max. adj. p-value
Significance values adjusted for ***other***	Max. adj. HR (95% CI)	Max. adj. HR (95% CI)	Max. adj. HR (95% CI)	Max. adj. HR (95% CI)	Max. adj. RR (95% CI)	Max. adj. RR (95% CI)
Significance values adjusted for ***other***	Max. adj. OR (95% CI)	Max. adj. OR (95% CI)	Max. adj. OR (95% CI)	Max. adj. OR (95% CI)	Max. adj. HR (95% CI)	Max. adj. HR (95% CI)

157. Measured at:	158. Right heart disease--diagosed by echocardiogram	159. Tracheostomy	160. Pulmonary hemorrhage	161. Air leak	162. Other	163. Other
Time post birth OR actual follow-up time (specify units)	n	n	n	n	Define	Define
iNO dosage	%n	%n	%n	%n	n	n
N	p-value	p-value	p-value	p-value	%n	%n
Indentify comparison for significance values (ex: ArmA vs. ArmB)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	p-value	p-value
Significance values adjusted for ***gestational age***	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	RR (95% CI)	RR (95% CI)
Significance values adjusted for ***birth weight***	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	HR (95% CI)	HR (95% CI)
Significance values adjusted for ***race***	Max. adj. p-value	Max. adj. p-value	Max. adj. p-value	Max. adj. p-value	OR (95% CI)	OR (95% CI)
Significance values adjusted for ***prenatal steroids***	Max. adj. RR (95% CI)	Max. adj. RR (95% CI)	Max. adj. RR (95% CI)	Max. adj. RR (95% CI)	Max. adj. p-value	Max. adj. p-value
Significance values adjusted for ***other***	Max. adj. HR (95% CI)	Max. adj. HR (95% CI)	Max. adj. HR (95% CI)	Max. adj. HR (95% CI)	Max. adj. RR (95% CI)	Max. adj. RR (95% CI)
Significance values adjusted for ***other***	Max. adj. OR (95% CI)	Max. adj. OR (95% CI)	Max. adj. OR (95% CI)	Max. adj. OR (95% CI)	Max. adj. HR (95% CI)	Max. adj. HR (95% CI)
					Max. adj. OR (95% CI)	Max. adj. OR (95% CI)

Respiratory Medications

164. Measured at:	165. Steroids, inhaled or systemic (specify)	166. Duration on steroids	167. Bronchodilators	168. Duration on bronchodilators	169. Diuretics	170. Duration on diuretics	171. Pulmonary
Time post birth OR actual follow-up time (specify units)	Specify	Mean	n	Mean	n	Mean	n
iNO dosage	n	SD	%n	SD	%n	SD	%n
N	%n	Median	p-value	Median	p-value	Median	p-value
Indentify comparison for significance values (ex: ArmA vs. ArmB)	p-value	Range	RR (95% CI)	Range	RR (95% CI)	Range	RR (95% CI)
Significance values adjusted for ***gestational age***	RR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)
Significance values adjusted for ***birth weight***		RR (95% CI)	OR (95% CI)	RR (95% CI)	OR (95% CI)	RR (95% CI)	OR (95% CI)

Respiratory Medications

164. Measured at:	165. Steroids, inhaled or systemic (specify)	166. Duration on steroids	167. Bronchodilators	168. Duration on bronchodilators	169. Diuretics	170. Duration on diuretics	171. Pulmonary vasodilators or sildenafil	172. Duration on pulmonary vasodilators or sildenafil
Time post birth OR actual follow-up time (specify units)	Specify	Mean	n	Mean	n	Mean	n	Mean
iNO dosage	n	SD	%n	SD	%n	SD	%n	SD
N	%n	Median	p-value	Median	p-value	Median	p-value	Median
Indentify comparison for significance values (ex: ArmA vs. ArmB)	p-value	Range	RR (95%CI)	Range	RR (95%CI)	Range	RR (95%CI)	Range
Significance values adjusted for ***gestational age***	RR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value
Significance values adjusted for ***birth weight***		RR (95%CI)	OR (95%CI)	RR (95%CI)	OR (95%CI)	RR (95%CI)	OR (95%CI)	
Significance values adjusted for ***race***	HR (95%CI)	HR (95%CI)	Max.adj. p-value	HR (95%CI)	Max.adj. p-value	HR (95%CI)	Max.adj. p-value	RR (95%CI)
Significance values adjusted for ***prenatal steroids***	OR (95%CI)	OR (95%CI)	Max.adj. RR (95%CI)	OR (95%CI)	Max.adj. RR (95%CI)	OR (95%CI)	Max.adj. RR (95%CI)	HR (95%CI)
Significance values adjusted for ***other***	Max.adj. p-value	Max.adj. p-value	Max.adj. HR (95%CI)	Max.adj. p-value	Max.adj. HR (95%CI)	Max.adj. p-value	Max.adj. HR (95%CI)	OR (95%CI)
Significance values adjusted for ***other***	Max.adj. RR (95%CI)	Max.adj. RR (95%CI)	Max.adj. OR (95%CI)	Max.adj. RR (95%CI)	Max.adj. OR (95%CI)	Max.adj. RR (95%CI)	Max.adj. OR (95%CI)	Max.adj. p-value
	Max.adj. HR (95%CI)	Max.adj. HR (95%CI)		Max.adj. HR (95%CI)		Max.adj. HR (95%CI)		Max.adj. RR (95%CI)
	Max.adj. OR (95%CI)	Max.adj. OR (95%CI)		Max.adj. OR (95%CI)		Max.adj. OR (95%CI)		Max.adj. HR (95%CI)
								Max.adj. OR (95%CI)

Neurodevelopmental Outcomes

Intraventricular Hemorrhage (IVH)

173. Measured at:	174. All Grades	175. Grades 1 and 2 (not severe)	176. Grades 3 and 4 (severe)	177. Grades 3 and 4 (severe) and / or PVL
Time post birth OR actual follow-up time (specify units)	n	n	n	n
iNO dosage	%n	%n	%n	%n
N	p-value	p-value	p-value	p-value
Indentify comparison for significance values (ex: ArmA vs. ArmB)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
Significance values adjusted for ***gestational age***	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Significance values adjusted for ***birth weight***	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Significance values adjusted for ***race***	Max. adj. p-value	Max. adj. p-value	Max. adj. p-value	Max. adj. p-value
Significance values adjusted for ***prenatal steroids***	Max. adj. RR (95% CI)	Max. adj. RR (95% CI)	Max. adj. RR (95% CI)	Max. adj. RR (95% CI)
Significance values adjusted for ***other***	Max. adj. HR (95% CI)	Max. adj. HR (95% CI)	Max. adj. HR (95% CI)	Max. adj. HR (95% CI)
Significance values adjusted for ***other***	Max. adj. OR (95% CI)	Max. adj. OR (95% CI)	Max. adj. OR (95% CI)	Max. adj. OR (95% CI)

178. Measured at:	179. All Grades	180. Grades 1 and 2 (not severe)	181. Grades 3 and 4 (severe)	182. Grades 3 and 4 (severe) and / or PVL
Time post birth OR actual follow-up time (specify units)	n	n	n	n
iNO dosage	%n	%n	%n	%n
N	p-value	p-value	p-value	P-value
Indentify comparison for significance values (ex: ArmA vs. ArmB)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
Significance values adjusted for ***gestational age***	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Significance values adjusted for ***birth weight***	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Significance values adjusted for ***race***	Max. adj. p-value	Max. adj. p-value	Max. adj. p-value	Max. adj. P-value
Significance values adjusted for ***prenatal steroids***	Max. adj. RR (95% CI)	Max. adj. RR (95% CI)	Max. adj. RR (95% CI)	Max. adj. RR (95% CI)
Significance values adjusted for ***other***	Max. adj. HR (95% CI)	Max. adj. HR (95% CI)	Max. adj. HR (95% CI)	Max. adj. HR (95% CI)
Significance values adjusted for ***other***	Max. adj. OR (95% CI)	Max. adj. OR (95% CI)	Max. adj. OR (95% CI)	Max. adj. OR (95% CI)

White Matter Injury (WMI) and Periventricular Leukomalacia (PVL)

183. Measured at:

- ☐ Time post birth OR actual follow-up time (specify units) ☐
- ☐ iNO dosage ☐
- ☐ N ☐
- ☐ Indentify comparison for significance values (ex: ArmA vs. ArmB) ☐
- ☐ *Significance values adjusted for* ***gestational age***
- ☐ *Significance values adjusted for* ***birth weight***
- ☐ *Significance values adjusted for* ***race***
- ☐ *Significance values adjusted for* ***prenatal steroids***
- ☐ *Significance values adjusted for* ***other*** ☐
- ☐ *Significance values adjusted for* ***other*** ☐

184. White Matter Injury

- ☐ Define ☐
- ☐ n ☐
- ☐ %n ☐
- ☐ p-value ☐
- ☐ RR (95% CI) ☐
- ☐ HR (95% CI) ☐
- ☐ OR (95% CI) ☐
- ☐ Max. adj. p-value ☐
- ☐ Max. adj. RR (95% CI) ☐
- ☐ Max. adj. HR (95% CI) ☐
- ☐ Max. adj. OR (95% CI) ☐

185. Periventricular Leukomalacia (PVL)

- ☐ n ☐
- ☐ %n ☐
- ☐ p-value ☐
- ☐ RR (95% CI) ☐
- ☐ HR (95% CI) ☐
- ☐ OR (95% CI) ☐
- ☐ Max. adj. p-value ☐
- ☐ Max. adj. RR (95% CI) ☐
- ☐ Max. adj. HR (95% CI) ☐
- ☐ Max. adj. OR (95% CI) ☐

186. Measured at:

- ☐ Time post birth OR actual follow-up time (specify units) ☐
- ☐ iNO dosage ☐
- ☐ N ☐
- ☐ Indentify comparison for significance values (ex: ArmA vs. ArmB) ☐
- ☐ *Significance values adjusted for* ***gestational age***
- ☐ *Significance values adjusted for* ***birth weight***
- ☐ *Significance values adjusted for* ***race***

187. White Matter Injury

- ☐ Define ☐
- ☐ n ☐
- ☐ %n ☐
- ☐ p-value ☐
- ☐ RR (95% CI) ☐
- ☐ HR (95% CI) ☐
- ☐ OR (95% CI) ☐

188. Periventricular Leukomalacia (PVL)

- ☐ n ☐
- ☐ %n ☐
- ☐ p-value ☐
- ☐ RR (95% CI) ☐
- ☐ HR (95% CI) ☐
- ☐ OR (95% CI) ☐
- ☐ Max. adj. p-value ☐

- [ ] *Significance values adjusted for* ***prenatal steroids***
- [ ] *Significance values adjusted for* ***other*** [ ]
- [ ] *Significance values adjusted for* ***other*** [ ]

- [ ] Max. adj. p-value [ ]
- [ ] Max. adj. RR (95% CI) [ ]
- [ ] Max. adj. HR (95% CI) [ ]
- [ ] Max. adj. OR (95% CI) [ ]

- [ ] Max. adj. RR (95% CI) [ ]
- [ ] Max. adj. HR (95% CI) [ ]
- [ ] Max. adj. OR (95% CI) [ ]

189. Measured at:

- [ ] Time post birth OR actual follow-up time (specify units) [ ]
- [ ] iNO dosage [ ]
- [ ] N [ ]
- [ ] Indentify comparison for significance values (ex: ArmA vs. ArmB) [ ]
- [ ] *Significance values adjusted for* ***gestational age***
- [ ] *Significance values adjusted for* ***birth weight***
- [ ] *Significance values adjusted for* ***race***
- [ ] *Significance values adjusted for* ***prenatal steroids***
- [ ] *Significance values adjusted for* ***other*** [ ]
- [ ] *Significance values adjusted for* ***other*** [ ]

190. White Matter Injury

- [ ] Define [ ]
- [ ] n [ ]
- [ ] %n [ ]
- [ ] p-value [ ]
- [ ] RR (95% CI) [ ]
- [ ] HR (95% CI) [ ]
- [ ] OR (95% CI) [ ]
- [ ] Max. adj. p-value [ ]
- [ ] Max. adj. RR (95% CI)
- [ ] Max. adj. HR (95% CI) [ ]
- [ ] Max. adj. OR (95% CI) [ ]

191. Periventricular Leukomalacia (PVL)

- [ ] n [ ]
- [ ] %n [ ]
- [ ] p-value [ ]
- [ ] RR (95% CI) [ ]
- [ ] HR (95% CI) [ ]
- [ ] OR (95% CI) [ ]
- [ ] Max. adj. p-value [ ]
- [ ] Max. adj. RR (95% CI) [ ]
- [ ] Max. adj. HR (95% CI) [ ]
- [ ] Max. adj. OR (95% CI) [ ]

192. Measured at:

- [ ] Time post birth OR actual follow-up time (specify units) [ ]
- [ ] iNO dosage [ ]
- [ ] N [ ]
- [ ] Indentify comparison for significance values (ex: ArmA vs. ArmB) [ ]
- [ ] *Significance values adjusted for* ***gestational age***
- [ ] *Significance values adjusted for* ***birth weight***
- [ ] *Significance values adjusted for* ***race***
- [ ] *Significance values adjusted for* ***prenatal steroids***
- [ ] *Significance values adjusted for* ***other*** [ ]
- [ ] *Significance values adjusted for* ***other*** [ ]

193. White Matter Injury

- [ ] Define [ ]
- [ ] n [ ]
- [ ] %n [ ]
- [ ] p-value [ ]
- [ ] RR (95% CI) [ ]
- [ ] HR (95% CI) [ ]
- [ ] OR (95% CI) [ ]
- [ ] Max adj. p-value [ ]
- [ ] Max adj. RR (95% CI) [ ]
- [ ] Max adj. HR (95% CI)
- [ ] Max adj. OR (95% CI) [ ]

194. Periventricular Leukomalacia (PVL)

- [ ] n [ ]
- [ ] %n [ ]
- [ ] p-value [ ]
- [ ] RR (95% CI) [ ]
- [ ] HR (95% CI) [ ]
- [ ] OR (95% CI) [ ]
- [ ] Max. adj. p-value [ ]
- [ ] Max. adj. RR (95% CI) [ ]
- [ ] Max. adj. HR (95% CI) [ ]
- [ ] Max. adj. OR (95% CI) [ ]

Cerebral Palsy (CP)

195. Measured at:		196. All CP		197. Mild CP		198. Moderate or severe CP	
Time post birth OR actual follow-up time (specify units)		n		Define		Define	
iNO dosage		%n		n		n	
N		p-value		%n		%n	
Indentify comparison for significance values (ex: ArmA vs. ArmB)		RR (95% CI)		p-value		p-value	
*Significance values adjusted for **gestational age***		HR (95% CI)		RR (95% CI)		RR (95% CI)	
*Significance values adjusted for **birth weight***		OR (95% CI)		HR (95% CI)		HR (95% CI)	
*Significance values adjusted for **race***		Max. adj. p-value		OR (95% CI)		OR (95% CI)	
*Significance values adjusted for **prenatal steroids***		Max. adj. RR (95% CI)		Max. adj. p-value		Max. adj. p-value	
*Significance values adjusted for **other***		Max. adj. HR (95% CI)		Max. adj. RR (95% CI)		Max. adj. RR (95% CI)	
*Significance values adjusted for **other***		Max. adj. OR (95% CI)		Max. adj. HR (95% CI)		Max. adj. HR (95% CI)	
				Max. adj. OR (95% CI)		Max. adj. OR (95% CI)	

199. Measured at:		200. All CP		201. Mild CP		202. Moderate or severe CP	
Time post birth OR actual follow-up time (specify units)		n		Define		Define	
iNO dosage		%n		n		n	
N		p-value		%n		%n	
Indentify comparison for significance values (ex: ArmA vs. ArmB)		RR (95% CI)		p-value		p-value	
*Significance values adjusted for **gestational age***		HR (95% CI)		RR (95% CI)		RR (95% CI)	
*Significance values adjusted for **birth weight***		OR (95% CI)		HR (95% CI)		HR (95% CI)	
*Significance values adjusted for **race***		Max. adj. p-value		OR (95% CI)		OR (95% CI)	
*Significance values adjusted for **race***		Max. adj. p-value		OR (95% CI)		OR (95% CI)	
*Significance values adjusted for **prenatal steroids***		Max. adj. RR (95% CI)		Max. adj. p-value		Max. adj. p-value	
*Significance values adjusted for **other***		Max. adj. HR (95% CI)		Max. adj. RR (95% CI)		Max. adj. RR (95% CI)	
*Significance values adjusted for **other***		Max. adj. OR (95% CI)		Max. adj. HR (95% CI)		Max. adj. HR (95% CI)	
				Max. adj. OR (95% CI)		Max. adj. OR (95% CI)	

203. Measured at:		204. All CP		205. Mild CP		206. Moderate or severe CP	
☐ Time post birth OR actual follow-up time (specify units)		☐ n		☐ Define		☐ Define	
☐ iNO dosage		☐ %n		☐ n		☐ n	
☐ N		☐ p-value		☐ %n		☐ %n	
☐ Indentify comparison for significance values (ex: ArmA vs. ArmB)		☐ RR (95% CI)		☐ p-value		☐ p-value	
☐ *Significance values adjusted for* ***gestational age***		☐ HR (95% CI)		☐ RR (95% CI)		☐ RR (95% CI)	
☐ *Significance values adjusted for* ***birth weight***		☐ OR (95% CI)		☐ HR (95% CI)		☐ HR (95% CI)	
☐ *Significance values adjusted for* ***race***		☐ Max. adj. p-value		☐ OR (95% CI)		☐ OR (95% CI)	
☐ *Significance values adjusted for* ***prenatal steroids***		☐ Max. adj. RR (95% CI)		☐ Max. adj. p-value		☐ Max. adj. p-value	
☐ *Significance values adjusted for* ***other***		☐ Max. adj. HR (95% CI)		☐ Max. adj. RR (95% CI)		☐ Max. adj. RR (95% CI)	
☐ *Significance values adjusted for* ***other***		☐ Max. adj.OR (95% CI)		☐ Max. adj. HR (95% CI)		☐ Max. adj. HR (95% CI)	
				☐ Max. adj. OR (95% CI)		☐ Max. adj. OR (95% CI)	

207. Measured at:		208. All CP		209. Mild CP		210. Moderate or severe CP	
☐ Time post birth OR actual follow-up time (specify units)		☐ n		☐ Define		☐ Define	
☐ iNO dosage		☐ %n		☐ n		☐ n	
☐ N		☐ p-value		☐ %n		☐ %n	
☐ Indentify comparison for significance values (ex: ArmA vs. ArmB)		☐ RR (95% CI)		☐ p-value		☐ p-value	
☐ *Significance values adjusted for* ***gestational age***		☐ HR (95% CI)		☐ RR (95% CI)		☐ RR (95% CI)	
☐ *Significance values adjusted for* ***birth weight***		☐ OR (95% CI)		☐ HR (95% CI)		☐ HR (95% CI)	
☐ *Significance values adjusted for* ***race***		☐ Max. adj. p-value		☐ OR (95% CI)		☐ OR (95% CI)	
☐ *Significance values adjusted for* ***prenatal steroids***		☐ Max. adj. RR (95% CI)		☐ Max. adj. p-value		☐ Max. adj. p-value	
☐ *Significance values adjusted for* ***other***		☐ Max. adj. HR (95% CI)		☐ Max. adj. RR (95% CI)		☐ Max. adj. RR (95% CI)	
☐ *Significance values adjusted for* ***other***		☐ Max. adj. OR (95% CI)		☐ Max. adj. HR (95% CI)		☐ Max. adj. HR (95% CI)	
				☐ Max. adj. OR (95% CI)		☐ Max. adj. OR (95% CI)	

Visual acuity/impairment

211. Measured at:		212. Any		213. Strabismus / Squint		214. Blindness		215. Other	
Time post birth OR actual follow-up time (specify units)		n		n		n		Define	
iNO dosage		%n		%n		%n		n	
N		unilateral		unilateral		unilateral		%n	
Indentify comparison for significance values (ex: ArmA vs. ArmB)		p-value		p-value		p-value		unilateral	
*Significance values adjusted for **gestational age***		RR (95% CI)		RR (95% CI)		RR (95% CI)		p-value	
*Significance values adjusted for **birth weight***		HR (95% CI)		HR (95% CI)		HR (95% CI)		RR (95% CI)	
*Significance values adjusted for **race***		OR (95% CI)		OR (95% CI)		OR (95% CI)		HR (95% CI)	
*Significance values adjusted for **prenatal steroids***		Max. adj. p-value		Max. adj. p-value		Max. adj. p-value		OR (95% CI)	
*Significance values adjusted for **other***		Max. adj. RR (95% CI)		Max. adj. RR (95% CI)		Max. adj. RR (95% CI)		Max. adj. p-value	
*Significance values adjusted for **other***		Max. adj. HR (95% CI)		Max. adj. HR (95% CI)		Max. adj. HR (95% CI)		Max. adj. RR (95% CI)	
		Max. adj. OR (95% CI)		Max. adj. OR (95% CI)		Max. adj. OR (95% CI)		Max. adj. HR (95% CI)	
								Max. adj. OR (95% CI)	

216. Measured at:		217. Any		218. Strabismus / Squint		219. Blindness		220. Other	
Time post birth OR actual follow-up time (specify units)		n		n		n		Define	
iNO dosage		%n		%n		%n		n	
N		unilateral		unilateral		unilateral		%n	
Indentify comparison for significance values (ex: ArmA vs. ArmB)		p-value		p-value		p-value		unilateral	
*Significance values adjusted for **gestational age***		RR (95% CI)		RR (95% CI)		RR (95% CI)		p-value	
*Significance values adjusted for **birth weight***		HR (95% CI)		HR (95% CI)		HR (95% CI)		RR (95% CI)	
*Significance values adjusted for **race***		OR (95% CI)		OR (95% CI)		OR (95% CI)		HR (95% CI)	
*Significance values adjusted for **prenatal steroids***		Max. adj. p-value		Max. adj. p-value		Max. adj. p-value		OR (95% CI)	
*Significance values adjusted for **other***		Max. adj. RR (95% CI)		Max. adj. RR (95% CI)		Max. adj. RR (95% CI)		Max. adj. p-value	
*Significance values adjusted for **other***		Max. adj. HR (95% CI)		Max. adj. HR (95% CI)		Max. adj. HR (95% CI)		Max. adj. RR (95% CI)	
		Max. adj. OR (95% CI)		Max. adj. OR (95% CI)		Max. adj. OR (95% CI)		Max. adj. HR (95% CI)	
								Max. adj. OR (95% CI)	

221. Measured at:		222. Any		223. Strabismus / Squint		224. Blindness		225. Other	
Time post birth OR actual follow-up time (specify units)		n		n		n		Define	

iNO dosage		%n		%n		%n		n	
N		unilateral		unilateral		unilateral		%n	
Indentify comparison for significance values (ex: ArmA vs. ArmB)		p-value		p-value		p-value		unilateral	
*Significance values adjusted for **gestational age***		RR (95% CI)		RR (95% CI)		RR (95% CI)		p-value	
*Significance values adjusted for **birth weight***		HR (95% CI)		HR (95% CI)		HR (95% CI)		RR (95% CI)	
*Significance values adjusted for **race***		OR (95% CI)		OR (95% CI)		OR (95% CI)		HR (95% CI)	
*Significance values adjusted for **prenatal steroids***		Max. adj. p-value		Max. adj. p-value		Max. adj. p-value		OR (95% CI)	
*Significance values adjusted for **other***		Max. adj. RR (95% CI)		Max. adj. RR (95% CI)		Max. adj. RR (95% CI)		Max. adj. p-value	
*Significance values adjusted for **other***		Max. adj. HR (95% CI)		Max. adj. HR (95% CI)		Max. adj. HR (95% CI)		Max. adj. RR (95% CI)	
		Max. adj. OR (95% CI)		Max. adj. OR (95% CI)		Max. adj. OR (95% CI)		Max. adj. HR (95% CI)	
								Max. adj. OR (95% CI)	

226. Measured at:		227. Any		228. Strabismus / Squint		229. Blindness		230. Other	
Time post birth OR actual follow-up time (specify units)		n		n		n		Define	
iNO dosage		%n		%n		%n		n	
N		unilateral		unilateral		unilateral		%n	
Indentify comparison for significance values (ex: ArmA vs. ArmB)		p-value		p-value		p-value		unilateral	
*Significance values adjusted for **gestational age***		RR (95% CI)		RR (95% CI)		RR (95% CI)		p-value	
*Significance values adjusted for **birth weight***		HR (95% CI)		HR (95% CI)		HR (95% CI)		RR (95% CI)	
*Significance values adjusted for **race***		OR (95% CI)		OR (95% CI)		OR (95% CI)		HR (95% CI)	
*Significance values adjusted for **prenatal steroids***		Max. adj. p-value		Max. adj. p-value		Max. adj. p-value		OR (95% CI)	
*Significance values adjusted for **other***		Max. adj. RR (95% CI)		Max. adj. RR (95% CI)		Max. adj. RR (95% CI)		Max. adj. p-value	
*Significance values adjusted for **other***		Max. adj. HR (95% CI)		Max. adj. HR (95% CI)		Max. adj. HR (95% CI)		Max. adj. RR (95% CI)	
		Max. adj. OR (95% CI)		Max. adj. OR (95% CI)		Max. adj. OR (95% CI)		Max. adj. HR (95% CI)	
								Max. adj. OR (95% CI)	

Hearing Impairment

231. Measured at:		232. Any		233. Requires a hearing aid		234. Deafness		235. Other	
Time post birth OR actual follow-up time (specify units)		n		n		n		Define	
iNO dosage		%n		%n		%n		n	
N		unilateral		unilateral		unilateral		%n	
Indentify comparison for significance values (ex: ArmA vs. ArmB)		p-value		p-value		p-value		unilateral	
*Significance values adjusted for **gestational age***		RR (95% CI)		RR (95% CI)		RR (95% CI)		p-value	
*Significance values adjusted for **birth weight***		HR (95% CI)		HR (95% CI)		HR (95% CI)		RR (95% CI)	
*Significance values adjusted for **race***		OR (95% CI)		OR (95% CI)		OR (95% CI)		HR (95% CI)	
*Significance values adjusted for **prenatal steroids***		Max. adj. p-value		Max. adj. p-value		Max. adj. p-value		OR (95% CI)	
*Significance values adjusted for **other***		Max. adj. RR (95% CI)		Max. adj. RR (95% CI)		Max. adj. RR (95% CI)		Max. adj. p-value	
*Significance values adjusted for **other***		Max. adj. HR (95% CI)		Max. adj. HR (95% CI)		Max. adj. HR (95% CI)		Max. adj. RR (95% CI)	
		Max. adj. OR (95% CI)		Max. adj. OR (95% CI)		Max. adj. OR (95% CI)		Max. adj. HR (95% CI)	
								Max. adj. OR (95% CI)	

236. Measured at:		237. Any		238. Requires a hearing aid		239. Deafness		240. Other	
Time post birth OR actual follow-up time (specify units)		n		n		n		Define	
iNO dosage		%n		%n		%n		n	
N		unilateral		unilateral		unilateral		%n	
Indentify comparison for significance values (ex: ArmA vs. ArmB)		p-value		p-value		p-value		unilateral	
*Significance values adjusted for **gestational age***		RR (95% CI)		RR (95% CI)		RR (95% CI)		p-value	
*Significance values adjusted for **birth weight***		HR (95% CI)		HR (95% CI)		HR (95% CI)		RR (95% CI)	
*Significance values adjusted for **race***		OR (95% CI)		OR (95% CI)		OR (95% CI)		HR (95% CI)	
*Significance values adjusted for **prenatal steroids***		Max. adj. p-value		Max. adj. p-value		Max. adj. p-value		OR (95% CI)	
*Significance values adjusted for **other***		Max. adj. RR (95% CI)		Max. adj. RR (95% CI)		Max. adj. RR (95% CI)		Max. adj. p-value	
*Significance values adjusted for **other***		Max. adj. HR (95% CI)		Max. adj. HR (95% CI)		Max. adj. HR (95% CI)		Max. adj. RR (95% CI)	
		Max. adj. OR (95% CI)		Max. adj. OR (95% CI)		Max. adj. OR (95% CI)		Max. adj. HR (95% CI)	
								Max. adj. OR (95% CI)	

241. Measured at:		242. Any		243. Requires a hearing aid		244. Deafness		245. Other	
Time post birth OR actual follow-up time (specify units)		n		n		n		Define	

iNO dosage		%n		%n		%n		n	
N		unilateral		unilateral		unilateral		%n	
Indentify comparison for significance values (ex: ArmA vs. ArmB)		p-value		p-value		p-value		unilateral	
*Significance values adjusted for **gestational age***		RR (95% CI)		RR (95% CI)		RR (95% CI)		p-value	
*Significance values adjusted for **birth weight***		HR (95% CI)		HR (95% CI)		HR (95% CI)		RR (95% CI)	
*Significance values adjusted for **race***		OR (95% CI)		OR (95% CI)		OR (95% CI)		HR (95% CI)	
*Significance values adjusted for **prenatal steroids***		Max. adj. p-value		Max. adj. p-value		Max. adj. p-value		OR (95% CI)	
*Significance values adjusted for **other***		Max. adj. RR (95% CI)		Max. adj. RR (95% CI)		Max. adj. RR (95% CI)		Max. adj. p-value	
*Significance values adjusted for **other***		Max. adj. HR (95% CI)		Max. adj. HR (95% CI)		Max. adj. HR (95% CI)		Max. adj. RR (95% CI)	
		Max. adj. OR (95% CI)		Max. adj. OR (95% CI)		Max. adj. OR (95% CI)		Max. adj. HR (95% CI)	
								Max. adj. OR (95% CI)	

246. Measured at:		247. Any		248. Requires a hearing aid		249. Deafness		250. Other	
Time post birth OR actual follow-up time (specify units)		n		n		n		Define	
iNO dosage		%n		%n		%n		n	
N		unilateral		unilateral		unilateral		%n	
Indentify comparison for significance values (ex: ArmA vs. ArmB)		p-value		p-value		p-value		unilateral	
*Significance values adjusted for **gestational age***		RR (95% CI)		RR (95% CI)		RR (95% CI)		p-value	
*Significance values adjusted for **birth weight***		HR (95% CI)		HR (95% CI)		HR (95% CI)		RR (95% CI)	
*Significance values adjusted for **race***		OR (95% CI)		OR (95% CI)		OR (95% CI)		HR (95% CI)	
*Significance values adjusted for **prenatal steroids***		Max. adj. p-value		Max. adj. p-value		Max. adj. p-value		OR (95% CI)	
*Significance values adjusted for **other***		Max. adj. RR (95% CI)		Max. adj. RR (95% CI)		Max. adj. RR (95% CI)		Max. adj. p-value	
*Significance values adjusted for **other***		Max. adj. HR (95% CI)		Max. adj. HR (95% CI)		Max. adj. HR (95% CI)		Max. adj. RR (95% CI)	
		Max. adj. OR (95% CI)		Max. adj. OR (95% CI)		Max. adj. OR (95% CI)		Max. adj. HR (95% CI)	
								Max. adj. OR (95% CI)	

Bayley Scale of Infant Development

251. Measured at:		252. Overall score		253. Physical development index (PDI)		254. Mental development index (MDI)	
Time post birth OR actual follow-up time (specify units)		Mean		Mean		Mean	
iNO dosage		Standard Deviation		Standard Deviation		Standard Deviation	
N		n w/ score below 1 SD below mean (<85)		n w/ score below 1 SD below mean (<85)		n w/ score below 1 SD below mean (<85)	
Indentify comparison for significance values (ex: ArmA vs. ArmB)		n w/ score below 2 SD below mean(<70)		n w/ score below 2 SD below mean(<70)		n w/ score below 2 SD below mean(<70)	
*Significance values adjusted for **gestational age***		n with severe		n with severe		n with severe	
*Significance values adjusted for **birth weight***		Define "severe"		Define "severe"		Define "severe"	
*Significance values adjusted for **race***		p-value		p-value		p-value	
*Significance values adjusted for **prenatal steroids***		RR (95% CI)		RR (95% CI)		RR (95% CI)	
*Significance values adjusted for **other***		HR (95% CI)		HR (95% CI)		HR (95% CI)	
*Significance values adjusted for **other***		OR (95% CI)		OR (95% CI)		OR (95% CI)	
		Max. adj. p-value		Max. adj. p-value		Max. adj. p-value	
		Max. adj. RR (95% CI)		Max. adj. RR (95% CI)		Max. adj. RR (95% CI)	
		Max. adj. HR (95% CI)		Max. adj. HR (95% CI)		Max. adj. HR (95% CI)	
		Max. adj. OR (95% CI)		Max. adj. OR (95% CI)		Max. adj. OR (95% CI)	

255. Measured at:		256. Overall score		257. Physical development index (PDI)		258. Mental development index (MDI)	
Time post birth OR actual follow-up time (specify units)		Mean		Mean		Mean	
iNO dosage		Standard Deviation		Standard Deviation		Standard Deviation	
N		n w/ score below 1 SD below mean (<85)		n w/ score below 1 SD below mean (<85)		n w/ score below 1 SD below mean (<85)	
Indentify comparison for significance values (ex: ArmA vs. ArmB)		n w/ score below 2 SD below mean(<70)		n w/ score below 2 SD below mean(<70)		n w/ score below 2 SD below mean(<70)	
*Significance values adjusted for **gestational age***		n with severe		n with severe		n with severe	
*Significance values adjusted for **birth weight***		Define "severe"		Define "severe"		Define "severe"	
*Significance values adjusted for **race***		p-value		p-value		p-value	
*Significance values adjusted for **prenatal steroids***		RR (95% CI)		RR (95% CI)		RR (95% CI)	
*Significance values adjusted for **other***		HR (95% CI)		HR (95% CI)		HR (95% CI)	
*Significance values adjusted for **other***		OR (95% CI)		OR (95% CI)		OR (95% CI)	
		Max. adj. p-value		Max. adj. p-value		Max. adj. p-value	
		Max. adj. RR (95% CI)		Max. adj. RR (95% CI)		Max. adj. RR (95% CI)	

		Max. adj. HR (95% CI)		Max. adj. HR (95% CI)		Max. adj. HR (95% CI)	
		Max. adj. OR (95% CI)		Max. adj. OR (95% CI)		Max. adj. OR (95% CI)	
259. Measured at:		260. Overall score		261. Physical development index (PDI)		262. Mental development index (MDI)	
Time post birth OR actual follow-up time (specify units)		Mean		Mean		Mean	
iNO dosage		Standard Deviation		Standard Deviation		Standard Deviation	
N		n w/ score below 1 SD below mean (<85)		n w/ score below 1 SD below mean (<85)		n w/ score below 1 SD below mean (<85)	
Indentify comparison for significance values (ex: ArmA vs. ArmB)		n w/ score below 2 SD below mean(<70)		n w/ score below 2 SD below mean(<70)		n w/ score below 2 SD below mean(<70)	
*Significance values adjusted for **gestational age***		n with severe		n with severe		n with severe	
*Significance values adjusted for **birth weight***		Define "severe"		Define "severe"		Define "severe"	
*Significance values adjusted for **race***		p-value		p-value		p-value	
*Significance values adjusted for **prenatal steroids***		RR (95% CI)		RR (95% CI)		RR (95% CI)	
*Significance values adjusted for **other***		HR (95% CI)		HR (95% CI)		HR (95% CI)	
*Significance values adjusted for **other***		OR (95% CI)		OR (95% CI)		OR (95% CI)	
		Max. adj. p-value		Max. adj. p-value		Max. adj. p-value	
		Max. adj. RR (95% CI)		Max. adj. RR (95% CI)		Max. adj. RR (95% CI)	
		Max. adj. HR (95% CI)		Max. adj. HR (95% CI)		Max. adj. HR (95% CI)	
		Max. adj. OR (95% CI)		Max. adj. OR (95% CI)		Max. adj. OR (95% CI)	
263. Measured at:		264. Overall score		265. Physical development index (PDI)		266. Mental development index (MDI)	
Time post birth OR actual follow-up time (specify units)		Mean		Mean		Mean	
iNO dosage		Standard Deviation		Standard Deviation		Standard Deviation	
N		n w/ score below 1 SD below mean (<85)		n w/ score below 1 SD below mean (<85)		n w/ score below 1 SD below mean (<85)	
Indentify comparison for significance values (ex: ArmA vs. ArmB)		n w/ score below 2 SD below mean(<70)		n w/ score below 2 SD below mean(<70)		n w/ score below 2 SD below mean(<70)	
*Significance values adjusted for **gestational age***		n with severe		n with severe		n with severe	
*Significance values adjusted for **birth weight***		Define "severe"		Define "severe"		Define "severe"	

Significance values adjusted for ***race***		p-value		p-value		p-value	
Significance values adjusted for ***prenatal steroids***		RR (95% CI)		RR (95% CI)		RR (95% CI)	
Significance values adjusted for ***other***		HR (95% CI)		HR (95% CI)		HR (95% CI)	
Significance values adjusted for ***other***		OR (95% CI)		OR (95% CI)		OR (95% CI)	
		Max. adj. p-value		Max. adj. p-value		Max. adj. p-value	
		Max. adj. RR (95% CI)		Max. adj. RR (95% CI)		Max. adj. RR (95% CI)	
		Max. adj. HR (95% CI)		Max. adj. HR (95% CI)		Max. adj. HR (95% CI)	
		Max. adj. OR (95% CI)		Max. adj. OR (95% CI)		Max. adj. OR (95% CI)	

Griffith Scale

267. Measured at:		268. Overall score		269. Physical development index (PDI)		270. Mental development index (MDI)	
Time post birth OR actual follow-up time (specify units)		Mean		Mean		Mean	
iNO dosage		Standard Deviation		Standard Deviation		Standard Deviation	
N		n w/ score below 1 SD below mean (<85)		n w/ score below 1 SD below mean (<85)		n w/ score below 1 SD below mean (<85)	
Indentify comparison for significance values (ex: ArmA vs. ArmB)		n w/ score below 2 SD below mean(<70)		n w/ score below 2 SD below mean(<70)		n w/ score below 2 SD below mean(<70)	
Significance values adjusted for ***gestational age***		n with severe		n with severe		n with severe	
Significance values adjusted for ***birth weight***		Define "severe"		Define "severe"		Define "severe"	
Significance values adjusted for ***race***		p-value		p-value		p-value	
Significance values adjusted for ***prenatal steroids***		RR (95% CI)		RR (95% CI)		RR (95% CI)	
Significance values adjusted for ***other***		HR (95% CI)		HR (95% CI)		HR (95% CI)	
Significance values adjusted for ***other***		OR (95% CI)		OR (95% CI)		OR (95% CI)	
		Max. adj. p-value		Max. adj. p-value		Max. adj. p-value	
		Max. adj. RR (95% CI)		Max. adj. RR (95% CI)		Max. adj. RR (95% CI)	
		Max. adj. HR (95% CI)		Max. adj. HR (95% CI)		Max. adj. R (95% CI)	
		Max. adj. OR (95% CI)		Max. adj. OR (95% CI)		Max. adj. OR (95% CI)	

271. Measured at:		272. Overall score		273. Physical development index (PDI)		274. Mental development index (MDI)	
Time post birth OR actual follow-up time (specify units)		Mean		Mean		Mean	
iNO dosage		Standard Deviation		Standard Deviation		Standard Deviation	
N		n w/ score below 1 SD below mean (<85)		n w/ score below 1 SD below mean (<85)		n w/ score below 1 SD below mean (<85)	
Indentify comparison for significance values (ex: ArmA vs. ArmB)		n w/ score below 2 SD below mean(<70)		n w/ score below 2 SD below mean(<70)		n w/ score below 2 SD below mean(<70)	

*Significance values adjusted for **gestational age***		n with severe		n with severe		n with severe	
*Significance values adjusted for **birth weight***		Define "severe"		Define "severe"		Define "severe"	
*Significance values adjusted for **race***		p-value		p-value		p-value	
*Significance values adjusted for **prenatal steroids***		RR (95% CI)		RR (95% CI)		RR (95% CI)	
*Significance values adjusted for **other***		HR (95% CI)		HR (95% CI)		HR (95% CI)	
*Significance values adjusted for **other***		OR (95% CI)		OR (95% CI)		OR (95% CI)	
		Max. adj. p-value		Max. adj. p-value		Max. adj. p-value	
		Max. adj. RR (95% CI)		Max. adj. RR (95% CI)		Max. adj. RR (95% CI)	
		Max. adj. HR (95% CI)		Max. adj. HR (95% CI)		Max. adj. HR (95% CI)	
		Max. adj. OR (95% CI)		Max. adj. OR (95% CI)		Max. adj. OR (95% CI)	
275. Measured at:		276. Overall score		277. Physical development index (PDI)		278. Mental development index (MDI)	
Time post birth OR actual follow-up time (specify units)		Mean		Mean		Mean	
iNO dosage		Standard Deviation		Standard Deviation		Standard Deviation	
N		n w/ score below 1 SD below mean (<85)		n w/ score below 1 SD below mean (<85)		n w/ score below 1 SD below mean (<85)	
Indentify comparison for significance values (ex: ArmA vs. ArmB)		n w/ score below 2 SD below mean(<70)		n w/ score below 2 SD below mean(<70)		n w/ score below 2 SD below mean(<70)	
*Significance values adjusted for **gestational age***		n with severe		n with severe		n with severe	
*Significance values adjusted for **birth weight***		Define "severe"		Define "severe"		Define "severe"	
*Significance values adjusted for **race***		p-value		p-value		p-value	
*Significance values adjusted for **prenatal steroids***		RR (95% CI)		RR (95% CI)		RR (95% CI)	
*Significance values adjusted for **other***		HR (95% CI)		HR (95% CI)		HR (95% CI)	
*Significance values adjusted for **other***		OR (95% CI)		OR (95% CI)		OR (95% CI)	
		Max. adj. p-value		Max. adj. p-value		Max. adj. p-value	
		Max. adj. RR (95% CI)		Max. adj. RR (95% CI)		Max. adj. RR (95% CI)	
		Max. adj. HR (95% CI)		Max. adj. HR (95% CI)		Max. adj. HR (95% CI	
		Max. adj. OR (95% CI)		Max. adj. OR (95% CI)		Max. adj. OR (95% CI)	

279. Measured at:

- Time post birth OR actual follow-up time (specify units)
- iNO dosage
- N
- Indentify comparison for significance values (ex. ArmA vs. ArmB)
- *Significance values adjusted for **gestational age***
- *Significance values adjusted for **birth weight***
- *Significance values adjusted for **race***
- *Significance values adjusted for **prenatal steroids***
- *Significance values adjusted for **other***
- *Significance values adjusted for **other***

280. Overall score

- Mean
- Standard Deviation
- n w/ score below 1 SD below mean (<85)
- n w/ score below 2 SD below mean(<70)
- n with severe
- Define " severe"
- p-value
- RR (95% CI)
- HR (95% CI)
- OR (95% CI)
- Max. adj. p-value
- Max. adj. RR (95% CI)
- Max. adj. HR (95% CI)
- Max. adj. OR (95% CI)

281. Physical development index (PDI)

- Mean
- Standard Deviation
- n w/ score below 1 SD below mean (<85)
- n w/ score below 2 SD below mean(<70)
- n with severe
- Define " severe"
- p-value
- RR (95% CI)
- HR (95% CI)
- OR (95% CI)
- Max. adj. p-value
- Max. adj. RR (95% CI)
- Max. adj. HR (95% CI)
- Max. adj. OR (95% CI)

282. Mental development index (MDI)

- Mean
- Standard Deviation
- n w/ score below 1 SD below mean (<85)
- n w/ score below 2 SD below mean(<70)
- n with severe
- Define " severe"
- p-value
- RR (95% CI)
- HR (95% CI)
- OR (95% CI)
- Max. adj. p-value
- Max. adj. RR (95% CI)
- Max. adj. HR (95% CI)
- Max. adj. OR (95% CI)

Other Neurodevelopment Outcomes

283. Measured at:

- Time post birth OR actual follow-up time (specify units)
- iNO dosage
- N
- Indentify comparison for significance values (ex. ArmA vs. ArmB)
- *Significance values adjusted for **gestational age***
- *Significance values adjusted for **birth weight***
- *Significance values adjusted for **race***
- *Significance values adjusted for **prenatal steroids***
- *Significance values adjusted for **other***
- *Significance values adjusted for **other***

284. Seizures / Fits

- n
- %n
- p-value
- RR (95% CI)
- HR (95% CI)
- OR (95% CI)
- Max. adj. p-value
- Max. adj. RR (95% CI)
- Max. adj. HR (95% CI)
- Max. adj. OR (95% CI)

285. Hydrocephalus--requiring medical treatment

- n
- %n
- p-value
- RR (95% CI)
- HR (95% CI)
- OR (95% CI)
- Max. adj. p-value
- Max. adj. RR (95% CI)
- Max. adj. HR (95% CI)
- Max. adj. OR (95% CI)

286. Ventriculomegaly

- n
- %n
- p-value
- RR (95% CI)
- HR (95% CI)
- OR (95% CI)
- Max. adj. p-value
- Max. adj. RR (95% CI)
- Max. adj. HR (95% CI)
- Max. adj. OR (95% CI)

287. Retinopathy of prematurity (ROP) requiring treatment by cryo or laser

- n
- %n
- p-value
- RR (95% CI)
- HR (95% CI)
- OR (95% CI)
- Max. adj. p-value
- Max. adj. RR (95% CI)
- Max. adj. HR (95% CI)
- Max. adj. OR (95% CI)

288. Measured at:

289. Seizures / Fits

290. Hydrocephalus--requiring medical treatment

291. Ventriculomegaly

292. Retinopathy of Prematurity (ROP) requiring treatment by cryo or laser

Time post birth OR actual follow-up time (specify units)	n	n	n	n
iNO dosage	%n	%n	%n	%n
N	p-value	p-value	p-value	p-value
Indentify comparison for significance values (ex. ArmA vs. ArmB)	RR (95%CI)	RR (95%CI)	RR (95%CI)	RR (95%CI)
*Significance values adjusted for **gestational age***	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)
*Significance values adjusted for **birth weight***	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
*Significance values adjusted for **race***	Max. adj. p-value	Max. adj. p-value	Max. adj. p-value	Max. adj. p-value
*Significance values adjusted for **prenatal steroids***	Max. adj. RR (95%CI)	Max. adj. RR (95%CI)	Max. adj. RR (95%CI)	Max. adj. RR (95%CI)
*Significance values adjusted for **other***	Max. adj. HR (95%CI)	Max. adj. HR (95%CI)	Max. adj. HR (95%CI)	Max. adj. HR (95%CI)
*Significance values adjusted for **other***	Max. adj. OR (95%CI)	Max. adj. OR (95%CI)	Max. adj. OR (95%CI)	Max. adj. OR (95%CI)

293. Measured at:	294. Seizures / Fits	295. Hydrocephalus--requiring medical treatment	296. Ventriculomegaly	297. Retinopathy ofPrematurity (ROP) requiring treatment by cryo or laser
Time post birth OR actual follow-up time (specify units)	n	n	n	n
iNO dosage	%n	%n	%n	%n
N	p-value	p-value	p-value	p-value
Indentify comparison for significance values (ex. ArmA vs. ArmB)	RR (95%CI)	RR (95%CI)	RR (95%CI)	RR (95%CI)
*Significance values adjusted for **gestational age***	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)
*Significance values adjusted for **birth weight***	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
*Significance values adjusted for **race***	Max. adj. p-value	Max. adj. p-value	Max. adj. p-value	Max. adj. p-value
*Significance values adjusted for **prenatal steroids***	Max. adj. RR (95%CI)	Max. adj. RR (95%CI)	Max. adj. RR (95%CI)	Max. adj. RR (95%CI)
*Significance values adjusted for **other***	Max. adj. HR (95%CI)	Max. adj. HR (95%CI)	Max. adj. HR (95%CI)	Max. adj. HR (95%CI)
*Significance values adjusted for **other***	Max. adj. OR (95%CI)	Max. adj. OR (95%CI)	Max. adj. OR (95%CI)	Max. adj. OR (95%CI)

298. Measured at:	299. Seizures / Fits	300. Hydrocephalus--requiring medical treatment	301. Ventriculomegaly	302. Retinopathy ofPrematurity (ROP) requiring treatment by cryo or laser
Time post birth OR actual follow-up time (specify units)	n	n	n	n
iNO dosage	%n	%n	%n	%n
N	p-value	p-value	p-value	p-value
Indentify comparison for significance values (ex. ArmA vs. ArmB)	RR (95%CI)	RR (95%CI)	RR (95%CI)	RR (95%CI)
*Significance values adjusted for **gestational age***	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)
*Significance values adjusted for **birth weight***	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
*Significance values adjusted for **race***	Max. adj. p-value	Max. adj. p-value	Max. adj. p-value	Max. adj. p-value
*Significance values adjusted for **prenatal steroids***	Max. adj. RR (95%CI)	Max. adj. RR (95%CI)	Max. adj. RR (95%CI)	Max. adj. RR (95%CI)
*Significance values adjusted for **other***	Max. adj. HR (95%CI)	Max. adj. HR (95%CI)	Max. adj. HR (95%CI)	Max. adj. HR (95%CI)
*Significance values adjusted for **other***	Max. adj. OR (95%CI)	Max. adj. OR (95%CI)	Max. adj. OR (95%CI)	Max. adj. OR (95%CI)

Other Neurodevelopment Outcomes

303. Measured at:	304. Other	305. Other	306. Other	307. Other	308. Other	309. Other	310. Other
Time post birth OR actual follow-up time (specify units)	Define	Define	Define	Define	Define	Define	Define
iNO dosage	n	n	n	n	n	n	n
N	%n	%n	%n	%n	%n	%n	%n
Indentify comparison for significance values (ex: ArmA vs. ArmB)	p-value	p-value	p-value	p-value	p-value	p-value	p-value
*Significance values adjusted for **gestational age***	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
*Significance values adjusted for **birth weight***	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
*Significance values adjusted for **race***	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
*Significance values adjusted for **prenatal steroids***	Max. adj. p-value	Max. adj. p-value	Max. adj. p-value	Max. adj. p-value	Max. adj. p-value	Max. adj. p-value	Max. adj. p-value
*Significance values adjusted for **other***	Max. adj. RR (95% CI)	Max. adj. RR (95% CI)	Max. adj. RR (95% CI)	Max. adj. RR (95% CI)	Max. adj. RR (95% CI)	Max. adj. RR (95% CI)	Max. adj. RR (95% CI)
*Significance values adjusted for **other***	Max. adj. HR (95% CI)	Max. adj. HR (95% CI)	Max. adj. HR (95% CI)	Max. adj. HR (95% CI)	Max. adj. HR (95% CI)	Max. adj. HR (95% CI)	Max. adj. HR (95% CI)
	Max. adj. OR (95% CI)	Max. adj. OR (95% CI)	Max. adj. OR (95% CI)	Max. adj. OR (95% CI)	Max. adj. OR (95% CI)	Max. adj. OR (95% CI)	Max. adj. OR (95% CI)

311. Measured at:	312. Other	313. Other	314. Other	315. Other	316. Other	317. Other	318. Other
Time post birth OR actual follow-up time (specify units)	Define	Define	Define	Define	Define	Define	Define
iNO dosage	n	n	n	n	n	n	n
N	%n	%n	%n	%n	%n	%n	%n
Indentify comparison for significance values (ex: ArmA vs. ArmB)	p-value	p-value	p-value	p-value	p-value	p-value	p-value
*Significance values adjusted for **gestational age***	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
*Significance values adjusted for **birth weight***	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
*Significance values adjusted for **race***	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
*Significance values adjusted for **prenatal steroids***	Max. adj. p-value	Max. adj. p-value	Max. adj. p-value	Max. adj. p-value	Max. adj. p-value	Max. adj. p-value	Max. adj. p-value
*Significance values adjusted for **other***	Max. adj. RR (95% CI)	Max. adj. RR (95% CI)	Max. adj. RR (95% CI)	Max. adj. RR (95% CI)	Max. adj. RR (95% CI)	Max. adj. RR (95% CI)	Max. adj. RR (95% CI)
*Significance values adjusted for **other***	Max. adj. HR (95% CI)	Max. adj. HR (95% CI)	Max. adj. HR (95% CI)	Max. adj. HR (95% CI)	Max. adj. HR (95% CI)	Max. adj. HR (95% CI)	Max. adj. HR (95% CI)
	Max. adj. OR (95% CI)	Max. adj. OR (95% CI)	Max. adj. OR (95% CI)	Max. adj. OR (95% CI)	Max. adj. OR (95% CI)	Max. adj. OR (95% CI)	Max. adj. OR (95% CI)

319. Measured at:	320. Other	321. Other	322. Other	323. Other	324. Other	325. Other	326. Other
Time post birth OR actual follow-up time (specify units)	Define	Define	Define	Define	Define	Define	Define
iNO dosage	n	n	n	n	n	n	n
N	%n	%n	%n	%n	%n	%n	%n
Indentify comparison for significance values (ex: ArmA vs. ArmB)	p-value	p-value	p-value	p-value	p-value	p-value	p-value
*Significance values adjusted for **gestational age***	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
*Significance values adjusted for **birth weight***	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
*Significance values adjusted for **race***	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
*Significance values adjusted for **prenatal steroids***	Max. adj. p-value	Max. adj. p-value	Max. adj. p-value	Max. adj. p-value	Max. adj. p-value	Max. adj. p-value	Max. adj. p-value
*Significance values adjusted for **other***	Max. adj. RR (95% CI)	Max. adj. RR (95% CI)	Max. adj. RR (95% CI)	Max. adj. RR (95% CI)	Max. adj. RR (95% CI)	Max. adj. RR (95% CI)	Max. adj. RR (95% CI)
*Significance values adjusted for **other***	Max. adj. HR (95% CI)	Max. adj. HR (95% CI)	Max. adj. HR (95% CI)	Max. adj. HR (95% CI)	Max. adj. HR (95% CI)	Max. adj. HR (95% CI)	Max. adj. HR (95% CI)
	Max. adj. OR (95% CI)	Max. adj. OR (95% CI)	Max. adj. OR (95% CI)	Max. adj. OR (95% CI)	Max. adj. OR (95% CI)	Max. adj. OR (95% CI)	Max. adj. OR (95% CI)

327. Measured at:	328. Other	329. Other	330. Other	331. Other	332. Other	333. Other	334. Other
Time post birth OR actual follow-up time (specify units)	Define	Define	Define	Define	Define	Define	Define
iNO dosage	n	n	n	n	n	n	n
N	%n	%n	%n	%n	%n	%n	%n
Indentify comparison for significance values (ex: ArmA vs. ArmB)	p-value	p-value	p-value	p-value	p-value	p-value	p-value
*Significance values adjusted for **gestational age***	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
*Significance values adjusted for **birth weight***	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
*Significance values adjusted for **race***	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
*Significance values adjusted for **prenatal steroids***	Max. adj. p-value	Max. adj. p-value	Max. adj. p-value	Max. adj. p-value	Max. adj. p-value	Max. adj. p-value	Max p-value
*Significance values adjusted for **other***	Max. adj. RR (95% CI)	Max. adj. RR (95% CI)	Max. adj. RR (95% CI)	Max. adj. RR (95% CI)	Max. adj. RR (95% CI)	Max. adj. RR (95% CI)	Max RR (95% CI)
*Significance values adjusted for **other***	Max. adj. HR (95% CI)	Max. adj. HR (95% CI)	Max. adj. HR (95% CI)	Max. adj. HR (95% CI)	Max. adj. HR (95% CI)	Max. adj. HR (95% CI)	Max HR (95% CI)
	Max. adj. OR (95% CI)	Max. adj. OR (95% CI)	Max. adj. OR (95% CI)	Max. adj. OR (95% CI)	Max. adj. OR (95% CI)	Max. adj. OR (95% CI)	Max OR (95% CI)

School readiness and behavioral impairment

335. Measured at:

- [ ] Time post birth OR actual follow-up time (specify units)
- [ ] iNO dosage
- [ ] N
- [ ] Indentify comparison for significance values (ex: ArmA vs. ArmB)
- [ ] *Significance values adjusted for* ***gestational age***
- [ ] *Significance values adjusted for* ***birth weight***
- [ ] *Significance values adjusted for* ***race***
- [ ] *Significance values adjusted for* ***prenatal steroids***
- [ ] *Significance values adjusted for* ***other***
- [ ] *Significance values adjusted for* ***other***

336. Define

337.

- [ ] n
- [ ] %n
- [ ] p-value
- [ ] RR (95% CI)
- [ ] HR (95% CI)
- [ ] OR (95% CI)
- [ ] Max adj.p-value
- [ ] Max adj.RR (95% CI)
- [ ] Max adj.HR (95% CI)
- [ ] Max adj. OR (95% CI)

338. Measured at:

- [ ] Time post birth OR actual follow-up time (specify units)
- [ ] iNO dosage
- [ ] N
- [ ] Indentify comparison for significance values (ex: ArmA vs. ArmB)
- [ ] *Significance values adjusted for* ***gestational age***
- [ ] *Significance values adjusted for* ***birth weight***
- [ ] *Significance values adjusted for* ***race***
- [ ] *Significance values adjusted for* ***prenatal steroids***
- [ ] *Significance values adjusted for* ***other***
- [ ] *Significance values adjusted for* ***other***

339. Define

340.

- [ ] n
- [ ] %n
- [ ] p-value
- [ ] RR (95% CI)
- [ ] HR (95% CI)
- [ ] OR (95% CI)
- [ ] Max adj. p-value
- [ ] Max adj. RR (95% CI)
- [ ] Max adj. HR (95% CI)
- [ ] Max adj. OR (95% CI)

341. Measured at:

342. Define

343.

- [ ] Time post birth OR actual follow-up time (specify units)
- [ ] iNO dosage
- [ ] N
- [ ] Indentify comparison for significance values (ex: ArmA vs. ArmB)
- [ ] *Significance values adjusted for* ***gestational age***
- [ ] *Significance values adjusted for* ***birth weight***
- [ ] *Significance values adjusted for* ***race***
- [ ] *Significance values adjusted for* ***prenatal steroids***
- [ ] *Significance values adjusted for* ***other***
- [ ] *Significance values adjusted for* ***other***

- [ ] n
- [ ] %n
- [ ] p-value
- [ ] RR (95% CI)
- [ ] HR (95% CI)
- [ ] OR (95% CI)
- [ ] Max adj. p-value
- [ ] Max adj. RR (95% CI)
- [ ] Max adj. HR (95% CI)
- [ ] Max adj. OR (95% CI)

344. Measured at:

345. Define

346.

- [ ] Time post birth OR actual follow-up time (specify units)
- [ ] iNO dosage
- [ ] N
- [ ] Indentify comparison for significance values (ex: ArmA vs. ArmB)
- [ ] *Significance values adjusted for* ***gestational age***
- [ ] *Significance values adjusted for* ***birth weight***
- [ ] *Significance values adjusted for* ***race***
- [ ] *Significance values adjusted for* ***prenatal steroids***

- [ ] n
- [ ] %n
- [ ] p-value
- [ ] RR (95% CI)
- [ ] HR (95% CI)
- [ ] OR (95% CI)
- [ ] Max adj. p-value
- [ ] Max adj. RR (95% CI)

☐ *Significance values adjusted for* ***other***		☐ Max adj. HR (95% CI)	
☐ *Significance values adjusted for* ***other***		☐ Max adj. OR (95% CI)	

Behavioral problems

347. Measured at:		348. Define	349.	
☐ Time post birth OR actual follow-up time (specify units)			☐ n	
☐ iNO dosage			☐ %n	
☐ N			☐ p-value	
☐ Indentify comparison for significance values (ex: ArmA vs. ArmB)			☐ RR (95% CI)	
☐ *Significance values adjusted for* ***gestational age***			☐ HR (95% CI)	
☐ *Significance values adjusted for* ***birth weight***			☐ OR (95% CI)	
☐ *Significance values adjusted for* ***race***			☐ Max adj. p-value	
☐ *Significance values adjusted for* ***prenatal steroids***			☐ Max adj. RR (95% CI)	
☐ *Significance values adjusted for* ***other***			☐ Max adj. HR (95% CI)	
☐ *Significance values adjusted for* ***other***			☐ Max adj. OR (95% CI)	

350. Measured at:		351. Define	352.	
☐ Time post birth OR actual follow-up time (specify units)			☐ n	
☐ iNO dosage			☐ %n	

- [ ] N
- [ ] Indentify comparison for significance values (ex: ArmA vs. ArmB)
- [ ] *Significance values adjusted for* ***gestational age***
- [ ] *Significance values adjusted for* ***birth weight***
- [ ] *Significance values adjusted for* ***race***
- [ ] *Significance values adjusted for* ***prenatal steroids***
- [ ] *Significance values adjusted for* ***other***
- [ ] *Significance values adjusted for* ***other***

- [ ] p-value
- [ ] RR (95% CI)
- [ ] HR (95% CI)
- [ ] OR (95% CI)
- [ ] Max adj. p-value
- [ ] Max adj. RR (95% CI)
- [ ] Max adj. HR (95% CI)
- [ ] Max adj. OR (95% CI)

353. Measured at:

- [ ] Time post birth OR actual follow-up time (specify units)
- [ ] iNO dosage
- [ ] N
- [ ] Indentify comparison for significance values (ex: ArmA vs. ArmB)
- [ ] *Significance values adjusted for* ***gestational age***
- [ ] *Significance values adjusted for* ***birth weight***
- [ ] *Significance values adjusted for* ***race***
- [ ] *Significance values adjusted for* ***prenatal steroids***

354. Define

355.

- [ ] n
- [ ] %n
- [ ] p-value
- [ ] RR (95% CI)
- [ ] HR (95% CI)
- [ ] OR (95% CI)
- [ ] Max adj. p-value
- [ ] Max adj. RR (95% CI)

☐ *Significance values adjusted for* ***other***			☐ Max adj. HR (95% CI)	
☐ *Significance values adjusted for* ***other***			☐ Max adj. OR (95% CI)	

356. Measured at:		357. Define	358.	
☐ Time post birth OR actual follow-up time (specify units)			☐ n	
☐ iNO dosage			☐ %n	
☐ N			☐ p-value	
☐ Indentify comparison for significance values (ex: ArmA vs. ArmB)			☐ RR (95% CI)	
☐ *Significance values adjusted for* ***gestational age***			☐ HR (95% CI)	
☐ *Significance values adjusted for* ***birth weight***			☐ OR (95% CI)	
☐ *Significance values adjusted for* ***race***			☐ Max adj. p-value	
☐ *Significance values adjusted for* ***prenatal steroids***			☐ Max adj. RR (95% CI)	
☐ *Significance values adjusted for* ***other***			☐ Max adj. HR (95% CI)	
☐ *Significance values adjusted for* ***other***			☐ Max adj. OR (95% CI)	

Social and emotional problems

359. Measured at:		360. Define	361.	
☐ Time post birth OR actual follow-up time (specify units)			☐ n	
☐ iNO dosage			☐ %n	
☐ N			☐ p-value	
☐ Indentify comparison for significance values (ex: ArmA vs. ArmB)			☐ RR (95% CI)	

☐ *Significance values adjusted for* ***gestational age***		☐ HR (95% CI)	
☐ *Significance values adjusted for* ***birth weight***		☐ OR (95% CI)	
☐ *Significance values adjusted for* ***race***		☐ Max adj. p-value	
☐ *Significance values adjusted for* ***prenatal steroids***		☐ Max adj. RR (95% CI)	
☐ *Significance values adjusted for* ***other***		☐ Max adj. HR (95% CI)	
☐ *Significance values adjusted for* ***other***		☐ Max adj. OR (95% CI)	

362. Measured at:		363. Define	364.	
☐ Time post birth OR actual follow-up time (specify units)			☐ n	
☐ iNO dosage			☐ %n	
☐ N			☐ p-value	
☐ Indentify comparison for significance values (ex: ArmA vs. ArmB)			☐ RR (95% CI)	
☐ *Significance values adjusted for* ***gestational age***			☐ HR (95% CI)	
☐ *Significance values adjusted for* ***birth weight***			☐ OR (95% CI)	
☐ *Significance values adjusted for* ***race***			☐ Max adj. p-value	
☐ *Significance values adjusted for* ***prenatal steroids***			☐ Max adj. RR (95% CI)	
☐ *Significance values adjusted for* ***other***			☐ Max adj. HR (95% CI)	
☐ *Significance values adjusted for* ***other***			☐ Max adj. OR (95% CI)	

365. Measured at:		366. Define	367.	
☐ Time post birth OR actual follow-up time (specify units)			☐ n	
☐ iNO dosage			☐ %n	

- [ ] N
- [ ] Indentify comparison for significance values (ex: ArmA vs. ArmB)
- [ ] *Significance values adjusted for* ***gestational age***
- [ ] *Significance values adjusted for* ***birth weight***
- [ ] *Significance values adjusted for* ***race***
- [ ] *Significance values adjusted for* ***prenatal steroids***
- [ ] *Significance values adjusted for* ***other***
- [ ] *Significance values adjusted for* ***other***

- [ ] p-value
- [ ] RR (95% CI)
- [ ] HR (95% CI)
- [ ] OR (95% CI)
- [ ] Max adj. p-value
- [ ] Max adj. RR (95% CI)
- [ ] Max adj. HR (95% CI)
- [ ] Max adj. OR (95% CI)

368. Measured at:

- [ ] Time post birth OR actual follow-up time (specify units)
- [ ] iNO dosage
- [ ] N
- [ ] Indentify comparison for significance values (ex: ArmA vs. ArmB)
- [ ] *Significance values adjusted for* ***gestational age***

369. Define

370.

- [ ] n
- [ ] %n
- [ ] p-value
- [ ] RR (95% CI)
- [ ] HR (95% CI)

- [ ] *Significance values adjusted for* ***birth weight***
- [ ] *Significance values adjusted for* ***race***
- [ ] *Significance values adjusted for* ***prenatal steroids***
- [ ] *Significance values adjusted for* ***other*** [ ]
- [ ] *Significance values adjusted for* ***other*** [ ]

- [ ] OR (95% CI) [ ]
- [ ] Max adj. p-value [ ]
- [ ] Max adj. RR (95% CI) [ ]
- [ ] Max adj. HR (95% CI) [ ]
- [ ] Max adj. OR (95% CI) [ ]

Growth

371.		372. Height (cm)		373. Weight (grams)		374. Head circumference (cm)	
[ ] n	[ ]	[ ] mean	[ ]	[ ] Mean	[ ]	[ ] Mean	[ ]
[ ] %n	[ ]	[ ] Standard Deviation	[ ]	[ ] Standard Deviation	[ ]	[ ] Standard Deviation	[ ]
[ ] N	[ ]	[ ] Median	[ ]	[ ] Median	[ ]	[ ] Median	[ ]
		[ ] Range (Specify if IQR)	[ ]	[ ] Range (Specify if IQR)	[ ]	[ ] Range (Specify if IQR)	[ ]
		[ ] p-value	[ ]	[ ] p-value	[ ]	[ ] p-value	[ ]
		[ ] RR (95% CI)	[ ]	[ ] RR (95% CI)	[ ]	[ ] RR (95% CI)	[ ]
		[ ] HR (95% CI)	[ ]	[ ] HR (95% CI)	[ ]	[ ] HR (95% CI)	[ ]
		[ ] OR (95% CI)	[ ]	[ ] OR (95% CI)	[ ]	[ ] OR (95% CI)	[ ]
		[ ] Z-score	[ ]	[ ] Z-score	[ ]	[ ] Z-score	[ ]
		[ ] Max adj. p-value	[ ]	[ ] Max adj. p-value	[ ]	[ ] Max adj. p-value	[ ]
		[ ] Max adj. RR (95% CI)	[ ]	[ ] Max adj. RR (95% CI)	[ ]	[ ] Max adj. RR (95% CI)	[ ]
		[ ] Max adj. HR (95% CI)	[ ]	[ ] Max adj. HR (95% CI)	[ ]	[ ] Max adj. HR (95% CI)	[ ]
		[ ] Max adj. OR (95% CI)	[ ]	[ ] Max adj. OR (95% CI)	[ ]	[ ] Max adj. OR (95% CI	[ ]

375. **COMMENTS**

[ ]

Submit Form and go to [ ] or Skip to Next

Appendix D: List of Excluded Articles

Caution over nitric oxide. Pharm. J. 2003; 271(7279):818.
No original data

Nitric oxide to prevent bronchopulmonary dysplasia. Arch. Dis. Child. 2006; 91(12):1022.
No original data

Abman, S. H. and Kinsella, J. P.. Inhaled nitric oxide for persistent pulmonary hypertension of the newborn: the physiology matters!. Pediatrics 95; 96(6):1153-5.
No original data

Abman, S. H. and Kinsella, J. P.. Inhaled nitric oxide therapy of pulmonary hypertension and respiratory failure in premature and term neonates.. Adv. Pharmacol. 95; 34:457-474.
No original data

Abman, S. H.. Inhaled nitric oxide therapy of severe neonatal pulmonary hypertension. ACTA Anaesthesiol. Scand. Suppl. 95; 39 (105):65-68.
No original data

Abman, S. H.. Neonatal pulmonary hypertension: A physiologic approach to treatment. Pediatr. Pulmonol. 2004; 37(Suppl. 26):127-128.
No original data

Abman, S. H.. New developments in the pathogenesis and treatment of neonatal pulmonary hypertension.. Pediatr Pulmonol Suppl 99; 18:201-204.
No original data
Abman, S. H.. Role of inhaled nitric oxide in treatment of neonatal pulmonary hypertension. Zhongguo Yao Li Xue Bao 1997; 18(6):542-5.
No original data

Adisesh, A. and Snashall, D.. Inhaled nitric oxide. Lancet 1996; 348(9039):1447-8.
No original data

Ahluwadia, J. S., Kelsall, A. W. R., Raine, J., Rennie, J. M., Mahmood, M., Oduro, A., Latimer, R., Pickett, J., and Higenbottam, T. W.. Safety of inhaled nitric oxide in premature neonates [6]. ACTA Paediatr. Int. J. Paediatr. 1994; 83(3):347-348.
No abstractable data
No original data

Ahluwalia, J., Tooley, J., Cheema, I., Sweet, D. G., Curley, A. E., Halliday, H. L., Field, D., Al'malik, H., Annamalai, S., Midgley, P., Hardy, P., Tomlin, K., and Elbourne, D.. A dose response study of inhaled nitric oxide in hypoxic respiratory failure in preterm infants. Early Hum. Dev. 2006; 82(7):477-483.
Article does not address any of the Key Questions

Aikio, O., Saarela, T., Pokela, M. L., and Hallman, M.. Nitric oxide treatment and acute pulmonary inflammatory response in very premature infants with intractable respiratory failure shortly after birth. Acta Paediatr. Int. J. Paediatr. 2003; 92(1):65-69.
Article does not address any of the Key Questions
Article address Key Question 1 or 2 ONLY and is not a randomized controlled trial

Aikio, O. and Hallman, M. Nitric oxide in the acute care of newborns and premature infants: Typpioksidi Vastasyntyneitten ja Keskosten Akuuttihoidossa. Duodecim. 2004; 120(15):1853-1858.
Unobtainable

Alano, M. A., Ngougmna, E., Ostrea, E. M. Jr, and Konduri, G. G.. Analysis of nonsteroidal antiinflammatory drugs in meconium and its relation to persistent pulmonary hypertension of the newborn. Pediatrics 2001; 107(3):519-23.
Article does not include infants born at less than 34 weeks gestation

Albert Bretons, D., Girona Comas, J., Casaldaliga Ferrer, J., Roqueta Mas, J., Perapoch Lopez, J., and Murtra Ferre, M.. Transposition of the great arteries and pulmonary hypertension: Inhaled nitric oxide as a therapy and surgical correction: Transposicion de grandes arterias e hipertension pulmonar: Tratamiento con oxido nitrico inhalado y correccion anatomica Precoz. An. Esp. Pediatr. 1997; 47(6):633-635.
Not written in English and cannot determine eligibility

Aly, H., Sahni, R., and Wung, J. T.. Weaning strategy with inhaled nitric oxide treatment in persistent pulmonary hypertension of the newborn. Arch Dis Child Fetal Neonatal Ed 1997; 76(2):F118-22.
Article does not address any of the Key Questions

Ambalavanan, N., Van Meurs, K. P., Perritt, R., Carlo, W. A., Ehrenkranz, R. A., Stevenson, D. K., Lemons, J. A., Poole, W. K., and Higgins, R. D.. Predictors of death or bronchopulmonary dysplasia in preterm infants with respiratory failure. J Perinatol 2008; 28(6):420-6.
No abstractable data

Andelfinger, G., Shirali, G. S., Raunikar, R. A., and Atz, A. M.. Functional pulmonary atresia in neonatal Marfan's Syndrome: Successful treatment with inhaled nitric oxide. Pediatr. Cardiol. 2001; 22(6):525-526.
Article does not include infants born at less than 34 weeks gestation

Arioni, C., Bellini, C., Mazzella, M., Zullino, E., Serra, G., and Toma, P.. Congenital right diaphragmatic hernia. Pediatr. Radiol. 2003; 33(11):807-808.
No original data
Article does not include infants born at less than 34 weeks gestation

Ashida, Y., Miyahara, H., Sawada, H., Mitani, Y., and Maruyama, K.. Anesthetic management of a neonate with vein of galen aneurysmal malformations and severe

pulmonary hypertension. Paediatr. Anaesth. 2005; 15(6):525-528.
Article does not include infants born at less than 34 weeks gestation
Article does not include pre-term infants who were treated with inhaled nitric oxide

Athavale, K., Claure, N., D'Ugard, C., Everett, R., Swaminathan, S., and Bancalari, E.. Acute effects of inhaled nitric oxide on pulmonary and cardiac function in preterm infants with evolving bronchopulmonary dysplasia. J Perinatol 2004; 24(12):769-74.
Article addresses Key Question 1 or 2 ONLY and is not a randomized controlled trial
Other reason

Athena IP-H. The effect of inhaled nitric oxide on medical andf functional Outcomes of premature infants at early school-age. American Pediatric Society/SocieTY for Pediatric Research Abstract. 2008. CODEN: RCT; ISSN: CN-00709184.
Unobtainable

Atz, A. M. and Wessel, D. L.. Inhaled nitric oxide in the neonate with cardiac disease. Semin Perinatol 1997; 21(5):441-55.
Article does not include infants born at less than 34 weeks gestation
Other reason

Atz, A. M. and Wessel, D. L.. Sildenafil ameliorates effects of inhaled nitric oxide withdrawal. Anesthesiology 1999; 91(1):307-10.
Article does not include infants born at less than 34 weeks gestation
Other reason

Atz, A. M., Munoz, R. A., Adatia, I., and Wessel, D. L.. Diagnostic and therapeutic uses of inhaled nitric oxide in neonatal Ebstein's Snomaly. Am J Cardiol 2003; 91(7):906-8.
Article does not include infants born at less than 34 weeks gestation
Article does not address any of the Key Questions

Bagolan, P., Casaccia, G., Crescenzi, F., Nahom, A., Trucchi, A., and Giorlandino, C.. Impact of a current treatment protocol on outcome of high-risk congenital diaphragmatic hernia. J Pediatr Surg 2004; 39(3):313-8; discussion 313-8.
Article does not include infants born at less than 34 weeks gestation
Article does not address any of the Key Questions

Ballard R; Avital Cnaan; William E.Truog; Richard J.Martin; Anna Maria Hibbs; Philip L.Ballard; Jeffrey D.Merrill; Xiangun Luan; Sandra R.Wadlinger, and The NO CLD Study Group. decreased health services utilization in preterm infants treated with inhaled nitric oxide. Conference Abstracts Online. 2007. CODEN: RCT; ISSN: CN-00709217.
Unobtainable

Ballard, P. L., Merrill, J. D., Truog, W. E., Godinez, R. I., Godinez, M. H., McDevitt, T. M., Ning, Y., Golombek, S. G., Parton, L. A., Luan, X., Cnaan, A., and Ballard, R. A.. Surfactant function and composition in premature infants treated with ihaled nitric oxide. Pediatrics 2007; 120(2):346-53.
No abstractable data

Ballard, P. L., Truog, W. E., Merrill, J. D., Gow, A., Posencheg, M., Golombek, S. G., Parton, L. A., Luan, X., Cnaan, A., and Ballard, R. A.. Plasma biomarkers of oxidative stress: relationship to lung disease and inhaled nitric oxide therapy in premature infants. Pediatrics 2008; 121(3):555-61.
Article does not address any of the Key Questions

Ballard, R. A.. Inhaled nitric oxide in preterm infants--correction. N Engl J Med 2007; 357(14):1444-5.
No abstractable data

Balzer DT, Kort HW, Day RW, Corneli HM, Kovalchin JP, Cannon BC, Kaine SF, Ivy DD, Webber SA, Rothman A, Ross RD, Aggarwal S, Takahashi M, and Waldman JD. Inhaled Nitric Oxide as a Preoperative Test (INOP Test I): the INOP Test Study Group.. Circulation 2002; 106(12 Suppl 1):I76-81.
Article does not include infants born at less than 34 weeks gestation
Article does not address any of the Key Questions

Banks BA, Pallotto E, and Ballard RA. A randomized, double blind, placebo controlled crossover pilot trial of inhaled nitric oxide (iNO) in preterm infants with evolving chronic lung disease (CLD). Pediatric Research 2001; 49(4):284A.
No abstractable data

Baraldi, E., Bonetto, G., Zacchello, F., and Filippone, M.. Low exhaled nitric oxide in school-age children with bronchopulmonary dysplasia and airflow limitation. Am. J. Respir. Crit. Care Med. 2005; 171(1):68-72.
Article does not address any of the Key Questions

Barrington, K. J. and Finer, N. N.. Inhaled nitric oxide for preterm infants: a systematic review. Pediatrics 2007; 120(5):1088-99.
No original data

Barton, L. L., Grant, K. L., and Lemen, R. J.. Changes in arterial oxygen tension when weaning neonates from inhaled nitric oxide. Pediatr. Pulmonol. 2001; 32(1):14-19.
Article does not include infants born at less than 34 weeks gestation

Bassler, D., Choong, K., McNamara, P., and Kirpalani, H.. Neonatal persistent pulmonary hypertension treated with milrinone: Four case reports. Biol. Neonate 2006; 89(1):1-5.
Article does not address any of the Key Questions

Appendix D: List of Excluded Articles

Beligere, N. and Rao, R.. Neurodevelopmental outcome of infants with meconium aspiration syndrome: report of a study and literature review. J Perinatol 2008; 28 Suppl 3:S93-101.
Article does not include infants born at less than 34 weeks gestation

Bell, S. G.. The story of nitric oxide: from rascally radical to miracle molecule. Neonatal Netw 2004; 23(4):47-51.
No original data
Other reason

Benitz, W. E., Rhine, W. D., Van Meurs, K. P., and Stevenson, D. K.. Nitrovasodilator therapy for severe respiratory distress syndrome.. J Perinatol 1996; 16(6):443-448.
Article does not include pre-term infants who were treated with inhaled nitric oxide
Article does not address any of the Key Questions

Benjamin, J. T., Hamm, C. R., Zayek, M., Eyal, F. G., Carlson, S., and Manci, E.. Acquired Left-Sided Pulmonary Vein Stenosis in an Extremely Premature Infant: A New Entity?. J. Pediatr. 2009; 154(3):459-459.e1.
Article does not address any of the Key Questions
Other reason

Benjamin, J. T.. Practice and guidelines.. Pediatrics 1996; 97(4):604-605.
No original data
Article does not include infants born at less than 34 weeks gestation

Betremieux, P., Gaillot, T., De La Pintiere, A., Beuchee, A., Pasquier, L., Habonimana, E., Le Bouar, G., Branger, B., Milon, J., Fremond, B., Wodey, E., Odent, S., Poulain, P., and Pladys, P.. Congenital diaphragmatic hernia: Prenatal diagnosis permits immediate intensive care with high survival rate in isolated cases. A population-based study. Prenat. Diagn. 2004; 24(7):487-493.
Article does not include infants born at less than 34 weeks gestation

Bhutani, V. K., Chima, R., and Sivieri, E. M.. Innovative neonatal ventilation and meconium aspiration syndrome. Indian J Pediatr 2003; 70(5):421-7.
Article does not include infants born at less than 34 weeks gestation

Biban, P., Trevisanuto, D., Pettenazzo, A., Ferrarese, P., Baraldi, E., and Zacchello, F.. Inhaled nitric oxide in hypoxaemic newborns who are candidates for extracorporeal life support. Eur. Respir. J. 1998; 11(2):371-376.
Article does not include infants born at less than 34 weeks gestation

Bland, R. D.. Inhaled nitric oxide: A premature remedy for chronic lung disease?. Pediatrics 1999; 103(3):667-670.
No original data

Bohnhorst, B., Poets, C., and Freihorst, J.. Inhaled nitric oxide in severe bronchopulmonary dysplasia: Inhalatives stickstoffmonoxid in der therapie der schweren bronchopulmonalen dysplasie. Monatsschr. Kinderheilkd. 2001; 149(7):686-690
Not written in English and cannot determine eligibility

Boloker, J., Bateman, D. A., Wung, J.-T., and Stolar, C. J. H.. Congenital diaphragmatic hernia in 120 infants treated consecutively with permissive hypercapnea/spontaneous respiration/elective repair. J. Pediatr. Surg. 2002; 37(3):357-366.
Article does not include infants born at less than 34 weeks gestation
Article does not address any of the Key Questions

Booth, G. R., Thornton, K., Jureidini, S., and Fleming, R. E.. Subendocardial infarction associated with ventricular hypertrophy in preterm infants with chronic lung disease. J. Perinatol. 2008; 28(8):580-583.
Article does not address any of the Key Questions

Bouchet, M., Renaudin, M.-H., Raveau, C., Mercier, J.-C., Dehan, M., and Zupan, V.. Safety requirement for use of inhaled nitric oxide in neonates [25]. LANCET 1993; 341(8850):968-969.
No human data included
Other reason

Braschi, A., Iannuzzi, M., Belliato, M., and Iotti, G. A.. Therapeutic use of nitric oxide in critical settings. Monaldi Arch Chest Dis 2001; 56(2):177-9.
No original data

Bruckheimer, E., Bulbul, Z., Pinter, E., Gailani, M., Kleinman, C. S., and Fahey, J. T.. Inhaled nitric oxide therapy in a critically ill neonate with Ebstein's anomaly. Pediatr. Cardiol. 1998; 19(6):477-479.
Article does not include infants born at less than 34 weeks gestation

Burchfield, D. J., Blackmon, L. R., and Barrington, K. J.. Postnatal steroids to treat or prevent chronic lung disease in preterm infants [4] (multiple letters). Pediatrics 2003; 111(1):221-222.
No original data

Cavallaro, G., Agazzani, E., Andaloro, L., Bottura, C., Cristofori, G., Mussini, P., Sacco, F., and Compagnoni, G.. [Sildenafil and nitric oxide inhalation in neonatal pulmonary hypertension. Three case reports]. Pediatr Med Chir 2008; 30(3):149-55.
Not written in English and cannot determine eligibility

Channick, R. N. and Rubin, L. J.. Combination therapy for pulmonary hypertension: a glimpse into the future?. Crit Care Med 2000; 28(3):896-7.
No original data

Chaudhari, M., Vogel, M., Wright, C., Smith, J., and Haworth, S. G.. Sildenafil in neonatal pulmonary hypertension due to impaired alveolarisation and plexiform pulmonary arteriopathy. Arch Dis Child Fetal Neonatal Ed 2005; 90(6):F527-8.
Article does not include infants born at less than 34 weeks gestation

Cheifetz, I. M.. Inhaled nitric oxide: plenty of data, no consensus. Crit Care Med 2000; 28(3):902-3.
No original data

Cheung, P. Y., Etches, P. C., and Radomski, M. W.. NO effect on hemostasis. J Pediatr 1999; 134(3):383-4.
No original data
Article address Key Question 1 or 2 ONLY and is not a randomized controlled trial

Cheung, P.-Y., Salas, E., Etches, P. C., Phillipos, E., Schulz, R., and Radomski, M. W.. Inhaled nitric oxide and inhibition of platelet aggregation in critically ill neonates. Lancet 1998; 351(9110):1181-1182.
Article address Key Question 1 or 2 ONLY and is not a randomized controlled trial
Other reason

Christopher Rhee, Sudhir Sriram Michael Schreiber William Meadow. Pediatrics University of Chicago Chicago IL.. Effects of Inhaled Nitric Oxide on Cardiac Output Using Point-Of-Care Bedside Echocardiography in Preterm Infants. PASAbstracts 2009; #volume#:#startpage#.
Article does not address any of the Key Questions
No abstractable data

Christou, H., Adatia, I., Van Marter, L. J., Kane, J. W., Thompson, J. E., Stark, A. R., Wessel, D. L., and Kourembanas, S.. Effect of inhaled nitric oxide on endothelin-1 and cyclic guanosine 5'- monophosphate plasma concentrations in newborn infants with persistent pulmonary hypertension. J. PEDIATR. 1997; 130(4):603-611.
Article does not include infants born at less than 34 weeks gestation

Christou, H., Magnani, B., Morse, D. S., Allred, E. N., Van Marter, L. J., Wessel, D. L., and Kourembanas, S.. Inhaled nitric oxide does not affect adenosine 5'-diphosphate-dependent platelet activation in infants with persistent pulmonary hypertension of the newborn. Pediatrics 98; 102(6):1390-1393.
Article does not include infants born at less than 34 weeks gestation

Claire-Marie Loys, Delphine Maucort-Boulch Guy Putet Stephane Hays. Neonatologie Hopital de la Croix Rousse Hospices Civils de Lyon Université Claude Bernard Lyon France and Biostatistique, Hopital Lyon Sud Hospices Civils de Lyon Université Claude Bernard Lyon France.. Early Risk Factors for Death or Severe Brain Lesions in Extremely Low Birth Weight Preterm Infants. PASAbstracts 2009; #volume#:#startpage#.
Article does not include pre-term infants who were treated with inhaled nitric oxide
No abstractable data

Clark, R. H., Bloom, B. T., Spitzer, A. R., and Gerstmann, D. R.. Reported medication use in the neonatal intensive care unit: data from a large national data set.. Pediatrics 2006; 117(6):1979-1987.
Article does not address any of the Key Questions
Other reason

Concheiro Guisan, A., Sousa Rouco, C., Suarez Traba, B., Paradela Carreira, A., Ocampo Cardalda, S., and Antelo Cortizas, J.. Inhaled iloprost: A therapeutic alternative for persistent pulmonary hypertension of the newborn [1]: Iloprost inhalado: Una alternativa terapeutica para la hipertension pulmonar persistente del recien nacido. An. Pediatr. 2005; 63(2):175-176.
Not written in English and cannot determine eligibility
Article does not include pre-term infants who were treated with inhaled nitric oxide

Cornfield, D. N. and Abman, S. H.. Inhalational nitric oxide in pulmonary parenchymal and vascular disease. J Lab Clin Med 1996; 127(6):530-9.
No original data
Other reason

Cui, X., Quezado, Z. M. N., and Eichacker, P. Q.. Inhaled nitric oxide: Is systemic host defense at risk?. Crit. Care Med. 2002; 30(4):945-946.
No original data
Article does not address any of the Key Questions

Dahlheim, M., Witsch, M., Demirakca, S., Lorenz, C., and Schaible, T.. Congenital diaphragmatic hernia - Results of an ECMO-centre: Angeborene zwerchfellhernie - Ergebnisse eines ECMO-zentrums. Klin. Padiatr. 2003; 215(4):213-222.
Not written in English and cannot determine eligibility

Dani, C., Bertini, G., and Rubaltelli, F. F.. Inhaled nitric oxide. N Engl J Med 2005; 353(15):1626-8; author reply 1626-8.
No abstractable data

Datin-Dorriere, V., Rouzies, S., Taupin, P., Walter-Nicolet, E., Benachi, A., Sonigo, P., and Mitanchez, D.. Prenatal prognosis in isolated congenital diaphragmatic hernia. Am J Obstet Gynecol 2008; 198(1):80.e1-5.
Article does not address any of the Key Questions

Datin-Dorriere, V., Walter-Nicolet, E., Rousseau, V., Taupin, P., Benachi, A., Parat, S., Hubert, P., Revillon, Y., and Mitanchez, D.. Experience in the management of eighty-two newborns with congenital diaphragmatic hernia treated with high-frequency oscillatory ventilation and delayed surgery without the use of extracorporeal

membrane oxygenation. J. Intensive Care Med. 2008; 23(2):128-135.
Other reason

Davis, C. F. and Sabharwal, A. J.. Management of congenital diaphragmatic hernia. Arch Dis Child Fetal Neonatal Ed 1998; 79(1):F1-3.
No original data

Day, R. W., Lynch, J. M., White, K. S., and Ward, R. M.. Acute response to inhaled nitric oxide in newborns with respiratory failure and pulmonary hypertension. Pediatrics 1996; 98(4 Pt 1):698-705.
Article does not include infants born at less than 34 weeks gestation
Article does not address any of the Key Questions

Day, R. W.. Cerebral blood flow velocity acutely decreases in newborns who respond to inhaled nitric oxide. Am. J. Perinatol. 2001; 18(4):185-194.
Article does not address any of the Key Questions
Article address Key Question 1 or 2 ONLY and is not a randomized controlled trial

Day, R. W.. Inhaled nitric oxide prevents severe hypoxemia in newborns with acute lung disease and pulmonary hypertension. Pediatrics 1998; 101(6):1093-4.
Article does not include infants born at less than 34 weeks gestation

Day, R. W.. Right ventricular size is acutely decreased by inhaled nitric oxide in newborns with pulmonary hypertension. Am J Perinatol 1998; 15(7):445-51.
Article does not include infants born at less than 34 weeks gestation
Article does not address any of the Key Questions

De Groote, K. and Van Overmeire, B.. Inhaled nitric oxide as treatment of persistent pulmonary hypertension in newborns: A review: INHALATIE VAN STIKSTOFMONOXIDE ALS BEHANDELING VAN PERSISTERENDE PULMONALE HYPERTENSIE BIJ DE PASGBORENE. EEN OVERZICHT. Tijdschr. Geneeskd. 1998; 54(12):817-823.
Not written in English and cannot determine eligibility

De Luca, D., Zecca, E., Vento, G., De Carolis, M. P., and Romagnoli, C.. Transient effect of epoprostenol and sildenafil combined with iNO for pulmonary hypertension in congenital diaphragmatic hernia [2]. Paediatr. Anaesth. 2006; 16(5):597-598.
Article does not include infants born at less than 34 weeks gestation

Di Fiore, J. M., Hibbs, A. M., Zadell, A. E., Merrill, J. D., Eichenwald, E. C., Puri, A. R., Mayock, D. E., Courtney, S. E., Ballard, R. A., and Martin, R. J.. The effect of inhaled nitric oxide on pulmonary function in preterm infants. J Perinatol 2007; 27(12):766-71.
No abstractable data

Dimitriou, G., Greenough, A., Kavvadia, V., Devane, S. P., and Rennie, J. M.. Outcome predictors in nitric oxide treated preterm infants. Eur. J. Pediatr. 1999; 158(7):589-591.
No abstractable data

Dobyns, E. L., Anas, N. G., Fortenberry, J. D., Deshpande, J., Cornfield, D. N., Tasker, R. C., Liu, P., Eells, P. L., Griebel, J., Kinsella, J. P., and Abman, S. H.. Interactive effects of high-frequency oscillatory ventilation and inhaled nitric oxide in acute hypoxemic respiratory failure in pediatrics. Crit. Care Med. 2002; 30(11):2425-2429.
Article does not address any of the Key Questions

Dobyns, E. L., Griebel, J., Kinsella, J. P., Abman, S. H., and Accurso, F. J.. Infant lung function after inhaled nitric oxide therapy for persistent pulmonary hypertension of the newborn. Pediatr Pulmonol 1999; 28(1):24-30.
Article does not include infants born at less than 34 weeks gestation

Dominguez, E. D., Vasallo, J. C., Berrueta, M., Acosta, L., Gaivironsky, R., and Polack, N.. High frequency ventilation and inhaled nitric oxide in pediatrics and neonatology: Avances en terapia intensiva neonatal y pediatrica. Ventilacion de alta frecuencia administracion de oxido nitrico inhalatorio. Prensa Med. Argent. 1998; 85(7):823-827.
Not written in English and cannot determine eligibility

Drinkwater Jr., D. C., Aharon, A. S., Quisling, S. V., Dodd, D., Reddy, V. S., Kavanaugh-McHugh, A., Doyle, T., Patel, N. R., Barr, F. E., Kambam, J. K., Graham, T. P., and Chang, P. A.. Modified norwood operation for hypoplastic left heart syndrome. Ann. Thorac. Surg. 2001; 72(6):2081-2087.
Article does not address any of the Key Questions

Drury, J. A., Nycyk, J. A., Subhedar, N. V., Shaw, N. J., and Cooke, R. W.. Inhaled nitric oxide does not increase lipid peroxidation in preterm infants. Eur J Pediatr 1998; 157(12):1033.
No abstractable data

Du, L.-Z., Shi, L.-P., Sun, M.-Y., Zhou, B.-H., Chen, C., Shao, X.-M., Zhang, X.-D., Lu, Y., and Sun, B.. Inhaled nitric oxide in preterm and term neonates with hypoxemic respiratory failure and persistent pulmonary hypertension. Acta Pharmacol. Sin. 2002; 23(SUPPL.):69-73.
No abstractable data

Dubois, A., Storme, L., Jaillard, S., Truffert, P., Riou, Y., Rakza, T., Pierrat, V., Gottrand, F., Pruvot, F. R., Leclerc, F., and Lequien, P.. Congenital diaphragmatic hernia: Retrospective study of 123 cases: Les hernies congenitales des coupoles diaphragmatiques. Etude retrospective de 123 observations recueillies dans le service de medecine neonatale du CHRU de Lille entre 1985 et 1996. Arch. Pediatr. 2000; 7(2):132-142.
Not written in English and cannot determine eligibility

Dursun, S. M. and Robertson, H.. Nitric oxide in neonates. Lancet 2000; 356(9237):1274-5.
No original data
Article does not include infants born at less than 34 weeks gestation

Duval, E. L. I. M., Leroy, P. L. J. M., Gemke, R. J. B. J., and Van Vught, A. J.. High-frequency oscillatory ventilation in RSV bronchiolitis patients. Respir. Med. 1999; 93(6):435-440.
Article does not address any of the Key Questions
Article address Key Question 1 or 2 ONLY and is not a randomized controlled trial

Dweik, R. A.. The promise and reality of nitric oxide in the diagnosis and treatment of lung disease. Cleve Clin J Med 2001; 68(6):486, 488, 490, 493.
No original data

Easa, D., Murai, D. T., Oka, B., Dressel, M., Vanderford, P., Pelke, S., and Balaraman, V.. Early experience with inhaled nitric oxide for the treatment of infants and children with pulmonary hypertension. Hawaii Med J 1996; 55(4):67-9.
Article does not include infants born at less than 34 weeks gestation

Ehlen, M. and Wiebe, B.. Iloprost in persistent pulmonary hypertension of the newborn.. Cardiol Young 2003; 13(4):361-363.
Article does not include infants born at less than 34 weeks gestation
Article does not address any of the Key Questions

Ehrenkranz, R. A.. Inhaled nitric oxide and treatment of hypoxic respiratory failure. Zhongguo Yao Li Xue Bao 1997; 18(6):546-7.
Article does not include infants born at less than 34 weeks gestation

Ellington Jr., M., O'Reilly, D., Allred, E. N., McCormick, M. C., Wessel, D. L., and Kourembanas, S.. Child health status, neurodevelopmental outcome, and parental satisfaction in a randomized, controlled trial of nitric oxide for persistent pulmonary hypertension of the newborn. Pediatrics 2001; 107(6):1351-1356.
Article does not include infants born at less than 34 weeks gestation

Ergenekon, E.. Inhaled nitric oxide in premature infants. J Pediatr 1998; 132(2):375.
No original data

Etches, P. C., Finer, N. N., Ehrenkranz, R. A., and Wright, L. L.. Clinical monitoring of inhaled nitric oxide. Pediatrics 1995; 95(4):620-1.
No original data
Article does not address any of the Key Questions

Favilli, S., De Simone, L., Pollini, I., Bettuzzi, M. G., Cianfrini, D., Crepaz, R., Santillo, V., Trevisanuto, D., Vignati, G., and Manetti, A.. Persistent pulmonary hypertension in newborns: Prevalence and clinical and echocardiographic features. A multicentric study: Prevalenza e caratteristiche della ipertensione polmonare persistente del neonato. Studio multicentrico. G. Ital. Cardiol. 1998; 28(11):1247-1252.
Article does not include pre-term infants who were treated with inhaled nitric oxide
Article does not address any of the Key Questions

Field, D. and Elbourne, D.. Use of inhaled nitric oxide to improve oxygenation in the neonate [4]. Arch. Dis. Child. Fetal Neonatal Ed. 2000; 82(3):F258-F259.
No original data

Field, D., Normand, C., and Elbourne, D.. Cost-effectiveness of inhaled nitric oxide in the treatment of neonatal respiratory failure in the US. Pediatrics 2003; 112(6 Pt 1):1422-3.
No original data
Article does not address any of the Key Questions

Field, D.. Trials of nitric oxide.. Biol. Neonate 2003; 84(1):103-104.
No original data

Figueras Aloy, J., Sorni Hubrecht, A., Botet Moussons, F., Rodriguez Miguelez, J. M., and Jimenez Gonzalez, R.. [The immediate response to the administration of inhaled nitric oxide in a newborn infant with congenital diaphragmatic hernia and pulmonary hypertension]. An Esp Pediatr 1996; 44(1):70-2.
Not written in English and cannot determine eligibility

Figueras-Aloy, J., Gomez, L., Rodriguez-Miguelez, J. M., Jordan, Y., Salvia, M. D., Jimenez, W., and Carbonell-Estrany, X.. Plasma nitrite/nitrate and endothelin-1 concentrations in neonatal sepsis. Acta Paediatr. Int. J. Paediatr. 2003; 92(5):582-587.
Article does not include pre-term infants who were treated with inhaled nitric oxide
Article does not address any of the Key Questions

Finer, N. N.. Inhaled nitric oxide for preterm infants: a therapy in search of an indication? The search continues. J Pediatr 2005; 146(3):301-3.
No original data

Firth, A. L. and Yuan, J. X.. Bringing down the ROS: a new therapeutic approach for PPHN. Am J Physiol Lung Cell Mol Physiol 2008; 295(6):L976-8.
No original data

Fletcher, G. and Daniel, M.. Problems in assessing the effect of nebulized prostacyclin in patients whose lungs are ventilated. Anesthesiology 1996; 84(1):242-3
No original data

Flieger, K.. The benefit of nitric oxide inhalation in premature infants is disputed: Nutzen der NO-inhalation

bei fruhgeborenen umstritten. Geburtshilfe Frauenheilkd. 2006; 66(3):216.
Not written in English and cannot determine eligibility

Fraisse, A., Geva, T., Gaudart, J., and Wessel, D. L.. Predictive factors of Doppler echocardiography in persistent pulmonary artery hypertension of the neonate: Facteurs predictifs de l'echocardiographie-Doppler dans l'hypertension arterielle pulmonaire persistante du nouveau-ne. Arch. Mal. Coeur Vaiss. 2004; 97(5):501-506.
Not written in English and cannot determine eligibility
Article does not include infants born at less than 34 weeks gestation

Fredly, S., Aksnes, G., Viddal, K. O., Lindemann, R., and Fugelseth, D.. The outcome in newborns with congenital diaphragmatic hernia in a Norwegian region. Acta Paediatr 2009; 98(1):107-11.
Article does not include infants born at less than 34 weeks gestation
Other reason

Frenckner, B.. Congenital diaphragmatic hernia. INT. J. ARTIF. ORGANS 1995; 18(10):579-583.
No original data
Article does not address any of the Key Questions

Frostell, C. G., Lonnqvist, P. A., Sonesson, S. E., Gustafsson, L. E., Lohr, G., and Noack, G.. Near fatal pulmonary hypertension after surgical repair of congenital diaphragmatic hernia. Successful use of inhaled nitric oxide. Anaesthesia 1993; 48(8):679-83.
Article does not include infants born at less than 34 weeks gestation

Frostell, C. G.. Clinical aspects of nitric oxide and surfactant replacement. Biol Neonate 1997; 71 Suppl 1:39-43.
No original data

Frostell, C. G.. Nitric oxide and acute respiratory failure. Monaldi Arch Chest Dis 1996; 51(6):538-42.
No original data

Fujikawa, S., Yang, L., Waffarn, F., and Lerner, M.. Persistent pulmonary hypertension of the newborn (PPHN) treated with inhaled nitric oxide: preliminary hearing outcomes. J Am Acad Audiol 1997; 8(4):263-8; quiz 297.
Article does not include infants born at less than 34 weeks gestation

Gaio, G., Santoro, G., Esposito, R., Bianco, G., Giliberti, P., Russo, M. G., and Calabro, R.. Patent ductus arteriosus 'stenting' as a life-saving approach in severe neonatal Ebstein's anomaly. J Cardiovasc Med (Hagerstown) 2007; 8(11):937-9.
Article does not include infants born at less than 34 weeks gestation

Gao, X. R., Wu, Y. Q., and Li, L.. [Clinical analysis of chronic lung disease in preterm infants]. Zhongguo Dang Dai Er Ke Za Zhi 2008; 10(4):539-40.
Not written in English and cannot determine eligibility

Gao, X. R., Wu, Y. Q., Peng, X. M., Huang, M., and Liu, X. H.. Inhaled nitric oxide for newborn infants with severe respiratory failure. Zhongguo Dang Dai Er Ke Za Zhi 2006; 8(2):155-157.
Not written in English and cannot determine eligibility

Gaston, B. and Keith, J. F. 3rd. Nitric oxide and bleeding time. Pediatrics 94; 94(1):134-5 No original data
Gaston, B., Keith III, J. F., Kinsella, J. P., and Abman, S. H.. Nitric oxide and bleeding time [4]. PEDIATRICS 1994; 94(1):134-135.
No original data
Article does not address any of the Key Questions

Geary, C. and Whitsett, J.. Inhaled nitric oxide for oligohydramnios-induced pulmonary hypoplasia: A report of two cases and review of the literature. J. Perinatol. 2002; 22(1):82-85.
Article does not address any of the Key Questions

Geggel, R. L.. Inhalational nitric oxide: a selective pulmonary vasodilator for treatment of persistent pulmonary hypertension of the newborn. J Pediatr 1993; 123(1):76-9.
No original data

George, T. N., Johnson, K. J., Bates, J. N., and Segar, J. L.. The effect of inhaled nitric oxide therapy on bleeding time and platelet aggregation in neonates. J. Pediatr. 1998; 132(4):731-734.
Article does not include infants born at less than 34 weeks gestation
Article does not address any of the Key Questions

Gessler, P., Nebe, T., Birle, A., Mueller, W., and Kachel, W.. A new side effect of inhaled nitric oxide in neonates and infants with pulmonary hypertension: Functional impairment of the neutrophil respiratory burst. INTENSIVE CARE MED. 1996; 22(3):252-258.
Article does not include infants born at less than 34 weeks gestation
Article address Key Question 1 or 2 ONLY and is not a randomized controlled trial

Gewillig, M., Brown, S. C., De Catte, L., Debeer, A., Eyskens, B., Cossey, V., Van Schoubroeck, D., Van Hole, C., and Devlieger, R.. Premature foetal closure of the arterial duct: Clinical presentations and outcome. Eur. Heart J. 2009; 30(12):1530-1536.
Article does not address any of the Key Questions

Gin-Mestan KK, Srisuparp P, Carlson AD, Thomas G, Lee G, Marks JD, and Schreiber MD. Inhaled nitric oxide improves oxygenation in premature infants with respiratory distress syndrome: preliminary results of a prospective, randomized trial. Pediatric research 2002; 51(4):348A.

No abstractable data

Gin-Mestan KK, Troyke S, Lee G, Hecox KE, and Schreiber MD. Improved neurodevelopmental outcome at one year in premature infants treated with inhaled nitric oxide: preliminary results of a prospective, randomized trial. Pediatric research 2002; 51(4):405A.
No abstractable data

Goldman, A. P., Tasker, R. C., Cook, P., and Macrae, D. J.. Transfer of critically ill patients with inhaled nitric oxide. Arch Dis Child 1995; 73(5):480.
Article does not include infants born at less than 34 weeks gestation

Golzand, E., Bar-Oz, B., and Arad, I.. Intravenous prostacyclin in the treatment of persistent pulmonary hypertension of the newborn refractory to inhaled nitric oxide. Isr Med Assoc J 2005; 7(6):408-9.
Article does not include infants born at less than 34 weeks gestation

Gonzalez, A., Fabres, J., D'Apremont, I., Urcelay, G., Avaca, M., Gandolfi, C., and Kattan, J.. Randomized controlled trial of early compared with delayed use of inhaled nitric oxide in newborns with a moderate respiratory failure and pulmonary hypertension. J. Perinatol. 2009; :#startpage#.
Article does not include infants born at less than 34 weeks gestation

Gorrotxategi Gorrotxategi, P., Eizaguirre Sexmilo, I., Iturrioz Mata, A., Miranda Abejon, G., Collado Espina, V., and Birritxinaga Gaztelurrutia, B.. [Use of nitric oxide in a newborn child with pulmonary cystic adenomatoid malformation]. Cir Pediatr 2000; 13(1):35-8.
Not written in English and cannot determine eligibility
No abstractable data

Gortner, L.. Neonatal intensive care medicine: Neonatologische intensivmedizin. Arzneim.-Forsch. Drug Res. 2004; 54(11):781-782.
Not written in English and cannot determine eligibility

Gothberg, S., Edberg, K. E., Tang, S. F., Michelsen, S., Winberg, P., Holmgren, D., Miller, O., Thaulow, E., and Lonnqvist, P. A.. Residual pulmonary hypertension in children after treatment with inhaled nitric oxide: a follow-up study regarding cardiopulmonary and neurological symptoms. Acta Paediatr 2000; 89(12):1414-9.
Article does not include infants born at less than 34 weeks gestation
Other reason

Graham, E. M., Bradley, S. M., and Atz, A. M.. Preoperative management of hypoplastic left heart syndrome. Expert Opin. Pharmacother. 2005; 6(5):687-693**.**
No original data

Greenough, A.. Respiratory support techniques for prematurely born infants: new advances and perspectives. Acta Paediatr Taiwan 2001; 42(4):201-6.
No original data

Gressens, P., Rogido, M., Paindaveine, B., and Sola, A.. The impact of neonatal intensive care practices on the developing brain. J Pediatr 2002; 140(6):646-53.
No original data

Gupta, A., Rastogi, S., Sahni, R., Bhutada, A., Bateman, D., Rastogi, D., Smerling, A., and Wung, J. T.. Inhaled nitric oxide and gentle ventilation in the treatment of pulmonary hypertension of the newborn--a single-center, 5-year experience. J Perinatol 2002; 22(6):435-41.
Article does not include infants born at less than 34 weeks gestation
Other reason

Guthrie, S. O., Walsh, W. F., Auten, K., and Clark, R. H.. Initial dosing of inhaled nitric oxide in infants with hypoxic respiratory failure. J Perinatol 2004; 24(5):290-4.
Article does not include infants born at less than 34 weeks gestation

Hallman, M. and Aikio, O.. Nitric oxide in critical respiratory failure of very low birth weight infants. Paediatr. Respir. Rev. 2004; 5(SUPPL. A):S249-S252.
No original data

Hamon I, Schroeder H, Buchweiller MC, Franck P, Nicolas MB, Fresson J, Dousset B, Nabet P, and Hascoet JM. Early effect of inhaled nitric oxide (iNO) on the oxidative balance in 23-32 weeks gestation infants: preliminary data from a randomized controlled trial. Pediatric Research 2001; 49(4):266A.
No abstractable data

Hanna MG; Shaltout FF; El-Fikky MA, and Gamal H. Assessment of the role of inhaled nitric oxide and high frequency oscillatory ventilation in persistent pulmonary hypertension of the newborn. Egyptian Journal of Anaesthesia. 2004; 20(1):47-52. CODEN: CCT; ISSN: CN-00515709.
Unobtainable

Hancock Friesen, C. L., Zurakowski, D., Thiagarajan, R. R., Forbess, J. M., del Nido, P. J., Mayer, J. E., and Jonas, R. A.. Total anomalous pulmonary venous connection: an analysis of current management strategies in a single institution. Ann Thorac Surg 2005; 79(2):596-606; discussion 596-606.
Other reason

Hansen, T. W. R.. Nitric oxide in the treatment of oxygenation difficulties in neonates: Nitrogenoksid I Behandlingen Av Oksygeneringssvikthos Nyfodte. Tidsskr. Nor. Laegeforen. 1995; 115(28):3493-3495.
Not written in English and cannot determine eligibility

Haruda, F. D. and Volpe, J. J.. The structure of blood vessels in the germinal matrix and the autoregulation of cerebral blood flow in premature infants [6]. Pediatrics 2001; 108(4):1050.
No original data
No human data included

Heal, C. A. and Spencer, S. A.. Methaemoglobinaemia with high-dose nitric oxide administration. Acta Paeddtr. Int. J. Paediatr. 1995; 84(11):1318-1319.
Article does not include infants born at less than 34 weeks gestation

Henneberg, S. W., Jepsen, S., Andersen, P. K., and Pedersen, S. A.. Inhalation of nitric oxide as a treatment of pulmonary hypertension in congenital diaphragmatic hernia. J. Pediatr. Surg. 1995; 30(6):853-855.
Article does not include infants born at less than 34 weeks gestation

Henrichsen, T., Goldman, A. P., and Macrae, D. J.. Inhaled nitric oxide can cause severe systemic hypotension. J Pediatr 1996; 129(1):18.3
Article does not include infants born at less than 34 weeks gestation

Hering, F.. Congress report on the 29th Neonatal and Infant Respiratory Symposium in Vail, February 13th to 16th, 2002: Kongressbericht uber das 29. Neonatal und Infant Respiratory Symposium in Vail, 13. bis 16. Februar 2002. Anasthesiol. Intensivmed. Notf.med. Schmerzther. 2002; 37(8):496-500.
Not written in English and cannot determine eligibility

Herkenhoff, M., Schaible, T., Reiss, I., Kandzora, J., Moller, J., and Gortner, L.. Persistent pulmonary hypertension of the newborn and preterm infant: Selective pulmonary vasodilatation with inhalational nitric oxide (iNO): Persistierende pulmonale hypertension (PPHN) im fruh- und neugeborenenalter: Selektive pulmonale vasodilatation mit inhalativem stickstoffmonoxid (iNO). Z. Geburtshilfe Neonatol. 1998; 202(1):25-29.
Not written in English and cannot determine eligibility

Hintz, S. R., Benitz, W. E., Halamek, L. P., Van Meurs, K. P., and Rhine, W. D.. Secondary infection presenting as recurrent pulmonary hypertension. J Perinatol 2000; 20(4):262-4.
Article does not include infants born at less than 34 weeks gestation

Hoehn, T., Gratopp, A., Raehse, K., and Koehne, P.. Effects of hyperoxia and nitric oxide on endogenous nitric oxide production in polymorphonuclear leukocytes. Neonatology 2008; 94(2):132-137.
Article does not include infants born at less than 34 weeks gestation
Article does not address any of the Key Questions

Hoehn, T., Krause, M., Wildberg, A., Pringsheim, W., and Leititis, J. U.. [Reversal of a right-left shunt and permanent improvement of oxygenation by inhalation of nitrogen monoxide in a premature infant with lung hypoplasia and asphyxia]. Z Geburtshilfe Neonatol 1997; 201(3):105-7.
Not written in English and cannot determine eligibility

Hoffman, G. M. and Nelin, L. D.. Mean airway pressure and response to inhaled nitric oxide in neonatal and pediatric patients. Lung 2005; 183(6):441-53.
Article does not include infants born at less than 34 weeks gestation

Hohn, T. and Schiffer, B.. Treatment of persistent pulmonary hypertension of the newborn by nitrogen monoxide inhalation: Die Behandlung der persistierenden pulmonalen Hypertonie des Neugeborenen mit inhalativem Stickstoffmonoxid (iNO).. Kinderkrankenschwester 1997; 16(10):422-424.
Not written in English and cannot determine eligibility

Holmer Fiori, H. and Machado Fiori, R.. Nitric oxide in persistent pulmonary hypertension of the newborn: Oxido nitrico na hipertensao pulmonar persistente do recem-nascido. J. PEDIATR. 96; 72(3):121-122.
Not written in English and cannot determine eligibility

Hoo, A.-F., Beardsmore, C. S., Castle, R. A., Ranganathan, S. C., Tomlin, K., Field, D., Elbourne, D., and Stocks, J.. Respiratory function during infancy in survivors of the INNOVO trial. Pediatr. Pulmonol. 2009; 44(2):155-16.1
No abstractable data

Hoshi, M., Suzumura, H., Nitta, A., Tsuboi, Y., Tsuboi, T., Inoue, H., Tanaka, G., and Arisaka, O.. Treatment of persistent pulmonary hypertension of the newborn. Dokkyo J. Med. Sci. 2002; 29(1):119-124.
Article does not include pre-term infants who were treated with inhaled nitric oxide

Hosono, S., Ohno, T., Kimoto, H., Shimizu, M., Takahashi, S., and Harada, K.. Developmental outcomes in persistent pulmonary hypertension treated with nitric oxide therapy. Pediatr Int 2009; 51(1):79-83.
Article does not include infants born at less than 34 weeks gestation

Hosono, S., Ohno, T., Kimoto, H., Shimizu, M., Takahashi, S., and Harada, K.. Inhaled nitric oxide therapy might reduce the need for hyperventilation therapy in infants with persistent pulmonary hypertension of the newborn. J. Perinat. Med. 2006; 34(4):333-337.
Article does not include infants born at less than 34 weeks gestation

Hsieh, W. S.. Role of nitric oxide in neonatal diseases. Acta Paediatr Taiwan 2002; 43(3):122-3.
No original data

Hsieh, W.-S.. Meconium-stained amniotic fluid, meconium aspiration syndrome, and persistent pulmonary hypertension of the newborn. Acta Paediatr. Taiwan. 2004; 45(4):197-199.

No original data

Hsu, H. T., Lin, J. Y., Tseng, H. I., Chang, Y. L., Yu, K. L., Cheng, K. I., and Tang, C. S.. Total intravenous anesthesia for repair of congenitral diaphragmatic hernia: a case report. Kaohsiung J Med Sci 2004; 20(9):465-9.
Article does not include infants born at less than 34 weeks gestation

Hsu, H.-Y., Huang, C.-B., Chen, C.-C., Huang, H.-C., Liu, C.-A., and Chung, M.-Y.. The therapeutic effect of inhaled nitric oxide in neonatal persistent pulmonary hypertension with and without Congenital Heart Disease. Clin. Neonatol. 2006; 13(1):1-5.
Article does not include infants born at less than 34 weeks gestation
Other reason

Hui, T. T., Danielson, P. D., Anderson, K. D., and Stein, J. E.. The impact of changing neonatal respiratory management on extracorporeal membrane oxygenation utilization. J. Pediatr. Surg. 2002; 37(5):703-705.
Article does not include infants born at less than 34 weeks gestation

Hutchin, M. E., Gilmer, C., and Yarbrough, W. G.. Delayed-onset sensorineural hearing loss in a 3-year-old survivor of persistent pulmonary hypertension of the newborn. Arch. Otolaryngol. Head Neck Surg. 2000; 126(8):1014-1017.
Article does not include infants born at less than 34 weeks gestation

Hwang, S. J., Lee, K. H., Hwang, J. H., Choi, C. W., Shim, J. W., Chang, Y. S., and Park, W. S.. Factors affecting the response to inhaled nitric oxide therapy in persistent pulmonary hypertension of the newborn infants. Yonsei Med J 2004; 45(1):49-55.
Article does not include infants born at less than 34 weeks gestation

Ibrahim TS and El-Mohamady HS. Inhaled nitric oxide and prone position: How far they can improve oxygenation in pediatric patients with acute respiratory distress syndrome?. Journal of Medical Sciences 2007; 7(3):390-5.
Article does not include infants born at less than 34 weeks gestation
Article does not address any of the Key Questions

Ichiba, H., Fujioka, H., Saitoh, M., and Shintaku, H.. Neonatal listeriosis with severe respiratory failure responding to nitric oxide inhalation. Pediatr Int 2000; 42(6):696-8.
Article does not include infants born at less than 34 weeks gestation

IJsselstijn, H. and Tibboel, D.. The lungs in congenital diaphragmatic hernia: Do we understand?. Pediatr. Pulmonol. 1998; 26(3):204-218.
No original data
Article does not address any of the Key Questions

Inamura, N., Kubota, A., Nakajima, T., Kayatani, F., Okuyama, H., Oue, T., and Kawahara, H.. A proposal of new therapeutic strategy for antenatally diagnosed congenital diaphragmatic hernia. J. Pediatr. Surg. 2005; 40(8):1315-1319.
No abstractable data

Iocono, J. A., Cilley, R. E., Mauger, D. T., Krummel, T. M., and Dillon, P. W.. Postnatal pulmonary hypertension after repair of congenital diaphragmatic hernia: Predicting risk and outcome. J. Pediatr. Surg. 1999; 34(2):349-353.
Article does not address any of the Key Questions

Islam, S., Masiakos, P., Schnitzer, J. J., Doody, D. P., and Ryan, D. P.. Diltiazem reduces pulmonary arterial pressures in recurrent pulmonary hypertension associated with pulmonary hypoplasia. J. Pediatr. Surg. 1999; 34(5):712-714.
Article does not include infants born at less than 34 weeks gestation

Izhar FM, Rumilla K, Kim Y-J, Hershenson MB, and Schreiber MD. Inhaled nitric oxide prevents the increase in tracheal aspirate IL-8 concentrations in premature newborn infants with respiratory distress syndrome. Pediatric Research 2001; 49(4):402A.
No abstractable data

Izhar FM, Rumilla KM, Borg MJ, Kim Y-J, Hershenson MB, and Schreiber MD. Pulmonary safety of inhaled nitric oxide in premature newborn infants with respiratory distress syndrome. Pediatric Research 2000; 47(4):362A.
No abstractable data

Janzen, P. R. and Darowski, M.. Nitric oxide in a premature infant in the operating room. Anesthesiology 1995; 83(6):1388.
Article does not address any of the Key Questions

Jerwood, D. C. and Stokes, M. A.. Nitric oxide in the management of persistent pulmonary hypertension of the newborn--an unusual cause of failure.. Paediatr Anaesth 1995; 5(3):193-195.
Article does not include infants born at less than 34 weeks gestation

Journois, D.; Lefebvre, D.; Deny, N.; Sidhom, N.; Djamouri, R.; Vaccaroni, L., and Safran, D. Treatment of the pulmonary hypertension with inhaled nitric oxide following surgey for congenital heart defects: Traitement De L'hypertension Arterielle Pulmonaire Par LE Monoxide D'azote Inhale Lors de la Correction Chirurgicale de Cardiopathies Congenitales. RBM Rev. Eur. Technol. Biomed. 1993; 15(3):167-174.
Unobtainable

Journois, D., Pouard, P., Mauriat, P., Malhere, T., Vouhe, P., and Safran, D.. Inhaled nitric oxide as a therapy for pulmonary hypertension after operations for congenital

heart defects. J Thorac Cardiovasc Surg 1994; 107(4):1129-35.
Other reason

Kachel, W., Varnholt, V., Lasch, P., Muller, W., Lorenz, C., and Wirth, H.. High-frequency oscillatory ventilation and nitric oxide: Alternative or complementary to ECMO. INT. J. ARTIF. ORGANS 1995; 18(10):589-597.
Article does not include pre-term infants who were treated with inhaled nitric oxide
Other reason

Kakuya, F., Takase, M., Ishii, N., Kajino, M., Hayashi, T., Miyamoto, K., Muraki, S., Iwamoto, J., and Okuno, A.. Inhaled nitric oxide therapy via nasopharyngeal tube in an infant with end-stage pulmonary hypertension. Acta Paediatr Jpn 1998; 40(2):155-8.
Article does not include infants born at less than 34 weeks gestation

Kamiyama, M., Kawahara, H., Okuyama, H., Oue, T., Kuroda, S., Kubota, A., and Okada, A.. Gastroesophageal reflux after repair of congenital diaphragmatic hernia. J. Pediatr. Surg. 2002; 37(12):1681-1684.
Article does not address any of the Key Questions

Karamanoukian, H. L., Glick, P. L., Zayek, M., Steinhorn, R. H., Zwass, M. S., Fineman, J. R., and Morin, F. C. 3rd. Inhaled nitric oxide in congenital hypoplasia of the lungs due to diaphragmatic hernia or oligohydramnios. Pediatrics 1994; 94(5):715-8.
Article does not include infants born at less than 34 weeks gestation

Kauffmann, F. and Nadif, R.. Candidate interactions. Eur Respir J 2007; 30(1):3-4.
No original data
Article does not include infants born at less than 34 weeks gestation

Kavvadia, V., Greenough, A., Lilley, J., Laubscher, B., Dimitriou, G., Boa, F., and Poyser, K.. Plasma arginine levels and the response to inhaled nitric oxide in neonates. Biol. Neonate 1999; 76(6):340-347.
Article does not address any of the Key Questions

Kawakami, H. and Ichinose, F.. Inhaled nitric oxide in pediatric cardiac surgery. Int Anesthesiol Clin 2004; 42(4):93-100
No original data

Keller RL, Hawgood S, Neuhaus JM, Farmer DL, Lee H, Albanese CT, Harrison MR, and Kitterman JA. Infant pulmonary function in a randomized trial of fetal tracheal occlusion for severe congenital diaphragmatic hernia.. Pediatric research 2004; 56(5):818-25.
Article does not address any of the Key Questions

Kelly, L. K., Porta, N. F., Goodman, D. M., Carroll, C. L., and Steinhorn, R. H.. Inhaled prostacyclin for term infants with persistent pulmonary hypertension refractory to inhaled nitric oxide. J Pediatr 2002; 141(6):830-2.
Article does not include infants born at less than 34 weeks gestation

Khawahur, H., Kattan, A., Al-Alaiyan, S., and Saidy, K.. Congenital diaphragmatic hernia: A local experience. Ann. Saudi Med. 1999; 19(6):501-504.
Article does not include infants born at less than 34 weeks gestation
Article does not address any of the Key Questions

Khemani, E., McElhinney, D. B., Rhein, L., Andrade, O., Lacro, R. V., Thomas, K. C., and Mullen, M. P.. Pulmonary artery hypertension in formerly premature infants with bronchopulmonary dysplasia: clinical features and outcomes in the surfactant era. Pediatrics 2007; 120(6):1260-9.
Article does not include pre-term infants who were treated with inhaled nitric oxide
Article does not address any of the Key Questions

Kieffer, F.; Kassis, M.; Coatantiec, Y.; Magny, J. F., and Voyer, M. Persistent pulmonary hypertension of the newborn and nitric oxide: From the physiology to the therapy: Hypertension arterielle pulmonaire persistante du nouvea-ne et monoxyde d'azote: De la physiologie a la therapeutique. J. Pediatr. Pueric. 1997; 10(4):195-199.
Unobtainable

Kiefer, A. S., Wickremasinghe, A. C., Johnson, J. N., Hartman, T. K., Hintz, S. R., Carey, W. A., and Colby, C. E.. Medical management of extremely low-birth-weight infants in the first week of life: a survey of practices in the United States. Am J Perinatol 2009; 26(6):407-18.
Article does not address any of the Key Questions

Kilbride, H. W. and Thibeault, D. W.. Strategies of cardiovascular and ventilatory management in preterm infants with prolonged rupture of fetal membranes and oligohydramnios. J Perinatol 2002; 22(6):510.
No original data

Kim do, H., Park, J. D., Kim, H. S., Shim, S. Y., Kim, E. K., Kim, B. I., Choi, J. H., and Park, G. W.. Survival rate changes in neonates with congenital diaphragmatic hernia and its contributing factors. J Korean Med Sci 2007; 22(4):687-92.
Article does not address any of the Key Questions
Article does not include pre-term infants who were treated with inhaled nitric oxide

Kinsella JP and Abman SH. High-frequency oscillatory ventilation augments the response to inhaled nitric oxide in persistent pulmonary hypertension of the newborn: Nitric Oxide Study Group.. Chest 1998; 114(1 Suppl):100S.
Article does not include infants born at less than 34 weeks gestation
Other reason

Kinsella, J. P. and Abman, S. H.. Clinical approach to inhaled nitric oxide therapy in the newborn with hypoxemia. J. Pediatr. 2000; 136(6):717-726.
No original data

Kinsella, J. P. and Abman, S. H.. Efficacy of inhalational nitric oxide therapy in the clinical management of persistent pulmonary hypertension of the newborn. Chest 1994; 105(3 Suppl):92S-94S.
Article does not include infants born at less than 34 weeks gestation

Kinsella, J. P. and Abman, S. H.. Methaemoglobin during nitric oxide therapy with high-frequency ventilation [4]. Lancet 93; 342(8871):615.
Article does not address any of the Key Questions
Other reason

Kinsella, J. P., Griebel, J., Schmidt, J. M., and Abman, S. H.. Use of inhaled nitric oxide during interhospital transport of newborns with hypoxemic respiratory failure. Pediatrics 2002; 109(1):158-161.
Article does not address any of the Key Questions

Kinsella, J. P., Neish, S. R., Shaffer, E., and Abman, S. H.. Low-dose inhalation nitric oxide in persistent pulmonary hypertension of the newborn. Lancet 1992; 340(8823):819-20.
Article does not include infants born at less than 34 weeks gestation

Kinsella, J. P., Parker, T. A., Ivy, D. D., and Abman, S. H.. Noninvasive delivery of inhaled nitric oxide therapy for late pulmonary hypertension in newborn infants with congenital diaphragmatic hernia. J. Pediatr. 2003; 142(4):397-401.
Article does not include infants born at less than 34 weeks gestation

Kinsella, J. P., Schmidt, J. M., Griebel, J., and Abman, S. H.. Inhaled nitric oxide treatment for stabilization and emergency medical transport of critically ill newborns and infants. Pediatrics 1995; 95(5):773-6.
Article does not include infants born at less than 34 weeks gestation

Kinsella, J. P., Torielli, F., Ziegler, J. W., Dunbar Ivy, D., and Abman, S. H.. Dipyridamole augmentation of response to nitric oxide [28]. LANCET 1995; 346(8975):647-648.
No original data
Article does not address any of the Key Questions

Kinsella, J. P., Truog, W. E., Walsh, W. F., Goldberg, R. N., Bancalari, E., Mayock, D. E., Redding, G. J., deLemos, R. A., Sardesai, S., McCurnin, D. C., Moreland, S. G., Cutter, G. R., and Abman, S. H.. Randomized, multicenter trial of inhaled nitric oxide and high-frequency oscillatory ventilation in severe, persistent pulmonary hypertension of the newborn. J Pediatr 1997; 131(1 Pt 1):55-62.
Article does not include infants born at less than 34 weeks gestation

Kinsella, J. P.. Clinical trials of inhaled nitric oxide therapy in the newborn. Pediatr Rev 1999; 20(11):e110-3.
No original data

Kissoon, N.. Nitric oxide: to inhale or not to inhale.. Pediatr Crit Care Med 2004; 5(2):196-198.
No original data

Knopf, D.. Neonatology: Help for preterm infants: Neonatologie: Hilfe fur fruhgeborene. Pharm. Ztg. 2005; 150(33):29.
Not written in English and cannot determine eligibility

Koh, T. H., Gandini, D., and Vijayakumar, P.. The neonatal inhaled nitric oxide study. J Pediatr 2001; 138(2):300.
No human data included
Other reason

Kohelet, D.. Nitric oxide inhalation and high frequency oscillatory ventilation for hypoxemic respiratory failure in infants. Isr. Med. Assoc. J. 2003; 5(1):19-23.
Article address Key Question 1 or 2 ONLY and is not a randomized controlled trial

Konig, K. and Henschke, P.. Successful weaning of nitric oxide facilitated by a single dose of sildenafil in a baby with persistent pulmonary hypertension of the newborn. Pediatr Pulmonol 2009; 44(8):837.
Article does not include infants born at less than 34 weeks gestation

Kruse-Ruijter, M. F. and Zimmermann, L. J. I.. Persistent pulmonary hypertension in a neonate caused by blood aspiration following vaginal blood loss: Persisterende pulmonale hypertensie bij een neonaat door bloedaspiratie ten gevolge van vaginaal bloedverlies. Ned. Tijdschr. Geneeskd. 2007; 151(28):1585-1588.
Not written in English and cannot determine eligibility

Kulkarni, A.. Changing trends in neonatal pharmacotherapy. Perinatology 2004; 6(5):231-236.
No original data

Lago, P., Meneghini, L., Chiandetti, L., Tormena, F., Metrangolo, S., and Gamba, P.. Congenital diaphragmatic hernia: Intensive care unit or operating room?. Am. J. Perinatol. 2005; 22(4):189-197.
Article does not include infants born at less than 34 weeks gestation
Article does not address any of the Key Questions

Lakatos, L. and Oroszlan, G.. Possible effect of D-penicillamine on the physiologic action of inhaled nitric oxide in neonates. J Pediatr 1994; 124(4):656-7.
No original data
No human data included

Lakatos, L.. [Effect of penicillamine D, nitric oxide, or both?]. Orv Hetil 1993; 134(41):2283.
Not written in English and cannot determine eligibility

Article does not include pre-term infants who were treated with inhaled nitric oxide

Laubscher, B., Greenough, A., Kavvadia, V., and Devane, S. P.. Response to nitric oxide in term and proterm infants. EUR. J. PEDIATR. 1997; 156(8):639-642.
Article does not address any of the Key Questions
No abstractable data

Lal, M. K. and Field, D. J. Clinical management of persistent pulmonary hypertension of the newborn. Perinatology. 2001; 3(5):249-261.
Unobtainable

Lee, S. K., McMillan, D. D., Ohlsson, A., Pendray, M., Synnes, A., Whyte, R., Chien, L. Y., and Sale, J.. Variations in practice and outcomes in the Canadian NICU network: 1996-1997. Pediatrics 2000; 106(5):1070-9.
Article does not address any of the Key Questions

Leipala, J. A., Williams, O., Sreekumar, S., Cheeseman, P., Rafferty, G. F., Hannam, S., Milner, A., and Greenough, A.. Exhaled nitric oxide levels in infants with chronic lung disease. Eur. J. Pediatr. 2004; 163(9):555-558
Article does not address any of the Key Questions

Lemke, R. P., Belik, J., Giddins, N. G., Fajardo, C. A., and Manitoba. Clinical experience in the use of inhaled nitric oxide in infants with pulmonary hypertension: Experience clinique relative a l'utilisation d'oxyde nitrique en inhalation chez les nourrissons atteints d'hypertension pulmonaire. Can. Respir. J. 1996; 3(5):295-300.
No abstractable data

Li, J. H.. [Treatment of periventricular leukomalacia in preterm infants]. Zhongguo Dang Dai Er Ke Za Zhi 2007; 9(4):327-9.
Not written in English and cannot determine eligibility

Lindner, W., Pohlandt, F., Grab, D., and Flock, F.. Acute respiratory failure and short-term outcome after premature rupture of the membranes and oligohydramnios before 20 weeks of gestation. J. Pediatr. 2002; 140(2):177-182.
Article does not address any of the Key Questions

Lindroth, M.. [Are there any cost-benefit limits in connection with neonatal care?]. Lakartidningen 2002; 99(3):208.
Not written in English and cannot determine eligibility

Lonnqvist, P. A. and Jonsson, B.. [Premature infants benefit from inhaled nitric oxide, too. Not only full-term infants with severe hypoxic respiratory failure]. Lakartidningen 2005; 102(50):3880-2.
Not written in English and cannot determine eligibility
Article does not include infants born at less than 34 weeks gestation

Lonnqvist, P. A., Jonsson, B., Winberg, P., and Frostell, C. G.. Inhaled nitric oxide in infants with developing or established chronic lung disease. Acta Paediatr 1995; 84(10):1188-92.
No abstractable data

Lonnqvist, P. A.. Efficacy and economy of inhaled nitric oxide in neonates accepted for extra-corporeal membrane oxygenation. Acta Physiol Scand 1999; 167(2):175-9.
Article does not include infants born at less than 34 weeks gestation
Article does not address any of the Key Questions

Lonnqvist, P. A.. Inhaled nitric oxide in newborn and paediatric patients with pulmonary hypertension and moderate to severe impaired oxygenation: Effects of doses of 3-100 parts per million. Intensive Care Med. 1997; 23(7):773-779.
Article does not include infants born at less than 34 weeks gestation

Lopez Herrera, M. C., Roman, L., Lopez De Heredia, J., and Valls Soler, I. A.. Nitric oxide administration [1]: Administracion de Oxido Nitrico [1]. An. Esp. Pediatr. 1995; 43(4):293-294.
Not written in English and cannot determine eligibility
Other reason

Lopez-Herce Cid, J., Garcia Sanchez, E., Garcia Sanz, C., Ruperez Lucas, M., Alcaraz Romero, A., and Carrillo Alvarez, A.. [Effects of prone position, inhaled nitric oxide and surfactant in children with hypoxemic pulmonary disease]. An Pediatr (Barc) 2003; 58(2):106-14.
Not written in English and cannot determine eligibility

Lopez-Herce Cid, J., Sanchez Galindo, A., Carrillo Alvarez, A., Sancho Perez, L., Serina Ramirez, C., and Cuesta Alvaro, P.. [Nitric oxide treatment in children: clinical course, toxicity and factors influencing its effects]. An Esp Pediatr 1997; 46(6):542-8.
Not written in English and cannot determine eligibility

Lopez-Herce Cid, J., Sanchez Galindo, A., Carrillo Alvarez, A., Sancho Perez, L., Serina Ramirez, C., and Cuesta Alvaro, P.. Nitric oxide treatment in children: Clinical evolution, toxicity and factors influencing its effects: Tratamiento con oxido nitrico en ninos: Evolucion clinica, toxicidad y factores que influyen en la respuesta. An. Esp. Pediatr. 1997; 46(6):542-548.
Not written in English and cannot determine eligibility

Lopez-Herce Cid, J.; Cueto Calvo, E.; Carrillo Alvarez, A.; Vazquez Garcia, P.; Bustinza Arriortua, A., and Moral Torrero, R. Acute effects of inhaled nitric oxide in children: Respuesta aguda a la administracion de oxido nitrico en ninos. An. Esp. Pediatr. 1997; 46(6):581-586.
Unobtainable

Lorch S A, Cnaan A, and Barnhart K. Cost-effectiveness of inhaled nitric oxide for the management of persistent pulmonary hypertension of the newborn (Structured abstract). Pediatrics 2004; 114(2):417-426.

Article does not include infants born at less than 34 weeks gestation
Article does not address any of the Key Questions

Lorch, S. A., Banks, B. A., Christie, J., Merrill, J. D., Althaus, J., Schmidt, K., Ballard, P. L., Ischiropoulos, H., and Ballard, R. A.. Plasma 3-nitrotyrosine and outcome in neonates with severe bronchopulmonary dysplasia after inhaled nitric oxide. Free Radic Biol Med 2003; 34(9):1146-52.
No abstractable data

Lu, Y. and Sun, B.. [Effect of inhaled nitric oxide on methemoglobin levels in children]. Zhongguo Dang Dai Er Ke Za Zhi 2008; 10(2):257-8.
Not written in English and cannot determine eligibility

Luis, A. L., Avila, L. F., Encinas, J. L., Andres, A. M., Suarez, O., Elorza, D., Rodriguez, I., Martinez, L., Murcia, J., Lassaletta, L., and Tovar, J. A.. Results of the treatment of congenital diaphagmatic hernia with conventional terapeutics modalities: Resultados en el tratamiento de la hernia diafragmaitica con terapias convencionales.. Cir Pediatr 2006; 19(3):167-172.
Not written in English and cannot determine eligibility

Maderuelo Rodriguez, E., Sanz Lopez, E., Franco Fernandez, M. L., Bernardo Atienza, B., and Sanchez Luna, M.. Rescue treatment with inhaled nitric oxide in preterm newborns with respiratory failure: Oxido nitrico inhalado como rescate en insuficiencia respiratoria del recien nacido inmaduro. An. Pediatr. 2005; 62(1):68-71.
Not written in English and cannot determine eligibility

Martin, R. J.. Nitric oxide for preemies--not so fast. N Engl J Med 2003; 349(22):2157-9.
No original data

Meadow, W., Lee, G., Lin, K., and Lantos, J.. Changes in mortality for extremely low birth weight infants in the 1990s: implications for treatment decisions and resource use. Pediatrics 2004; 113(5):1223-9.
Article does not include pre-term infants who were treated with inhaled nitric oxide
Article does not address any of the Key Questions

Mercier, J. C., Zupan, V., Renaudin, M. H., Raveau, C., and Dehan, M.. Inhaled nitric oxide in newborns: Inhalation de Monoxide d'Azote: Espoirs et Precautions en Neonatologie. RBM Rev. Eur. Technol. Biomed. 1993; 15(3):150-155.
Not written in English and cannot determine eligibility

Mercier, J. C.. Uncertainties about the use of inhaled nitric oxide in preterm infants. Acta Paediatr Suppl 2001; 90(436):15-8.
No original data

Mercier, J.-C., Lacaze, T., Storme, L., Roze, J.-C., Dinh-Xuan, A. T., Dehan, M., Zupan, V., Gouyon, J. B., Francoise, M., Durand, P., Galperine, I., Oriot, D., Menget, A., Daoud, P., Jouvet, P., Morville, P., Devaux, A. M., Desfreres, L., Magny, J. F., and Simeoni, U.. Disease-related response to inhaled nitric oxide in newborns with severe hypoxaemic respiratory failure. Eur. J. Pediatr. 1998; 157(9):747-752.
No abstractable data

Mercier, J.-C., Zupan, V., Dehan, M., Renaudin, M.-H., Bouchet, M., and Raveau, C.. Device to monitor concentration of inhaled nitric oxide [5]. Lancet 1993; 342(8868):431-432.
No original data
Article does not address any of the Key Questions

Mersal, A., Attili, I., and Alkhotani, A.. Severe neonatal pulmonary hypertension secondary to antenatal maternal diclofenac ingestion reversed by inhaled nitric oxide and oral sildenafil. Ann Saudi Med 2007; 27(6):448-9.
Article does not include infants born at less than 34 weeks gestation

Migliazza, L., Bellan, C., Alberti, D., Auriemma, A., Burgio, G., and Colombo, G. L. e. A.. Retrospective study of 111 cases of congenital diaphragmatic hernia treated with early high-frequency oscillatory ventilation and presurgical stabilization. J. Pediatr. Surg. 2007; 42(9):1526-1532.
Article does not include infants born at less than 34 weeks gestation
Article does not address any of the Key Questions

Miller, A. A.. Diseases of progress in neonatal care [1]. J. Perinatol. 2005; 25(8):557.
No original data

Milner, A. D. and Aiton, N.. Nitric oxide inhalation.. Pediatr Pulmonol Suppl 1995; 11:100-101.
No original data

Moore, F. A. and Haenel, J. B.. Ventilatory strategies for acute respiratory failure. Am J Surg 1997; 173(1):53-6; discussion 57-8.
No original data
Article does not address any of the Key Questions

Morin, F. C. 3rd and Stenmark, K. R.. Persistent pulmonary hypertension of the newborn. Am J Respir Crit Care Med 1995; 151(6):2010-32.
No original data

Mosca, F., Bray, M., Stucchi, I., and Fumagalli, M.. Pulmonary hypertension after ibuprofen prophylaxis in very preterm infants [5]. Lancet 2002; 360(9338):1023-1024.
Article does not address any of the Key Questions

Motti, A., Tissot, C., Rimensberger, P. C., Prina-Rousso, A., Aggoun, Y., Berner, M., Beghetti, M., and Da Cruz, E.. Intravenous adenosine for refractory pulmonary hypertension in a low-weight premature newborn: A

potential new drug for rescue therapy. Pediatr. Crit. Care Med. 2006; 7(4):380-382.
Article does not address any of the Key Questions

Mourani, P. M., Ivy, D. D., Gao, D., and Abman, S. H.. Pulmonary vascular effects of inhaled nitric oxide and oxygen tension in bronchopulmonary dysplasia. Am J Respir Crit Care Med 2004; 170(9):1006-13.
Article does not include infants born at less than 34 weeks gestation
Article does not include pre-term infants who were treated with inhaled nitric oxide

Movahhedian, H. R., Kashani, I. A., Sine, D., Bull, D., Lyons Jones, K., and Rothman, A.. Pulmonary hypertension and trisomy 16. Pediatr. Cardiol. 1998; 19(2):187-189.
Article does not include infants born at less than 34 weeks gestation

Muller, W., Kachel, W., Kuntz, S., Lasch, P., and Varnholt, V.. Treatment of severe persistent pulmonary hypertension of the newborn (PPHN) with nitric oxide (NO): DIE BEHANDLUNG DER PERSISTIERENDEN PULMONALEN HYPERTONIE DES NEUGEBORENEN (PPHN) DURCH STICKOXIDINHALATION (NO). MONATSSCHR. KINDERHEILKD. 1995; 143(5):466-474.
Not written in English and cannot determine eligibility

Munshi, U. K. and Clark, D. A.. Meconium aspiration syndrome. Contemp. Clin. Gynecol. Obstet. 2002; 2(3):247-254.
No original data

Mupanemunda, R. H. and Edwards, A. D.. Treatment of newborn infants with inhaled nitric oxide. Arch Dis Child Fetal Neonatal Ed 1995; 72(2):F131-4.
No original data

Nakajima, W., Ishida, A., Arai, H., and Takada, G.. Methaemoglobinaemia after inhalation of nitric oxide in infant with pulmonary hypertension. Lancet 9197; 350(9083):1002-3.
Article does not include infants born at less than 34 weeks gestation

Namachivayam P, Theilen U, Butt WW, Cooper SM, Penny DJ, and Shekerdemian LS. Sildenafil prevents rebound pulmonary hypertension after withdrawal of nitric oxide in children.. American journal of respiratory and critical care medicine 2006; 174(9):1042-7.
Article does not address any of the Key Questions
Other reason

Nawaz, A., Shawis, R., Matta, H., Jacobsz, A., and Al-Salem, A.. Congenital diaphragmatic hernia: The impact of preoperative stabilization on outcome. Ann. Saudi Med. 1999; 19(6):541-543.
Article does not include infants born at less than 34 weeks gestation
Article does not include pre-term infants who were treated with inhaled nitric oxide

Ng, G. Y., Derry, C., Marston, L., Choudhury, M., Holmes, K., and Calvert, S. A.. Reduction in ventilator-induced lung injury improves outcome in congenital diaphragmatic hernia?. Pediatr Surg Int 2008; 24(2):145-50.
Article does not address any of the Key Questions

Ng, P. C., Fok, T. F., Lee, C. H., Cheung, K. L., So, K. W., To, K. F., and Wong, W.. Congenital cytomegalovirus infection presenting as severe persistent pulmonary hypertension of the newborn.. J Perinatol 1998; 18(3):234-237.
Article does not include infants born at less than 34 weeks gestation

Ngougmna, E., Ostrea Jr., E. M., and Konduri, G. G.. Analysis of nonsteroidal antiinflammatory drugs in meconium and its relation to persistent pulmonary hypertension of the newborn. Pediatrics 2001; 107(3):519-523.
Article does not include infants born at less than 34 weeks gestation

Nicholl, R.. Nitric oxide in preterm babies. Arch Dis Child 2002; 86(1):59-60.
No original data

Noori, S., Friedlich, P., Wong, P., Garingo, A., and Seri, I.. Cardiovascular effects of sildenafil in neonates and infants with congenital diaphragmatic hernia and pulmonary hypertension. Neonatology 2007; 91(2):92-100.
No abstractable data

Norden, M. A., Butt, W., and McDougall, P.. Predictors of survival for infants with congenital diaphragmatic hernia. J Pediatr Surg 1994; 29(11):1442-6.
Article does not include infants born at less than 34 weeks gestation
Other reason

Normand, C. E., Field, D., Elbourne, D., and Truesdale, A.. Nitric oxide is not licensed for preterm neonates. BMJ 2002; 325(7374):1244.
No original data

Obara, H., MIkawa, K., Nishina, K., Maekawa, N., Kawai, S., Hisano, K., Shiga, M., Suzuki, K., Iga, K., and Ri, Y.. Inhalational nitric oxide therapy for pulmonary hypertension. Masui 1994; 43 Suppl:S207-215.
Not written in English and cannot determine eligibility

Ochikubo, C. G., Waffarn, F., Turbow, R., and Kanakriyeh, M.. Echocardiographic evidence of improved hemodynamics during inhaled nitric oxide therapy for persistent pulmonary hypertension of the newborn. Pediatr Cardiol 1997; 18(4):282-7.
Article does not include infants born at less than 34 weeks gestation
Article does not address any of the Key Questions

Okawada, M., Okazaki, T., Yamataka, A., Yanai, T., Kato, Y., Kobayashi, H., Lane, G. J., and Miyano, T.. Efficacy of protocolized management for congenital diaphragmatic hernia. a review of 100 cases. Pediatr Surg Int 2006; 22(11):925-30.
Article does not include infants born at less than 34 weeks gestation

Okazaki, T., Okawada, M., Shiyanagi, S., Shoji, H., Shimizu, T., Tanaka, T., Takeda, S., Kawashima, K., Lane, G. J., and Yamataka, A.. Significance of pulmonary artery size and blood flow as a predictor of outcome in congenital diaphragmatic hernia. Pediatr Surg Int 2008; 24(12):1369-73.
Article does not include infants born at less than 34 weeks gestation

Okuyama, H., Kubota, A., Kawahara, H., Oue, T., Kitayama, Y., and Yagi, M.. Correlation between lung scintigraphy and long-term outcome in survivors of congenital diaphragmatic hernia. Pediatr. Pulmonol. 2006; 41(9):882-886.
Article does not include infants born at less than 34 weeks gestation
Article does not address any of the Key Questions

Okuyama, H., Kubota, A., Oue, T., Kuroda, S., Ikegami, R., Kamiyama, M., Kitayama, Y., and Yagi, M.. Inhaled nitric oxide with early surgery improves the outcome of antenatally diagnosed congenital diaphragmatic hernia. J Pediatr Surg 2002; 37(8):1188-90.
Article does not include infants born at less than 34 weeks gestation

Oriot, D., Boussemart, T., Berthier, M., Bonneau, D., and Coisne, D.. Paradoxical effect of inhaled nitric oxide in a newborn with pulmonary hypertension. Lancet 1993; 342(8867):364-5.
Article does not include infants born at less than 34 weeks gestation

Osiovich, H. C.. Improving survival of neonates with isolated congenital diaphragmatic hernia. Indian Pediatr 2004; 41(11):1138-42.
Article does not include infants born at less than 34 weeks gestation

Parker, T. A., Ivy, D. D., Kinsella, J. P., Torielli, F., Ruyle, S. Z., Thilo, E. H., and Abman, S. H.. Combined therapy with inhaled nitric oxide and intravenous prostacyclin in an infant with alveolar-capillary dysplasia. Am. J. Respir. Crit. Care Med. 1997; 155(2):743-746.
Article does not include infants born at less than 34 weeks gestation

Parker, T. A., Kinsella, J. P., and Abman, S. H.. Response to inhaled nitric oxide in persistent pulmonary hypertension of the newborn: relationship to baseline oxygenation. J Perinatol 1998; 18(3):221-5.
Article does not include infants born at less than 34 weeks gestation

Patole, S., Lee, J., and Whitehall, J.. Adenosine infusion in the management of a micropremi neonate with pulmonary hypertension. Indian Pediatr. 1999; 36(3):307-310.
Article does not include pre-term infants who were treated with inhaled nitric oxide
Article does not address any of the Key Questions

Pawlik, T. D., Porta, N. F., Steinhorn, R. H., Ogata, E., and deRegnier, R. A.. Medical and financial impact of a neonatal extracorporeal membrane oxygenation referral center in the nitric oxide era. Pediatrics 2009; 123(1):e17-24.
Article does not include infants born at less than 34 weeks gestation
Article does not address any of the Key Questions

Peliowski, A., Finer, N. N., Etches, P. C., Tierney, A. J., and Ryan, C. A.. Inhaled nitric oxide for premature infants after prolonged rupture of the membranes. J Pediatr 1995; 126(3):450-3.
Article does not address any of the Key Questions

Perreault, T. ECMO or no ECMO: Do no harm: ECMO o no ECMO: No hacer dano. An. Esp. Pediatr. 2002; 57(1):1-4.
Unobtainable

Peterson, A. L., Deatsman, S., Frommelt, M. A., Mussatto, K., and Frommelt, P. C.. Correlation of echocardiographic markers and therapy in persistent pulmonary hypertension of the newborn. Pediatr Cardiol 2009; 30(2):160-5.
Article does not include infants born at less than 34 weeks gestation
Article does not address any of the Key Questions

Petros, A. J., Cox, P. B., and Bohn, D.. Simple method for monitoring concentration of inhaled nitric oxide [21]. Lancet 1992; 340(8828):1167.
Article does not address any of the Key Questions
Other reason

Pierce, C. M., Petros, A. J., and Fielder, A. R.. No evidence for severe retinopathy of prematurity following sildenafil [14]. Br. J. Ophthalmol. 2005; 89(2):250.
No original data

Posencheg, M. A., Gow, A. J., Truog, W. E., Ballard, R. A., Cnaan, A., Golombek, S. G., and Ballard, P. L.. Inhaled nitric oxide in premature infants: effect on tracheal aspirate and plasma nitric oxide metabolites. J Perinatol 2009.
No abstractable data

Puckett, B.. Congenital diaphragmatic hernia: two case studies with atypical presentations. Neonatal Netw 2006; 25(4):239-49.
Article does not include infants born at less than 34 weeks gestation

Raimondi, F., Migliaro, F., Capasso, L., Ausanio, G., Bisceglia, M., Giliberti, P., Messina, F., Salvia, G., and Paludetto, R.. Intravenous magnesium sulphate vs. inhaled nitric oxide for moderate, persistent pulmonary hypertension of the newborn. A Multicentre, retrospective study. J Trop Pediatr 2008; 54(3):196-9.
Article does not include infants born at less than 34 weeks gestation

Reliability and Accuracy of Cranial Ultrasound in the NICHD Randomized Controlled Trial of Inhaled Nitric Oxide for Premature Infants with Severe Respiratory Failure. American Pediatric Society/SocieTY for Pediatric Research Abstract. 2006. CODEN: RCT; ISSN: CN-00711876.
Unobtainable

Rennie, J. M. and Bokhari, S. A.. Recent advances in neonatology. Arch Dis Child Fetal Neonatal Ed 1999; 81(1):F1-4.
No original data

Reyes, C., Chang, L. K., Waffarn, F., Mir, H., Warden, M. J., and Sills, J.. Delayed repair of congenital diaphragmatic hernia with early high-frequency oscillatory ventilation during preoperative stabilization. J Pediatr Surg 1998; 33(7):1010-4; discussion 1014-6.
Article does not include pre-term infants who were treated with inhaled nitric oxide

Riddle, E. M., Feltes, T. F., Rosen, K., Fraley, J. K., Mott, A. R., and Kovalchin, J. P.. Association of nitric oxide dose and methemoglobin levels in patients with congenital heart disease and pulmonary hypertension. Am J Cardiol 2002; 90(4):442-4.
Article does not include infants born at less than 34 weeks gestation
Other reason

Rieger-Fackeldey, E., Genzel-Boroviczeny, O., and Schulze, A.. Severe systemic cytomegalovirus infection of premature infants acquired through breastmilk: Schwere systemische zytomegalie-virusinfektion fruhgeborener uber die muttermilch. Monatsschr. Kinderheilkd. 2001; 149(10):1059-1062.
Not written in English and cannot determine eligibility

Rite Gracia, S., Ruiz Moreno, J. A., Sanchez Gimeno, J., Molina Chica, M. I., Marco Tello, A., and Rite Montanes, S.. [Inhaled nitric oxide in the treatment of persistent pulmonary hypertension in a newborn]. An Esp Pediatr 1999; 51(2):181-5.
Not written in English and cannot determine eligibility

Roberts, J. D. Jr. Inhaled nitric oxide for treatment of pulmonary artery hypertension in the newborn and infant. Crit Care Med 1993; 21(9 Suppl):S374-6.
No original data

Roberts, J. D., Polaner, D. M., Lang, P., and Zapol, W. M.. Inhaled nitric oxide in persistent pulmonary hypertension of the newborn. Lancet 1992; 340(8823):818-819.
Article does not include infants born at less than 34 weeks gestation

Roberta AB. Improved Outcome with Inhaled Nitric Oxide in Preterm Infants Mechanically Ventilated at 7–21 Days of Age. American Pediatric Society/SocieTY for Pediatric Research Abstract. 2006. Coden: RCT; ISSN: CN-00711486.
Unobtainable

Robinson, T., Stewart, D. L., and Hilbert, T.. Use of inhaled nitric oxide for the treatment of persistent pulmonary hypertension of the newborn (PPHN). J Ky Med Assoc 1999; 97(3):100-4.
No original data
Article does not include infants born at less than 34 weeks gestation

Rocha, G. M., Bianchi, R. F., Severo, M., Rodrigues, M. M., Baptista, M. J., Correia-Pinto, J., and Guimaraes, H. A.. Congenital diaphragmatic hernia - The neonatal period (Part I). Eur. J. Pediatr. Surg. 2008; 18(4):219-223.
Article does not include infants born at less than 34 weeks gestation
Article does not address any of the Key Questions

Roofthooft, M. T. R., Bergman, K. A., Waterbolk, T. W., Ebels, T., Bartelds, B., and Berger, R. M. F.. Persistent Pulmonary Hypertension of the Newborn With Transposition of the Great Arteries. Ann. Thorac. Surg. 2007; 83(4):1446-1450.
No abstractable data
Article does not include pre-term infants who were treated with inhaled nitric oxide

Rosati, E., Butera, G., Bossone, E., De Felice, C., and Latini, G.. Inhaled nitric oxide and oral nifedipine in a preterm infant with bronchopulmonary dysplasia and pulmonary hypertension. Eur. J. Pediatr. 2007; 166(7):737-738.
No abstractable data

Rosenberg, A. A.. Inhaled nitric oxide in the premature infant with severe hypoxemic respiratory failure: A time for caution. J. Pediatr. 1998; 133(6):720-722.
No original data

Roze, J.-C., Storme, L., Zupan, V., Morville, P., Dinh-Xuan, A. T., and Mercier, J.-C.. Echocardiographic investigation of inhaled nitric oxide in newborn babies with severe hypoxaemia. Lancet 1994; 344(8918):303-305.
No abstractable data

Rutter, N.. Persistent pulmonary hypertension of the newborn. Care Crit. Ill 1993; 9(5):206-208.
No original data

Ryan, A. and Tobias, J. D.. A 5-year survey of nitric oxide use in a pediatric intensive care unit. Am J Ther 2007; 14(3):253-8.
Article does not address any of the Key Questions

Sarici, S. U., Kul, M., Candemir, G., Gursel, O., Alpay, F., and Gokcay, E.. Inhaled nitric oxide in a preterm newborn with severe hypoxemic respiratory failure. Gulhane Med. J. 2004; 46(3):255-257.
Article does not address any of the Key Questions

Saugstad, O. D.. Inhaled nitric oxide for preterm infants - Still an experimental therapy. Lancet 1999; 354(9184):1047-1048.
No original data

Saura, L., Castanon, M., Prat, J., Albert, A., Caceres, F., Moreno, J., and Gratacos, E.. Impact of fetal intervention on postnatal management of congenital diaphragmatic hernia. Eur J Pediatr Surg 2007; 17(6):404-7.
Article does not address any of the Key Questions
Other reason

Saw, H.-P., Ho, M.-L., and Chen, J.-Y.. Hearing impairment in very low birth weight infants incidence, risks factors analysis and follow up. Clin. Neonatol. 2005; 12(1):30-35.
Article does not address any of the Key Questions
Other reason

Saxena, A. K., Haxihja, E., Kleinlein, B., and Hollwarth, M. E.. Lymphoceles in premature infants after congenital diaphragmatic hernia repair: Thoracoscopic management. J. Thorac. Cardiovasc. Surg. 2007; 133(2):584-585.
Article does not address any of the Key Questions

Saygili, A., Ledieu, C., Casterman, P., Leke, A., Maingourd, Y., and Krim, G.. [Value of nitric oxide (NO) in neonatal right ventricular dysfunction]. Arch Pediatr 1998; 5(1):93-4.
Not written in English and cannot determine eligibility

Schmolzer, G., Urlesberger, B., Reiterer, F., Haim, M., Kutschera, J., Resch, B., and Muller, W.. Inhaled Nitric Oxide by Pulmonary Hypertension: Comparison Preterm Infants versus Newborn Infants: Inhalative Therapie mit Stickstoffmonoxid bei pulmonaler Hypertension: Vergleich des Effektes bei Fruh- und Neugeborenen. Klin. Padiatr. 2003; 215(5):257-261.
Not written in English and cannot determine eligibility

Schnapf, B. M., Barness, E. G., Ackerman, J., and Pomerance, H. H.. A newborn infant with tachypnea, intercostal retractions, and poor oxygen saturation. Pediatr. Pathol. Mol. Med. 2000; 19(1):73-84.
Article does not include infants born at less than 34 weeks gestation

Schreiber, M. D. and Marks, J. D.. No definitive recommendation for iNO in preterm infants. J Pediatr 2006; 149(1):146-7; author reply 147.
No abstractable data

Schreiber, M. D., Gin-Mestan, K., Marks, J. D., Huo, D., Lee, G., Srisuparp, P., and Meau-Petit, V.. Inhaled nitric oxide in premature infants with the respiratory distress syndrome: Commentary. Arch. Pediatr. 2004; 11(11):1367-1368.
No original data

Schreiber, M. D.. Methylene blue: NO panacea. J Pediatr 1996; 129(6):790-3.
No original data

Sebald, M., Friedlich, P., Burns, C., Stein, J., Noori, S., Ramanathan, R., and Seri, I.. Risk of need for extracorporeal membrane oxygenation support in neonates with congenital diaphragmatic hernia treated with inhaled nitric oxide. J. Perinatol. 2004; 24(3):143-146.
Article does not address any of the Key Questions

Seeniraj, K.. Respiratory distress in new born: Surgical causes and management. Ind. J. Pract. Pediatr. 2004; 6(1):27-31.
No original data

Sehgal, A., Callander, I., Stack, J., Momsen, T., and Sterling-Levis, K.. Experience with inhaled nitric oxide therapy in hypoxic respiratory failure of the newborn. Indian J Chest Dis Allied Sci 2005; 47(4):245-9.
Article does not address any of the Key Questions

Sehgal, A.. Continuous positive airway pressure - A gentler approach to ventilation [3]. Indian Pediatr. 2005; 42(4):393-394.
No original data
No human data included

Shah, N., Jacob, T., Exler, R., Morrow, S., Ford, H., Albanese, C., Wiener, E., Rowe, M., Billiar, T., Simmons, R., and et, a. l.. Inhaled nitric oxide in congenital diaphragmatic hernia. J Pediatr Surg 1994; 29(8):1010-4; discussion 1014-5.
Article does not include infants born at less than 34 weeks gestation

Shiyanagi, S., Okazaki, T., Shoji, H., Shimizu, T., Tanaka, T., Takeda, S., Kawashima, K., Lane, G. J., and Yamataka, A.. Management of pulmonary hypertension in congenital diaphragmatic hernia: nitric oxide with prostaglandin-E1 versus nitric oxide alone. Pediatr Surg Int 2008; 24(10):1101-4.
Article does not include infants born at less than 34 weeks gestation

Singh, M. and Kumar, L.. Management of respiratory failure.. Indian J Pediatr 1996; 63(1):53-60.
No original data

Siobal, M. S.. Combining heliox and inhaled nitric oxide as rescue treatment for pulmonary interstitial emphysema. Respir. Care 2009; 54(7):976-977.

Appendix D: List of Excluded Articles

Article does not address any of the Key Questions

Skimming JW, Bender KA, Hutchison AA, and Drummond WH. Nitric oxide inhalation in infants with respiratory distress syndrome.. The Journal of pediatrics 1997; 130(2):225-30.
No abstractable data

Skimming JW, Burchfield DJ, Wood CE, and Banner MJ. Nitric oxide inhalation facilitates carbon dioxide elimination in preterm infants with respiratory distress syndrome. Pediatric Research 2001; 49(4):283A.
Article does not address any of the Key Questions

Skott, O.. Renin. Am. J. Physiol. Regul. Integr. Comp. Physiol. 2002; 282(4 51-4):R937-R939.
No original data

Smyth, R. L.. Inhaled nitric oxide treatment for preterm infants with hypoxic respiratory failure. Thorax 2000; 55 Suppl 1:S51-5.
No original data

Soares, S., Rocha, G., Pissarra, S., Carrico, A., Azevedo, I., Simoes, J. S., and Guimaraes, H.. Pertussis with severe pulmonary hypertension in a newborn with good outcome - Case report: Infeccao por Bordetella pertussis com hipertensao pulmonar grave num recem-nascido com boa evolucao clinica - Caso clinico. Rev. Port. Pneumol. 2008; 14(5):687-692.
Article does not include infants born at less than 34 weeks gestation

Sokol, G. M., Fineberg, N. S., Wright, L. L., and Ehrenkranz, R. A.. Changes in arterial oxygen tension when weaning neonates from inhaled nitric oxide. Pediatr Pulmonol 2001; 32(1):14-9.
Article does not include infants born at less than 34 weeks gestation

Sood, B. G.. Re: Neonatal nitric oxide use: predictors of response and financial implications. J Perinatol 2004; 24(2):132; author reply 133.
No original data
Article does not address any of the Key Questions

Sreenan, C., Etches, P., and Osiovich, H.. The western Canadian experience with congenital diaphragmatic hernia: Perinatal factors predictive of extracorporeal membrane oxygenation and death. Pediatr. Surg. Int. 2001; 17(2-3):196-200.
Article does not include infants born at less than 34 weeks gestation
Article does not address any of the Key Questions

Steinhorn, R. H., Cox, P. N., Fineman, J. R., Finer, N. N., Rosenberg, E. M., Silver, M. M., Tyebkhan, J., Zwass, M. S., and Morin, F. C. 3rd. Inhaled nitric oxide enhances oxygenation but not survival in infants with alveolar capillary dysplasia. J Pediatr 1997; 130(3):417-22.
Article does not include infants born at less than 34 weeks gestation

Steinhorn, R. H.. Persistent pulmonary hypertension of the newborn.. Acta Anaesthesiol Scand Suppl 1997; 111:135-140.
No original data

Stoll, B. J. and Hansen, N.. Infections in VLBW infants: Studies from the NICHD Neonatal Research Network. Semin. Perinatol. 2003; 27(4):293-301.
No original data

Stranak, Z., Janota, J., Pycha, K., Snajdauf, J., and Simak, J.. [Delayed surgery in congenital diaphragmatic hernia without drainage of the ipsilateral hemithorax]. Rozhl Chir 1999; 78(12):622-6..
Not written in English and cannot determine eligibility

Stranak, Z., Zabrodsky, V., and Simak, J.. Changes in alveolar-arterial oxygen difference and oxygenation index during low-dose nitric oxide inhalation in 15 newborns with severe respiratory insufficiency. Eur J Pediatr 1996; 155(10):907-10
Article does not address any of the Key Questions
Other reason

Stranak, Z., Zabrodsky, V., and Simak, J.. Inhalation of nitric oxide in critically ill newborns. First clinical experience at the Inst. for the Care of Mother and Child, Prague: Inhalace Oxidu Dusnateho U Kriticky Nemocnych Novorozenco. Prvniklinicke Zkusenostiv Upmd Praha. Cesko-Slov. Pediatr. 1995; 50(5):275-279.
Not written in English and cannot determine eligibility

Subhedar NV and Shaw NJ. Neurodevelopmental outcome with inhaled nitric oxide therapy.. The Journal of pediatrics 1999; 135(2 Pt 1):266-7.
No abstractable data

Subhedar, N. and Dewhurst, C.. Is nitric oxide effective in preterm infants?. Arch Dis Child Fetal Neonatal Ed 2007; 92(5):F337-41.
No original data

Subhedar, N. V. and Shaw, N. J.. Changes in oxygenation and pulmonary haemodynamics in preterm infants treated with inhaled nitric oxide. Arch Dis Child Fetal Neonatal Ed 1997; 77(3):F191-7.
No abstractable data

Subhedar, N. V. and Shaw, N. J.. Inhaled nitric oxide in preterm infants at high risk of developing chronic lung disease (CLD). Early Hum. Dev. 1997; 49(3):211-212.
Article does not address any of the Key Questions

Subhedar, N. V., Jauhari, P., and Natarajan, R.. Cost of inhaled nitric oxide therapy in neonates [8]. Lancet 2002; 359(9319):1781-1782.
No original data
Article does not address any of the Key Questions

Sun, B.. Current progress of clinical trials for new drug evaluation in neonatal and pediatric clinics in China. Zhongguo Yao Li Xue Bao 1997; 18(6):537-9.
No original data

Susan RH. Neurodevelopmental Outcomes of the NICHD Randomized Controlled Trial of iNO for Premature Infants with Severe Respiratory Failure. American Pediatric Society/SocieTY for Pediatric Research Abstract. 2006. CODEN: RCT; ISSN: CN-00711875.
Unobtainable

Tang, S. F. and Miller, O. I.. Inhaled nitric oxide during emergency neonatal transportation. J Paediatr Child Health 1996; 32(6):539-41.
Article does not include infants born at less than 34 weeks gestation

Tang, S. F. and Miller, O. I.. Low-dose inhaled nitric oxide for neonates with pulmonary hypertension. J Paediatr Child Health 1996; 32(5):419-23.
Article does not include infants born at less than 34 weeks gestation

Tavares, A. P., Pimenta Junior, A. G., and Evora, P. R.. Basis for the therapeutic use of inhaled nitric oxide: Fundamentos para o uso terapeutico do oxido nitrico pela via inalatoria.. Arq. Bras. Cardiol. 1995; 64(1):45-52.
Not written in English and cannot determine eligibility

Ten Eick, A. P. and Gormley, A.. Phosphodiesterase inhibitors and persistent pulmonary hypertension of the newborn. Hosp. Pharm. 2004; 39(9):831-834.
No original data
Article does not address any of the Key Questions

Tolsa, J. F.. [Physiologic aspects of lung circulation in adjustment to extra-uterine life]. Arch Pediatr 2000; 7 Suppl 2:269s-270s.
Not written in English and cannot determine eligibility

Tommasoni, N., Gamba, P. G., Midrio, P., Biban, P., Pettenazzo, A., Zanon, G. F., and Guglielmi, M.. Congenital diaphragmatic hernia: the use of ECMO and other modern therapeutic strategies: Ernia congenita diaframmatica: impiego dell'ECMO e di altre moderne strategie terapeutiche.. Pediatr Med Chir 1996; 18(3):295-300.
Not written in English and cannot determine eligibility

Trevisanuto, D., Ferrarese, P., Biban, P., Cantarutti, F., and Zanardo, V.. Oxygenation response to NO in newborns with severe pulmonary hypertension [3]. Acta Paediatr. Int. J. Paediatr. 1996; 85(11):1387.
Article does not address any of the Key Questions

Truffert, P., Llado-Paris, J., Mercier, J. C., Dehan, M., and Breart, G.. Early inhaled nitric oxide in moderately hypoxemic preterm and term newborns with RDS: the RDS subgroup analysis of the Franco-Belgian iNO Randomized Trial. Eur J Pediatr 2003; 162(9):646-7.
No abstractable data

Truog, W. E., Ballard, P. L., Norberg, M., Golombek, S., Savani, R. C., Merrill, J. D., Parton, L. A., Cnaan, A., Luan, X., and Ballard, R. A.. Inflammatory markers and mediators in tracheal fluid of premature infants treated with inhaled nitric oxide. Pediatrics 2007; 119(4):670-678.
No abstractable data

Truog, W. E., Pallotto, E., Clark, P., Banks, B., Kaftan, H. A., Ekekezie, I. I., Norberg, M., and Ballard, R. A.. Interaction of endogenous endothelin-1 and inhaled nitric oxide in term and preterm infants. Clin. Sci. 2002; 103(SUPPL. 48):294S-297S.
Article does not address any of the Key Questions

Tung, B. J.. The use of nitric oxide therapy in the transport of newborns with persistent pulmonary hypertension. Air Med J 2001; 20(5):10-1.
No original data
Article does not include infants born at less than 34 weeks gestation

Turanlahti, M., Pesonen, E., Pohjavuori, M., Lassus, P., Fyhrquist, F., and Andersson, S.. Plasma cyclic guanosine monophosphate reflecting the severity of persistent pulmonary hypertension of the newborn. Biol Neonate 2001; 80(2):107-12.
No abstractable data

Turbow, R., Waffarn, F., Yang, L., Sills, J., and Hallman, M.. Variable oxygenation response to inhaled nitric oxide in severe persistent pulmonary hypertension of the newborn. Acta Paediatr 1995; 84(11):1305-8.
Article does not include infants born at less than 34 weeks gestation

Van Marter, L. J.. Epidemiology of bronchopulmonary dysplasia. Semin Fetal Neonatal Med 2009; 14(6):358-66.
No original data

Van Meurs, K. P., Rhine, W. D., Asselin, J. M., Durand, D. J., Peverini, R., Dudell, G., Butler, S., Durand, D., Asselin, J., Van Meurs, K., and Rhine, W.. Response of premature infants with severe respiratory failure to inhaled nitric oxide. PEDIATR. PULMONOL.1997; 24(5):319-323.
No abstractable data

Vento, M., Aguar, M., and Brugada, M.. Extremely premature infant: Overcoming inflammation and oxidative stress. Pediatr. Health 2008; 2(4):397-400.
No original data

Vieux, R., Fresson, J., Hascoet, J. M., Blondel, B., Truffert, P., Roze, J. C., Matis, J., Thiriez, G., Arnaud, C., Marpeau, L., and Kaminski, M.. Improving perinatal regionalization by predicting neonatal intensive care requirements of preterm infants: an EPIPAGE-based cohort study.. Pediatrics 2006; 118(1):84-90.

Appendix D: List of Excluded Articles

Article does not address any of the Key Questions

Von Buch, Ch. and Kachel, W.. Initiative application of nitric oxide in the treatment of persistent pulmonary hypertension of the newborn pretem baby - A case report: Inhalative stickoxid (NO)-anwendung zur behandlung der persistierenden pulmonalen hypertonie des fruhgeborenen fallberich. Monatsschr. Kinderheilkd. 1997; 145(7):708-711.
Not written in English and cannot determine eligibility
Article does not address any of the Key Questions

Vosatka, R. J.. Persistent pulmonary hypertension of the newborn [3]. New Engl. J. Med. 2002; 346(11):864.
No original data

Vyas, J. R., Currie, A. E., Shuker, D. E., Field, D. J., and Kotecha, S.. Concentration of nitric oxide products in bronchoalveolar fluid obtained from infants who develop chronic lung disease of prematurity. Arch Dis Child Fetal Neonatal Ed 1999; 81(3):F217-20.
Article does not include pre-term infants who were treated with inhaled nitric oxide
Article does not address any of the Key Questions

Westrope, C., Roberts, N., Nichani, S., Hunt, C., Peek, G. J., and Firmin, R.. Experience with mobile inhaled nitric oxide during transport of neonates and children with respiratory insufficiency to an extracorporeal membrane oxygenation center. Pediatr Crit Care Med 2004; 5(6):542-6.
Article does not include infants born at less than 34 weeks gestation
Article does not address any of the Key Questions

Whitelaw, A.. Towards a molecular basis for intraventricular haemorrhage: nitric oxide and impaired cerebral autoregulation. Acta Paediatr 2002; 91(4):373-4.
No original data

Wilkowski, J.. [Inhaled nitric oxide in the therapy of acute hypoxemic respiratory failure of newborn]. Med Wieku Rozwoj 2001; 5(4):301-14.
Not written in English and cannot determine eligibility

Williams, O., Hutchings, G., Debieve, F., and Debauche, C.. Contemporary neonatal outcome following rupture of membranes prior to 25 weeks with prolonged oligohydramnios. Early Hum. Dev. 2009; 85(5):273-277.
No abstractable data

Xiao, Z. H., Andre, P., Lacaze-Masmonteil, T., Audibert, F., Zupan, V., and Dehan, M.. Outcome of premature infants delivered after prolonged premature rupture of membranes before 25 weeks of gestation. Eur. J. Obstet. Gynecol. Reprod. Biol. 2000; 90(1):67-71.
No abstractable data

Yamaguchi, N. and Togari, H.. A multicenter clinical retrospective study of inhaled nitric oxide in neonates. ACTA NEONATOL. JPN. 1996; 32(3):464-471.
Not written in English and cannot determine eligibility

Yamaguchi, N., Togari, H., Takase, M., Hattori, S., Yamanami, S., Hasegawa, H., Hoshino, R., Tamura, M., Mimura, S., Suzuki, S., Futamura, M., Aotani, H., Sumi, K., Kusuda, S., Ichiba, H., Yong-Kye, L., Uetani, Y., Nakao, H., and Higuchi, R.. A prospective clinical study on inhaled nitric oxide therapy for neonates in Japan. Pediatr Int 2001; 43(1):20-5.
Article address Key Question 1 or 2 ONLY and is not a randomized controlled trial

Yao, C.-T., Wang, J.-N., Lin, C.-H., Yeh, C.-N., Tai, Y.-T., Wu, M.-H., and Wu, J.-M.. Prediction of outcome in infants with congenital diaphragmatic hernia or severe diaphragmatic eventration. Acta Paediatr. Taiwan. 2004; 45(3):131-135.
Article does not address any of the Key Questions

Yao, C.-T., Wang, J.-N., Lin, C.-H., Yeh, C.-N., Tai, Y.-T., Wu, M.-H., and Wu, J.-M.. Prediction of outcome in infants with congenital diaphragmatic hernia or severe diaphragmatic eventration. Acta Paediatr. Taiwan. 2004; 45(3):131-135.
Other reason

Yeh, T.-F.. Persistent pulmonary hypertension in preterm infants with respiratory distress syndrome. Pediatr. Pulmonol. 2001; 32(Suppl. 23):103-106.
No original data

Young, J. D.. The use of inhaled nitric oxide in the acute respiratory distress syndrome. Br J Hosp Med 1997; 57(4):126-7.
No original data

Yu, V. Y. H.. Persistent pulmonary hypertension in the newborn. Early Hum. Dev. 1993; 33(3):163-175.
No original data

Zamakhshary, M., Mah, K., Mah, D., Cameron, B., Bohn, D., Bass, J., Scott, L., and Kim, P. C. W.. Physiologic predictors for the need for patch closure in neonatal congenital diaphragmatic hernia. Pediatr. Surg. Int. 2008; 24(6):667-670.
Article does not include infants born at less than 34 weeks gestation

Zamakhshary, M., Mah, K., Mah, D., Cameron, B., Bohn, D., Bass, J., Scott, L., and Kim, P. C.. Physiologic predictors for the need for patch closure in neonatal congenital diaphragmatic hernia. Pediatr Surg Int 2008; 24(6):667-70.
Article does not address any of the Key Questions

Zecca, E., De Luca, D., Costa, S., Marras, M., and Romagnoli, C.. Neonatal intensive care and outcomes of extremely preterm infants: Changes over a decade. Ital. J. Pediat. 2006; 32(1):48-54.
Other reason

Zhan, Q. Y.. [The role of high frequency oscillatory ventilation in the treatment of acute respiratory distress syndrome]. Zhonghua Jie He He Hu Xi Za Zhi 2007; 30(10):740-1.
Not written in English and cannot determine eligibility

Ziebinski, M. and Walas, W.. The use of nitric oxide during transport of newborns with critical respiratory insufficiency: own experience, preliminary report: Wstepne doswiadczenia wlasne w stosowaniu tlenku azotu podczas transportu noworodkow z krytyczna niewydolnoscia oddechowa.. Prz. Lek. 2002; 59 Suppl 1:60-62.
Not written in English and cannot determine eligibility

Zorc, J. J. and Kanic, Z.. A cyanotic infant: True blue or otherwise?. Pediatr. Ann. 2001; 30(10):597-601.
No original data

Appendix E. Evidence Tables

Evidence Table 1: Risk of bias in randomized controlled trials.

Author, year	Followup studies	sequence adequately generated	allocation adequately concealed	allocated intervention adequately prevented for personnel during the study(ST)	allocated intervention adequately prevented for outcome assessors during the study (LT)	allocated intervention adequately prevented for personnel during the study(LT)	allocated intervention adequately prevented for outcome assessors during the study (LT)	incomplete outcome data adequately addressed (ST)	incomplete outcome data adequately addressed (LT)	reports of the study free of suggestion of selective outcome reporting	free of other problem s that could put it at a high risk of bias	RoB Score
Ballard, 2006[1]	HIbbs, 2007[2] Walsh, 2010[3]	+	+	+	+	+	+	+	+	+	+	**good**
Dani, 2006[4]		0	+	-	-					+	-	**poor**
Fanco-Belgium, 1999[5]			+		+	-	- +	0	0	+	+	**fair**
Field, 2005[6]	Huddy, 2008[7]	-	+	-	-	-	-	-	-	-	-	**poor**
Hascoet, 2005[8]	Hamon, 2005 [9]	+	+	0	0	0	0	+	+	0	+	**fair**
Kinsella, 1999[10]		+	+	+	+	+	+	+	+	+	+	**good**
KinsellaM, 2006[11]	Watson, 2009[12]	+	+	+	+			+		+	+	**good**
Mercier, 2010{#12262}		+	+	+	+	+	+	+	0		+	**fair**

Appendix E. Evidence Tables

Evidence Table 1: Risk of bias ion randomized controlled trials (continued).

Author, year	Followup studies	sequence adequately generated	allocation adequately concealed	allocated intervention adequately prevented for personnel during the study(ST)	allocated intervention adequately prevented for outcome assessors during the study (LT)	allocated intervention adequately prevented for personnel during the study(LT)	allocated intervention adequately prevented for outcome assessors during the study (LT)	incomplete outcome data adequately addressed (ST)	incomplete outcome data adequately addressed (LT)	reports of the study free of suggestion of selective outcome reporting	free of other problem s that could put it at a high risk of bias	RoB Score
Schreiber, 2003[13]	Mestan, 2005[14]	+	+	+	+			+		+	+	**good**
Srisuparp, 2002[15]		+	0	0	0	0	0	-	+	-	-	**poor**
Su, 2008[16]		+	0	-	0	-	0	-	0	+	0	**poor**
Subhedar, 1997[17]	Bennett, 2001[18]	+	0	-	-	0	0	+	0	0	-	**poor**
Van Meurs, 2005[19]	Chock, 2009[20] Hintz, 2007[21]	+	+	+	+			+		+	+	**good**
Van Meurs, 2007[22]	Chock[20]	+	+	+	+	+	+	+	+	+	+	**good**

Appendix E. Evidence Tables

Evidence Table 1: Risk of bias ion randomized controlled trials (continued).

KEY				
Category	**Question**	**Yes**	**No**	**Unclear**
Sequence generation:	Was the allocation sequence adequately generated?	+	-	0
Allocation concealment:	Was the allocation adequately concealed	+	-	0
Blinding of personnel (short-term outcomes)	Was knowledge of the allocation intervention adequately prevented for personnel during the study?	+	-	0
Blinding of outcome assessors (short-term outcomes)	Was knowledge of the allocated intervention adequately preventes for outcome assessors during the study?	+	-	0
Blinding of personnel long-term outcomes)	Was knowledge of the allocation intervention adequately prevented for personnel during the study?	+	-	0
Blinding of outcome assessors Long-term outcomes)	Was knowledge of the allocated intervention adequately preventes for outcome assessors during the study?	+	-	0
Incomplete outcome data (short-term)	Were incomplete data adequately addressed?	+	-	0
Incomplete outcome data (short-term)	Were incomplete data adequately addressed?	+	-	0
Selective outcome reporting	Are reports of the study free of suggestion of selective outcome reporting?	+	-	0
Other sources of bias	Was the study apparently free of other problems that could put it at high risk of bias?	+	-	0

good = all criteria were present "yes"
fair = greater than or equal to 50% of criteria are present
poor = less than 50% of criteria are present or unclear

Appendix E. Evidence Tables

Reference List

1. Ballard RA, Truog WE, Cnaan A *et al*. Inhaled nitric oxide in preterm infants undergoing mechanical ventilation. New Engl. J. Med. 2006; 355(4):343-53.
2. Hibbs AM, Walsh MC, Martin RJ *et al*. One Year Respiratory Outcomes of the Preterm Infants Enrolled in the NO CLD Trial of Inhaled Nitric Oxide (iNO). N/A 2007.
3. Walsh MC, Hibbs AM, Martin CR *et al*. Two-year neurodevelopmental outcomes of ventilated preterm infants treated with inhaled nitric oxide. J Pediatr 2010; 156(4):556-61.e1.
4. Dani C, Bertini G, Pezzati M, Filippi L, Cecchi A, Rubaltelli FF. Inhaled nitric oxide in very preterm infants with severe respiratory distress syndrome. Acta Paediatr 2006; 95(9):1116-23.
5. Franco-Belgium Collaborative NO Trial Group. Early compared with delayed inhaled nitric oxide in moderately hypoxaemic neonates with respiratory failure: a randomised controlled trial. The Franco-Belgium Collaborative NO Trial Group. Lancet 1999; 354(9184):1066-71.
6. Field D, Elbourne D, Truesdale A *et al*. Neonatal Ventilation With Inhaled Nitric Oxide Versus Ventilatory Support Without Inhaled Nitric Oxide for Preterm Infants With Severe Respiratory Failure: the INNOVO multicentre randomised controlled trial (ISRCTN 17821339). Pediatrics 2005; 115(4):926-36.
7. Huddy CL, Bennett CC, Hardy P *et al*. The INNOVO multicentre randomised controlled trial: neonatal ventilation with inhaled nitric oxide versus ventilatory support without nitric oxide for severe respiratory failure in preterm infants: follow up at 4-5 years. Arch Dis Child Fetal Neonatal Ed 2008; 93(6):F430-5.
8. Hascoet JM, Fresson J, Claris O *et al*. The safety and efficacy of nitric oxide therapy in premature infants. J. Pediatr. 2005; 146(3):318-23.
9. Hamon I, Fresson J, Nicolas MB, Buchweiller MC, Franck P, Hascoet JM. Early inhaled nitric oxide improves oxidative balance in very preterm infants. Pediatr Res 2005; 57(5 Pt 1):637-43.
10. Kinsella JP, Walsh WF, Bose CL *et al*. Inhaled nitric oxide in premature neonates with severe hypoxaemic respiratory failure: A randomised controlled trial. Lancet 1999; 354(9184):1061-5.
11. Kinsella JP, Cutter GR, Walsh WF *et al*. Early inhaled nitric oxide therapy in premature newborns with respiratory failure. N Engl J Med 2006; 355(4):354-64.
12. Watson RS, Clermont G, Kinsella JP *et al*. Clinical and economic effects of iNO in premature newborns with respiratory failure at 1 year. Pediatrics 2009; 124(5):1333-43.
13. Schreiber MD, Gin-Mestan K, Marks JD, Huo D, Lee G, Srisuparp P. Inhaled Nitric Oxide in Premature Infants with the Respiratory Distress Syndrome. New Engl. J. Med. 2003; 349(22):2099-107.
14. Mestan KK, Marks JD, Hecox K, Huo D, Schreiber MD. Neurodevelopmental outcomes of premature infants treated with inhaled nitric oxide. N Engl J Med 2005; 353(1):23-32.
15. Srisuparp P, Heitschmidt M, Schreiber MD. Inhaled nitric oxide therapy in premature infants with mild to moderate respiratory distress syndrome. J Med Assoc Thai 2002; 85 Suppl 2:S469-78.
16. Su PH, Chen JY. Inhaled nitric oxide in the management of preterm infants with severe respiratory failure. J Perinatol 2008; 28(2):112-6.
17. Subhedar NV, Ryan SW, Shaw NJ. Open randomised controlled trial of inhaled nitric oxide and early dexamethasone in high risk preterm infants. Arch Dis Child Fetal Neonatal Ed 1997; 77(3):F185-90.
18. Bennett AJ, Shaw NJ, Gregg JE, Subhedar NV. Neurodevelopmental outcome in high-risk preterm infants treated with inhaled nitric oxide. Acta Paediatr 2001; 90(5):573-6.
19. Van Meurs KP, Wright LL, Ehrenkranz RA *et al*. Inhaled nitric oxide for premature infants with severe respiratory failure. N Engl J Med 2005; 353(1):13-22.
20. Chock VY, Van Meurs KP, Hintz SR *et al*. Inhaled nitric oxide for preterm premature rupture of membranes, oligohydramnios, and pulmonary hypoplasia. Am J Perinatol 2009; 26(4):317-22.
21. Hintz SR, Van Meurs KP, Perritt R *et al*. Neurodevelopmental outcomes of premature infants with severe respiratory failure enrolled in a randomized controlled trial of inhaled nitric oxide. J Pediatr 2007; 151(1):16-22, 22.e1-3.
22. Van Meurs KP, Hintz SR, Ehrenkranz RA *et al*. Inhaled nitric oxide in infants >1500 g and <34 weeks gestation with severe respiratory failure. J Perinatol 2007; 27(6):347-52.

Appendix E. Evidence Tables

Evidence Table 2: Risk of bias in observational studies.

Author, year	Represent-ativeness of the treated cohort	Selection of the control cohort	Selection of treated patients	Demonstration that outcome of interest was present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was followup long enough for outcomes to occur?	Were incomplete outcome data adequately addressed?	RoB score
Banks, 1999[1]	+		0	+		0	0	+	**fair**
Cheung, 1998[2]	-		-	-		0	-	-	**poor**
Clark, 2002[3]	0		+	+		0	+	-	**fair**
Dewhurst, 2010[4]	0	0	0	0		0	0	0	**poor**
Kumar, 2007[5]	+	-	+	+	+	0	0	+	**fair**
Uga, 2004[6]	0	+	0	+	0	0	+	+	**fair**
Tanaka, 2007[7]	+	+	+	+	0	0	+	0	**fair**
Yadav, , 1999[8]	-		+	+		0	0	-	**poor**

Appendix E. Evidence Tables

Evidence Table 2: Risk of bias in observational studies (continued).

KEY						
Category	Question	Score				
Selection	Representativeness of treated cohort	Truly representative	Somewhat representative	No description		
		+	-	0		
	Selection of control cohort	Same NICU or group of NICUs	Different source	No description		
		+	-	0		
	Selection of treated patients	Medical record	other	no description		
		+	-	0		
	Demonstration that outcoems of interest was not present at start of study	Yes	No	Unclear		
		+	-	0		
Comparability	Comparability of cohorts on the basis of the design or analysis	Yes	No	Unclear		
		+	-	0		
Outcome	Assessment of outcome	Independent blind assessment	record linkage	parent report	teacher report	not description
		+	+	-	-	0
	Was follow-up long enough four outcomes to occur?	Yes	Yes for at least 1 outcome of interest	No	Unclear	
		+	+	-	0	
	Were incomplete outcome data adequately addressed	Yes	No	unclear		
		+	-	0		

good = all criteria were present "yes"
fair = greater than or equal to 50% of criteria are present
poor = less than 50% of criteria are present or unclear

Appendix E. Evidence Tables

Reference List

1. Banks BA, Seri I, Ischiropoulos H, Merrill J, Rychik J, Ballard RA. Changes in oxygenation with inhaled nitric oxide in severe bronchopulmonary dysplasia. Pediatrics 1999; 103(3):610-8.
2. Cheung P-Y, Peliowski A, Robertson CMT. The outcome of very low birth weight neonates ((less-than or equal to)1500 g) rescued by inhaled nitric oxide: Neurodevelopment in early childhood. J. Pediatr. 1998; 133(6):735-9.
3. Clark PL, Ekekezie II, Kaftan HA, Castor CA, Truog WE. Safety and efficacy of nitric oxide in chronic lung disease. Arch Dis Child Fetal Neonatal Ed 2002; 86(1):F41-5.
4. Dewhurst C, Ibrahim H, Gothberg S, Jonsson B, Subhedar N. Use of inhaled nitric oxide in the new born period: Results from the European inhaled nitric oxide registry. Acta Paediatr. Int. J. Paediatr. 2010; 99(6):854-60.
5. Kumar VH, Hutchison AA, Lakshminrusimha S, Morin FC 3rd, Wynn RJ, Ryan RM. Characteristics of pulmonary hypertension in preterm neonates. J Perinatol 2007; 27(4):214-9.
6. Uga N, Ishii T, Kawase Y, Arai H, Tada H. Nitric oxide inhalation therapy in very low-birthweight infants with hypoplastic lung due to oligohydramnios. Pediatr. Int. 2004; 46(1):10-4.
7. Tanaka Y, Hayashi T, Kitajima H, Sumi K, Fujimura M. Inhaled nitric oxide therapy decreases the risk of cerebral palsy in preterm infants with persistent pulmonary hypertension of the newborn. Pediatrics 2007; 119(6):1159-64.
8. Yadav M, Emmerson AJ. Inhaled nitric oxide in premature neonates. Lancet 1999; 354(9196):2162-3

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Appendix E. Evidence Tables

Evidence Table 3: Study characteristics

Author, Year	Study Design	Study site-Study location	Recruitment date	Planned length of follow-up	Inclusion criteria	Exclusion criteria	Risk of Bias
Ballard, 2006[1]	RCT	Multi-Center - North America	Start date: May-2000 – End date: Apr-2005	60 Weeks PMA	Age: 7-21 days GA:<= 32 weeks BW: 500-1250 Vent support: "undergoing mechanical ventilation" between 7-21 days of age Other: NCPAP for those with BW 500-799g	Congen: complex anomalies IVH: bilateral grade IV Other: previous iNO exposure	Good
Follow-up of Ballard, 2006[1] Hibbs, 2007[2]	RCT	Multi-Center - North America		12 Months	Age: 7-21 days of age BW: 500-1250 grams Vent support: required vent support via CPAP or tracheal intubation		Good
Follow-up of Ballard 2006[1] Walsh, 2010[3]	RCT	Multi-Center - North America			Age: 7-21 days from birth BW: <1250 g Vent support: intubated and on mechanical ventilation		Good

Appendix E. Evidence Tables

Evidence Table 3: Study characteristics (continued)

Author, Year	Study Design	Study site-Study location	Recruitment date	Planned length of follow-up	Inclusion criteria	Exclusion criteria	Risk of Bias
Banks, 1999[4]	Phase II open label, non-controlled pilot study	Single Center - North America	Start date: Oct-1995 – End date: Aug-1997		Age: >4 weeks chronologic age FiO2: >/=45% MAP: >/=10mmHg BPD: vent dependent Other: No improvement in resp. status in previous 3 days with optimal use of all standard BPD therapy: glucocorticoids, bronchodilators, diuretics per attending physician	Congen: congenital heart disease	Fair
Cheung, 1998[5]	Prospective cohort	Single Center - North America	Start date: Dec-1993 – End date: Oct-1997	Early childhood	GA:24-30 weeks BW: </=1500 grams Hypoxemia: hypoxemia with FiO2 > 90%, and MAP 15+/-2	Congen: "congenital anomalies"	Poor
Clark, 2002[6]		Multi-Center - North America	Start date: Jun-97— End date: Jun-99	44 wks PMA	Age: < 30 days but > 10 days; BW: <1250; FiO2: > 40% w/o fluctuations of > 25% in the preceding 24 hours; Oligho: clinical and radiographic finding consistent with CLD	Bleeding: Plts< 100,000; Congen: CHD, and lethal anomalies; iBetaAnt: if given within preceding 48 hours; IVH: progressive IVH; Corticostrds: initiation	

Appendix E. Evidence Tables

Evidence Table 3: Study characteristics (continued)

Author, Year	Study Design	Study site-Study location	Recruitment date	Planned length of follow-up	Inclusion criteria	Exclusion criteria	Risk of Bias
						of drug within preceding 48 hours; Sepsis: 2 blood cultures yielding single organism in preceding 48 hours	
Dani, 2006[7]	RCT	Single Center - Europe	Start date: Jan-2001 – End date: Jun-2004		Age: <=7 days GA:< 30 wks; Inborn RDS: Classic symptoms (need for O2, tachypnea, retractions, and grunting) and typical Xray findings (reduced air content, reticulogranular pattern of lungs and air bronchograms) FiO2: FIO2>0.5 (50%) and arterial-alveolar oxygen ratio <0.15 Surfactant Vent support	Bleeding: Platelet count <50,000/mm3 and bleeding tendency (hematuria; blood from ETT; gastric aspirate or stools; oozing from puncture sites) Congen: major congenital malformations Hydrops	Fair
Dewhurst, 2010 [8]	Retrospective Cohort	Multi-Center - Europe	Start date: Jan- 2006 End date: Dec- 2007		Age: <10 days GA: <31 weeks		
Field, 2005[9]	RCT	Multi-Center - Europe	Start date: Feb-1997 – End date: Dec-2001	1 year Corrected age	Age: <28 days GA:<34 weeks Surfactant: treatment if appropriate	Bleeding: Plts < 50,000 and PTT>72 sec IVH: Grade 4 IVH Other: severe	Poor

Appendix E. Evidence Tables

Evidence Table 3: Study characteristics (continued)

Author, Year	Study Design	Study site-Study location	Recruitment date	Planned length of follow-up	Inclusion criteria	Exclusion criteria	Risk of Bias
						anomalies; lethal chromosomal anomaly	
Follow-up of Field 2005[9] Huddy, 2008[10]	RCT	Multi-Center - Europe	Start date: Feb-1997 – End date: Dec-2001	4-5 Years	Age: <28 days GA:<34 wks Respfail: severe Vent support: intubation and mechanical ventilation		Poor
Franco-Belgium Collaborative NO Trial Group, 1999[11]	RCT	Multi-Center - Europe	Start date: Apr-1995 – End date: Jun-1997	Until hospital discharge	Age: <7 days of age GA:<33 weeks OI: 12.5-30	OI: > the upper limits requiring inhaled nitric oxide; according to the French Drug Agency recommendations Congen: fatal anomalies; cardiac anomalies Dshunting: PDA with severe left to right shunting Hypoxemia: Other forms of pulmonary hypoplasia IVH: grade 3 or 4 Pulmonary hypoplasia: raised pulmonary blood flow Refractory septic shock Other: abnormal neuro	Fair

Appendix E. Evidence Tables

Evidence Table 3: Study characteristics (continued)

Author, Year	Study Design	Study site-Study location	Recruitment date	Planned length of follow-up	Inclusion criteria	Exclusion criteria	Risk of Bias
						exam due to birth asphyxia or grade 3-4 IVH	
Hascoet, 2005[12]	RCT	Multi-Center - Europe	Start date: Jul-1999 – End date: Feb-2001	28 Days	GA:<32 weeks	Bleeding: platelets <50,000/mm3 Congen: major fetal abnormality Hypoxemia: refractory hypoxemia (PO2<50 mmHg & PCO2 <50mmHg on FiO2 100% prior to 6 hours of age)	Fair
Follow-up of Hascoet 2005[12] Hamon, 2005[13]	RCT	Single Center - Europe	Start date: Jul-1999 – End date: Feb-2001	28 Days	Age: < 48 hours GA:< 32 wks FiO2: > 0.40 Other: aAO2 < 0.22	Bleeding: Plts < 50,000 Congen: major abnormality Refractory hypoxemia	Fair
Kinsella, 1999[14]	RCT	Multi-Center - North America		Hospital discharge	Age: =< 7 days chronological age GA: 34 weeks or less Hypoxemia: Arterial/alveolar oxygen ratio <0.1 on 2 sequential ABGs despite mechanical vent and surfactant Vent Support: mechanical ventilation	Congen: fatal congenital anomaly; congenital heart disease (except ASD; VSD)	Good

Appendix E. Evidence Tables

Evidence Table 3: Study characteristics (continued)

Author, Year	Study Design	Study site-Study location	Recruitment date	Planned length of follow-up	Inclusion criteria	Exclusion criteria	Risk of Bias
Kinsella, 2006[15]	RCT	Multi-Center - North America	Start date: Mar- 2001 – End date: Jun -2005		Age: <48 hours GA:<=34 wks BW: 500-1250g Respfail: requiring intubation and mechanical vent Vent Support: intubation & mechanical ventilation	Congen: lethal, congenital heart disease except atrial septal defect <= 1 cm or ventricular septal defect <=2 mm) Pneumothorax: unevaluated Pulmhem: active Vent Support: expected duration of mechanical ventilation of <48 hours	Good
Follow-up of Kinsella 2006[15] Watson, 2009[16]	RCT	Multi-Center - North America	Start date: Mar 2001 – End date: Jun- 2005	1 Year	Age: <48 hours GA:<=34 weeks BW: 500-1250g Vent Support: mechanical ventilation	Congen: lethal anomalies, CHD Pneumothorax: unevacuated Pulmhem: active hemorrhage Vent Support: expected mechanical ventilation for < 48 hours	Good
Mercier, 2010 [17]	RCT	Multi-center - Europe	Start date: May-2005 End date: May-2008	1, 2 and 7 years	GA: <34 weeks		
Schreiber, 2003[18]	RCT	Single Center - North America	Start date: Oct-1998 – End date : Oct-2001		Age: <72 hours GA:<34 weeks BW: <2000 g RDS: clinical diagnosis	Congen: Major congenital malformations Hydrops	Good

Appendix E. Evidence Tables

Evidence Table 3: Study characteristics (continued)

Author, Year	Study Design	Study site- Study location	Recruitment date	Planned length of follow-up	Inclusion criteria	Exclusion criteria	Risk of Bias
					Surfactant: Must be treated with surfactant Vent support: Require intubation and mechanical ventilation		
Follow-up of Schreiber, 2003[18] Mestan, 2005[19]	RCT	Single Center - North America	Start date: Oct-1998 – End date : Oct-2001	Two years of age			Good
Srisuparp, 2002[20]	RCT	Single Center - North America	Start date: Jul-1997 – End date: Jan-1998	Neonatal period, to 28 days of age	Age: < 72 hours BW: <2000g OI: >=4 if birthweight (BW) <= 1000g; >=6 if BW 1001-1250g; >= 8 of BW 1251-1500g; >= 10 if BW 1501-1750 g; >=12 if BW 1751-2000g ArtrCath RDS Vent Support: mechanical ventilation	Congen: major anomalies Hydrops	Poor
Su, 2008[21]	RCT	Single center - Asia	Start date: Jul-2000 – End date: Jul-2006		GA:</= 31 weeks BW: </= 1500g RDS: severe RDS - clinical signs (IC rtxs, flaring, grunting) or CXR findings severe diffuse reticulo-	Bleeding: uncorrectable Congen: severe congenital abnormalities IVH: Severe III or IV	Fair

Appendix E. Evidence Tables

Evidence Table 3: Study characteristics (continued)

Author, Year	Study Design	Study site-Study location	Recruitment date	Planned length of follow-up	Inclusion criteria	Exclusion criteria	Risk of Bias
					granular infiltrates w/low lung volumes Respfail: OI >/=25 Vent Support: mechanical ventilation	Other: lethal chromosomal anomalies	
Subhedar, 1997[22]	RCT	Single Center - Europe	Start date: Aug-1995 – End date: Sep-1996	Not specified in article	Age: 96 hours of age GA:<32 weeks RDS: requiring mechanical ventilation Surfactant Vent Support: mechanically ventilated since birth Other: high risk for CLD by prediction score	Bleeding: Plts< 50 Congen: major anomalies; structual cardiac anomalies Dshunting: significant IVH: with parenchymal involvement Pulmhem Sepsis: Culture positive Other: GI bleed	Poor
Follow-up of Subhedar, 1997[22] Bennett, 2001[23]	RCT	Single Center - Europe		30 Months corrected age	GA:<32 weeks	Intrprncyml: parenchymal involvement at trial entry	Poor
Tanaka, 2007[24]	Retrospective cohort	Single Center - Asia	Start date: Jan-1988 – End date: Dec-1999	3 Years	GA:< 34 weeks Shuting: Rt-to-L shunt at PDA or R-to-L at arterial level Hypoxemia: due to PPHN	Multiple birth: Singleton only Congen: No structural heart disease	Fair

Appendix E. Evidence Tables

Evidence Table 3: Study characteristics (continued)

Author, Year	Study Design	Study site-Study location	Recruitment date	Planned length of follow-up	Inclusion criteria	Exclusion criteria	Risk of Bias
					PPHN: Clinical: >5% difference in Pre- & Post-ductal SaO2, or recurrent desats <85% over 12hours despite optimal treatment of lung disease, AND Echo evidence (w/o structural heart disease): peak systolic PAP >35mmHg or >2/3 systemic systolic pressure - indicated by R-to-L shunting at PDA or arterial level		
Uga, 2004[25]	Retrospective cohort	Single Center - Asia	Start date: Jan-1999 End date: NS	NS	BW: <1500 grams FiO2: 100% MAP: >8 Oligho: >5 days with PROM PPHN: defined by no response to surfactant, oligohydramnios/PROM>5 days, refractory hypoxemia PPROM: >5 days Respfail: insufficient arterial oxygenation on 100% FiO2, MAP >8cmH20 Surfactant: with no response		
Van Meurs, 2005[26]	RCT	Multi-Center - North America	Start date: Jan-2001 – End date: Sep-03		Age: 4 to 120 hours after birth GA:< 34 weeks	Bleeding: Bleeding diathesis or platelet count at or below 50,000 per cu. mm.	Good

Appendix E. Evidence Tables

Evidence Table 3: Study characteristics (continued)

Author, Year	Study Design	Study site- Study location	Recruitment date	Planned length of follow-up	Inclusion criteria	Exclusion criteria	Risk of Bias
					BW: 401-1500g OI: at least 10 on 2 ABGs between 30 min and 12 hours apart; revised to OI of at least 5.0 followed within 30 min to 12 hours of OI of at least 7.5 ArtrCath: eligible from 4 to 120 hours after birth Congen: Ventricular Septal Defect, patent ductus arteriosus and atrial level shunt permitted PPHN: idiopathic Pneumonia Pulmonary hypoplasia: suspected RDS Sepsis Surfactant: at least 4 hours before Vent Support: required assisted ventilation Other: Aspiration Syndrome	(thrombocytopenia) Congen: Congenital Heart Disease, major congenital anomaly involving respiratory system	
Sub analysis of	RCT	Multi-Center - North America	Start date: Jan- 2001 – End date: Sep- 2003	18 to 22 Months	GA:<34 wks; <34 wks		

Appendix E. Evidence Tables

Evidence Table 3: Study characteristics (continued)

Author, Year	Study Design	Study site-Study location	Recruitment date	Planned length of follow-up	Inclusion criteria	Exclusion criteria	Risk of Bias
Van Meurs, 2005[26] Chock, 2009[27]					BW: 401-1500g (iNO trial); some >1500g (larger Preemie Pilot study) Oligho: documented on U/S 5+ days prior to delivery Pulmhyp: interpretation of CXR w/small, hypoplastic-appearing lungs Respfail: 4 hours following surfactant		
Follow-up of Van Meurs, 2005[26] Hintz, 2007[28]	RCT	Multi-Center - North America	Start date: Jan -2001– End date: Sep- 03	18 - 22 Months corrected age	GA:< 34 wks BW: 401 - 1500 g OI: >/=10 on 2 consecutive blood gases 30 min to 12 h apart; revised to OI >/=5 followed by OI>/=7.5 w/in 30 min to 24 hours Respfail: severe (defined in original iNO trial) Surfactant:x1 dose at least 4hr before meeting OI criteria Vent support: Mechanical		Good
Van Meurs, 2007[29]	RCT	Multicenter - North America	Start date: Jan- 2001– End date: Sep- 2003	18-22 Months	GA:<34 wks BW: >1500 g OI: OI >/=15 x2 ABGs 30 min-12 hrs apart; OI >/=10 then OI>/=12.5 within 30	Bleeding: Platelets <50,000; or bleeding diathesis Congen heart disease Other: decision not to	Good

Appendix E. Evidence Tables

Evidence Table 3: Study characteristics (continued)

Author, Year	Study Design	Study site-Study location	Recruitment date	Planned length of follow-up	Inclusion criteria	Exclusion criteria	Risk of Bias
					min-24 hrs PPHN: idiopathic Pneumonia Pulmonary hypoplasia Sepsis RDS Surfactant: at least 1 dose >4hrs prior Vent Support: mechanical ventilation Other: Aspiration syndromes	provide full treatment	
Yadav, 1999[30]	Retrospective cohort	Single Center - Europe	Start year: 1993 – End year: 1997	Hospital discharge	GA: "preterm" Hypoxemia: "severe hypoxemia despite max therapy	Congen: major malformation;	Poor

ArtrCath: Arterial catheter, BPD: Bronchopulmonary dysplasia , BW: Birth weight, Congen: Congenital anomaly/malformation, Dshunting: Ductal Shunting, FiO2: Fraction of Inspired Oxygen, g:grams, GA: Gestational age, iNO: inhaled Nitric Oxide, intrprncyml:Intraparenchymal lesion, IVH: Intraventricular Hemorrhage, MAP: Mean airway pressure, OI: Oxygenation Index, Oligho : Oligohydramnios, PMA: post menstrual age, PPHN: Persistent Pulmonary Hypertension of the Newborn, Pulmhyp: Pulmonary hypoplasia, RDS: Respiratory distress syndrome, Respfail: Respiratory failure , Vent Support: Ventilation Support

Reference List

1. Ballard RA, Truog WE, Cnaan A *et al*. Inhaled nitric oxide in preterm infants undergoing mechanical ventilation. New Engl. J. Med. 2006;

355(4):343-53.
2. Hibbs AM, Walsh MC, Martin RJ *et al*. One Year Respiratory Outcomes of the Preterm Infants Enrolled in the NO CLD Trial of Inhaled Nitric Oxide (iNO). N/A 2007.
3. Walsh MC, Hibbs AM, Martin CR *et al*. Two-year neurodevelopmental outcomes of ventilated preterm infants treated with inhaled nitric oxide. J Pediatr 2010; 156(4):556-61.e1.
4. Banks BA, Seri I, Ischiropoulos H, Merrill J, Rychik J, Ballard RA. Changes in oxygenation with inhaled nitric oxide in severe bronchopulmonary dysplasia. Pediatrics 1999; 103(3):610-8.
5. Cheung P-Y, Peliowski A, Robertson CMT. The outcome of very low birth weight neonates ((less-than or equal to)1500 g) rescued by inhaled nitric oxide: Neurodevelopment in early childhood. J. Pediatr. 1998; 133(6):735-9.
6. Clark PL, Ekekezie II, Kaftan HA, Castor CA, Truog WE. Safety and efficacy of nitric oxide in chronic lung disease. Arch Dis Child Fetal Neonatal Ed 2002; 86(1):F41-5.
7. Dani C, Bertini G, Pezzati M, Filippi L, Cecchi A, Rubaltelli FF. Inhaled nitric oxide in very preterm infants with severe respiratory distress syndrome. Acta Paediatr 2006; 95(9):1116-23.
8. Dewhurst C, Ibrahim H, Gothberg S, Jonsson B, Subhedar N. Use of inhaled nitric oxide in the new born period: Results from the European inhaled nitric oxide registry. Acta Paediatr. Int. J. Paediatr. 2010; 99(6):854-60.
9. Field D, Elbourne D, Truesdale A *et al*. Neonatal Ventilation With Inhaled Nitric Oxide Versus Ventilatory Support Without Inhaled Nitric Oxide for Preterm Infants With Severe Respiratory Failure: the INNOVO multicentre randomised controlled trial (ISRCTN 17821339). Pediatrics 2005; 115(4):926-36.
10. Huddy CL, Bennett CC, Hardy P *et al*. The INNOVO multicentre randomised controlled trial: neonatal ventilation with inhaled nitric oxide versus ventilatory support without nitric oxide for severe respiratory failure in preterm infants: follow up at 4-5 years. Arch Dis Child Fetal Neonatal Ed 2008; 93(6):F430-5.
11. Franco-Belgium Collaborative NO Trial Group. Early compared with delayed inhaled nitric oxide in moderately hypoxaemic neonates with respiratory failure: a randomised controlled trial. The Franco-Belgium Collaborative NO Trial Group. Lancet 1999; 354(9184):1066-71.
12. Hascoet JM, Fresson J, Claris O *et al*. The safety and efficacy of nitric oxide therapy in premature infants. J. Pediatr. 2005; 146(3):318-23.
13. Hamon I, Fresson J, Nicolas MB, Buchweiller MC, Franck P, Hascoet JM. Early inhaled nitric oxide improves oxidative balance in very preterm infants. Pediatr Res 2005; 57(5 Pt 1):637-43.
14. Kinsella JP, Walsh WF, Bose CL *et al*. Inhaled nitric oxide in premature neonates with severe hypoxaemic respiratory failure: A randomised controlled trial. Lancet 1999; 354(9184):1061-5.
15. Kinsella JP, Cutter GR, Walsh WF *et al*. Early inhaled nitric oxide therapy in premature newborns with respiratory failure. N Engl J Med 2006; 355(4):354-64.
16. Watson RS, Clermont G, Kinsella JP *et al*. Clinical and economic effects of iNO in premature newborns with respiratory failure at 1 year. Pediatrics 2009; 124(5):1333-43.
17. Mercier JC, Hummler H, Durrmeyer X *et al*. Inhaled nitric oxide for prevention of bronchopulmonary dysplasia in premature babies (EUNO): a randomised controlled trial. Lancet 2010.
18. Schreiber MD, Gin-Mestan K, Marks JD, Huo D, Lee G, Srisuparp P. Inhaled Nitric Oxide in Premature Infants with the Respiratory Distress Syndrome. New Engl. J. Med. 2003; 349(22):2099-107.
19. Mestan KK, Marks JD, Hecox K, Huo D, Schreiber MD. Neurodevelopmental outcomes of premature infants treated with inhaled nitric oxide. N Engl J Med 2005; 353(1):23-32.
20. Srisuparp P, Heitschmidt M, Schreiber MD. Inhaled nitric oxide therapy in premature infants with mild to moderate respiratory distress syndrome. J Med Assoc Thai 2002; 85 Suppl 2:S469-78.
21. Su PH, Chen JY. Inhaled nitric oxide in the management of preterm infants with severe respiratory failure. J Perinatol 2008; 28(2):112-6.
22. Subhedar NV, Ryan SW, Shaw NJ. Open randomised controlled trial of inhaled nitric oxide and early dexamethasone in high risk preterm infants. Arch Dis Child Fetal Neonatal Ed 1997; 77(3):F185-90.
23. Bennett AJ, Shaw NJ, Gregg JE, Subhedar NV. Neurodevelopmental outcome in high-risk preterm infants treated with inhaled nitric oxide. Acta Paediatr 2001; 90(5):573-6.
24. Tanaka Y, Hayashi T, Kitajima H, Sumi K, Fujimura M. Inhaled nitric oxide therapy decreases the risk of cerebral palsy in preterm infants with persistent pulmonary hypertension of the newborn. Pediatrics 2007; 119(6):1159-64.
25. Uga N, Ishii T, Kawase Y, Arai H, Tada H. Nitric oxide inhalation therapy in very low-birthweight infants with hypoplastic lung due to oligohydramnios. Pediatr. Int. 2004; 46(1):10-4.
26. Van Meurs KP, Wright LL, Ehrenkranz RA *et al*. Inhaled nitric oxide for premature infants with severe respiratory failure. N Engl J Med 2005; 353(1):13-22.
27. Chock VY, Van Meurs KP, Hintz SR *et al*. Inhaled nitric oxide for preterm premature rupture of membranes, oligohydramnios, and pulmonary hypoplasia. Am J Perinatol 2009; 26(4):317-22.
28. Hintz SR, Van Meurs KP, Perritt R *et al*. Neurodevelopmental outcomes of premature infants with severe respiratory failure enrolled in a randomized controlled trial of inhaled nitric oxide. J Pediatr 2007; 151(1):16-22, 22.e1-3.
29. Van Meurs KP, Hintz SR, Ehrenkranz RA *et al*. Inhaled nitric oxide in infants >1500 g and <34 weeks gestation with severe respiratory failure. J Perinatol 2007; 27(6):347-52.
30. Yadav M, Emmerson AJ. Inhaled nitric oxide in premature neonates. Lancet 1999; 354(9196):2162-3.

Appendix E. Evidence Tables

Evidence Table 4. Participant Characteristics

Author, year	Control Interventions	N at baseline	Gestational age (weeks)	Birth weight (grams)	Race n(%)	Mode of Ventilation, n(%)	Participant age at enrollment	Oxygenation Index	iNO Dose	iNO Duration
Ballard, 2006[1]	Placebo	288	Mean: 26 SD: 1.5	Mean: 759 SD: 155	W: 145 (50.3) B: 90 (31.3) H: 43 (14.9) Other: 10 (3.)	HFV: 74 (25.7) CMV: 191 (66.3) CPAP: 23 (8)	Median:16 Range:13-19 IQR Units: Days	NA		
	iNO	294	Mean: 26 SD: 1.5	Mean: 766 SD: 161	W: 170 (57.8) B: 76 (25.9) H: 32 (10.9) Other: 16 (5.4)	HFV: 65 (22.1) CMV: 202 (68.7) CPAP: 27 (9.2)	Median:16 Range:12-19 IQR Units: Days	NA	20ppm x48-96hours: titrate every 7days for a minimum of 2 days exposure	

Appendix E. Evidence Tables

Evidence Table 4. Participant Characteristics (continued)

Author, year	Control Interventions	N at baseline	Gestational age (weeks)	Birth weight (grams)	Race n(%)	Mode of Ventilation, n(%)	Participant age at enrollment	Oxygenation Index	iNO Dose	iNO Duration
Follow-up of Ballard, 2006[1] Hibbs, 2007[2]	Placebo	225	Mean: 25.7 SD: 1.5	Mean: 762 SD: 150	W: 121 (53.8) B: 64 (28.4) H: 31 (13.8) Other: 9 (4)	NA	NA	NA		
	iNO	230	Mean: 25.8 SD: 1.4	Mean: 769 SD: 163	W: 141 (61.3) B: 56 (24.2) H: 22 (9.5) Other:: 11 (4.8)	NA	NA	NA	20ppm: weaned over at least 24days	
Follow-up of Ballard 2006[1] Walsh, 2010[3]	Placebo gas	234	Mean: 25.7 SD:1.5	Mean: 764 SD: 153	W: 124(53) Other: 110(47)	NA	Median: 16 Range: 13-20 IQR Unit: days	NA		
	iNO	243	Mean:25.8 SD: 1.4	Mean: 765 SD:163	W: 151(62) Other: 92(38)	NA	Median: 17 Range: 13-19 IQR Unit: days	NA	20ppm x24hours: decrease to 10ppm x1week decrease to 5ppm x1week decrease to 2ppm x1week	
Banks, 1999[4]	iNO	16	Median: 25.5 Range: 24-	Median: 787 Range:	NA	HFV: 5 (31.25)	Median: 2.5 Range: 1-7	NA	20ppm x72hours:	

Appendix E. Evidence Tables

Evidence Table 4. Participant Characteristics (continued)

Author, year	Control Interventions	N at baseline	Gestational age (weeks)	Birth weight (grams)	Race n(%)	Mode of Ventilation, n(%)	Participant age at enrollment	Oxygenation Index	iNO Dose	iNO Duration
			29	448-1790		CMV :11 (68.75)	Units: Months		responders weaned by 20% every 3day	
Cheung, 1998[5]	iNO treated cohort	24	Median: 25 Range: 24-27 (25% and 75 %)	Median: 860 Range: 668-1068 (25% and 75 %)	NA	CMV : 24 (100)	NA	Median:32 Range: 28-52 (25% and 75 %)	20ppm: decrease by 5ppm within 2hours s/p initial dose decrease by 5ppm q15-30min to lowest dose w/ + response	
Clark, 2002[6]	iNO	33	Mean: 25.3; Range: 23-29	Mean: 736 Range: 509-1250	W: 11 (33) B: 21 (64) H: 1 (3)		Mean: 19 Range: 9-29 Units: Days		20ppm x36hours: decrease to 15ppm and decrease by 2-3ppm every12hours; discontinued by 7 days.	
Dani, 2006[7]	Control	20	Mean: 26.7 SD: 1.9	Mean: 825 SD: 299	NA	HFV: 11 (55)	NA	Mean: 15.1 SD: 4.9		
	iNO	20	Mean: 26.3 SD: 2.6	Mean: 937 SD: 298	NA	HFV: 10 (50)	NA	Mean:16.4 SD: 5.1	5ppm: Increase by 5ppm every 30min to max 15ppm	
	No responders	6	Mean: 25.4 SD: 2.6	Mean: 748 SD: 321.4	NA	CPAP: 4 (67)	NA	Mean:18.1 SD: 4.2	5ppm: Increase by 5ppm every 30min to max 15ppm	
	Responders	14	Mean: 26.7 SD: 1.9	Mean: 1022.7 SD: 243.1	NA	CPAP: 13 (93)	NA	Mean:14.7 SD: 3.9	5ppm: Increase by 5ppm every 30min to max	

Appendix E. Evidence Tables

Evidence Table 4. Participant Characteristics (continued)

Author, year	Control Interventions	N at baseline	Gestational age (weeks)	Birth weight (grams)	Race n(%)	Mode of Ventilation, n(%)	Participant age at enrollment	Oxygenation Index	iNO Dose	iNO Duration
									15ppm	
Dewhurst, 2010 [8]	Responders	26	Median: 26 Range: 25-29	Median: 920 Range: 655-1538	NA		Median: 53 Range: 37-217 Units: Hours	Median: 47 Range: 30-78	10ppm: titrated	
	Non-responders	8	Median: 29 Range: 27-30	Median: 915 Range: 723-183	NA		Median: 75 Range: 20-183 Units: Hours	Median: 23 Range: 8-54	20ppm: titrated	
Field, 2005[9]	Control	53	Mean: 26.3 SD: 2.4	Mean: 890 SD: 343	NA	HFV: 39 (74%)	Median:1 Range:1-5 IQR Units: Days	Median:31.9 Range: 17.4-51.8 IQR		
	iNO	55	Mean: 27.4 SD: 2.6	Mean: 1006 SD: 395	NA	HFV: 33 (60)	Median:1 Range:0-6 IQR Units: Days	Median:32.9 Range: 22.2-49.8 IQR,	5ppm: double dose every 15min to max 40ppm	
Follow-up of Field 2005[9] Huddy, 2008[10]	Control	16	Mean: 28.2 SD: 2.7	Mean: 1142 SD: 440	NA	NA	Median: 1 Range: IQR 1.5 Units: Days	Median: 25.9 Range: IQR 41.3		
	iNO	22	Mean: 28.5 SD: 2.4	Mean: 1191 SD: 403	NA	NA	Median: 1 Range: IQR 3 Units: Days	Median: 30.1 Range: IQR 20.5	5ppm: double dose every 15min until PaO2 increases >22.5mmHg to max 40ppm	
Franco-Belgium Collaborative NO Trial Group,	Control	45	Median: 29 Range: 3.1 IQR	Median: 1150 Range: 520 IQR	NA	HFV: 34 (76) CMV : 11 (24)	Median:1 Range: 1 IQR Units: Days	Median: 18 Range: 7.4 IQR		

Appendix E. Evidence Tables

Evidence Table 4. Participant Characteristics (continued)

Author, year	Control Interventions	N at baseline	Gestational age (weeks)	Birth weight (grams)	Race n(%)	Mode of Ventilation, n(%)	Participant age at enrollment	Oxygenation Index	iNO Dose	iNO Duration
1999[11]										
	iNO	40	Median: 29.6 Range: 2.6 IQR	Median: 1200 Range: 570 IQR	NA	HFV: 30 (75) CMV : 10 (25)	Range: 1.5 Units: Days	Median:20.2 Range: 8.3 IQR	10ppm x2-3hours: decreased to 5ppm then slowly wean off if deteriorating condition, increased dose to 20ppm	
Hascoet, 2005[12]	Control with hypoxemic respiratory failure	84	NA	BW<750: 19 (22) BW 750-999: 17 (20), BW 1000-1500: 32 (39) BW >1500: 16 (19)	NA	NA	NA	Mean:12 SD: 5.6		
	iNO with hypoxemic respiratory failure	61	NA	BW <750g: 10 (16.5) BW 750-999g: 14 (23) BW 1000-1500g: 27 (44) BW >1500g: 10 (16.5)	NA	NA	NA	OI Mean:14.6 SD: 8.9	5ppm: if aAO2 increase >0.22 decrease iNO to 2ppm if aAO2 increase <0.22 but >25% iNO remains at 5ppm if aAO2 unchanged increase iNO to 10ppm	

Appendix E. Evidence Tables

Evidence Table 4. Participant Characteristics (continued)

Author, year	Control Interventions	N at baseline	Gestational age (weeks)	Birth weight (grams)	Race n(%)	Mode of Ventilation, n(%)	Participant age at enrollment	Oxygenation Index	iNO Dose	iNO Duration
Follow-up of Hascoet 2005[12] Hamon, 2005[13]	Hypoxemic respiratory failure, no iNO	39	Mean: 27.9 SD: 0.4	Mean: 1102 SD: 54	NA	NA	Mean:15.9 SD: 1.8 Units: Hours	NA		
	iNO treated hypoxemic respiratory failure	37	Mean: 27.3 SD: 0.4	Mean: 1083 SD: 58	NA	NA	Mean:14.1 SD:1.4 Units: Hours	NA	5ppm: aAO2 increase >0.22 decrease iNO to 2ppm aAO2 increase <0.22 but >25% iNO remains at 5ppm aAO2 unchanged increase iNO to 10ppm	Median: 35.1 hours
Kinsella, 1999[14]	Control	32	Mean: 26.8 SD: 2.5	Mean: 988 SD: 387	NA	NA	Mean: 27 SD:37 Units: Hours	NA		
	iNO	48	Mean: 27.1 SD: 2.5	Mean: 1040 SD: 461	NA	NA	Mean:30 SD: 38 Units: Hours	NA	5ppm x 7days: if OI increase >15%, iNO restarted	
Kinsella, 2006[15]	Placebo gas, Total sample	395	Mean: 25.6 SD: 1.8	Mean: 788 SD: 185	W: 234 of 394 (59.4) B: 98 of 394 (24.9) H: 48 of 394 (12.2) Other: 14 of 394 (3.6)	HFV: 113 of 389 (29) CMV : 276 of 389 (71)	Mean:30.1 SD:13.2 Units: Hours	Mean:5.8, SD:6.7		
	iNO, Total	398	Mean: 25.6	Mean: 796	W: 249 of	HFV: 113 of	Mean:30.5	Mean:5.4	5ppm x	Median: 14

Appendix E. Evidence Tables

Evidence Table 4. Participant Characteristics (continued)

Author, year	Control Interventions	N at baseline	Gestational age (weeks)	Birth weight (grams)	Race n(%)	Mode of Ventilation, n(%)	Participant age at enrollment	Oxygenation Index	iNO Dose	iNO Duration
	sample		SD: 1.7	SD: 190	397(62.7) B: 94 of 397(23.7) H: 41 of 397(10.3) Other: 13 of 397 (3.3)	393 (28.8) CMV : 280 of 393 (71.2)	SD:13.4 Units: Hours	SD: 5.2	21days	days
Follow-up of Kinsella 2006[15] Watson, 2009[16]	Control - detailed outcome cohort	320	Mean: 25.7 SD: 1.9	Mean: 791 SD: 186	W: 192 (60) B: 71 (22.2) H: 44 (13.8) Asian/Other: 13 (4.1)	NA	NA	Median:4.1 Range: 2.7-6.4 IQR		
	iNO- detailed outcome cohort	332	Mean: 25.6 SD: 1.7	Mean: 797 SD: 190	W: 205 (61.8) B: 76 (22.9) H: 38 (11,5) Asian/Other: 13 (3.9)	NA	NA	Median:4.1 Range: 2.8-6.2 IQR	5ppm x21days or until extubated	
Mercier, 2010 [17]	Control	401	Mean: 26.6 SD: 1.3	Mean: 864 SD: 192	W: 328 (82) B: 48 (12)	CPAP: 42 (10)	NA	Mean: 8.6 SD: 12.7	5ppm	

Appendix E. Evidence Tables

Evidence Table 4. Participant Characteristics (continued)

Author, year	Control Interventions	N at baseline	Gestational age (weeks)	Birth weight (grams)	Race n(%)	Mode of Ventilation, n(%)	Participant age at enrollment	Oxygenation Index	iNO Dose	iNO Duration
					A: 2 (<1) Other: 23 (6)					
	iNO	399	Mean: 26.4 SD: 1.3	Mean: 851 SD: 207	W: 329 (82) B: 39 (10) A: 4 (1) Other: 27 (7)	CPAP: 41 (10)	NA	Mean: 8.0 SD: 10.7	5ppm	
Schreiber, 2003[18]	Placebo	102	Mean: 27 SD: 2.8	Mean: 949 SD: 387	W: 12 (11.8) B: 74 (72.6) Other: 16 (15.7)	HFV: 48 (47) CMV : 54 (52.9)	Median:14 Range: IQR 7.6-28.5	Median:6.8 Range: 4.4-12.7 IQR		
iNO		105	Mean: 27.4 SD: 2.5	Mean: 1017 SD: 369	W: 18 (17.1) B: 71 (67.6) Other: 16 (15.2)	HFV: 54 (51.4) CMV : 51 (48.6)	Median: 12.9 Range: IQR 7.0-25.2	Median:7.3 Range: IQR 4.1-12.3	10ppm x12-24hours: decrease to 5ppm and hold 6day or 1hour before extubation if PaO2 decrease by 15%, restart iNO and decrease by 1ppm every 6hours	
Follow-up	Control	68	Mean: 27.2	Mean: 958	W: 8 (12)	NA	SD: 8.4	Median: 7.2		

Appendix E. Evidence Tables

Evidence Table 4. Participant Characteristics (continued)

Author, year	Control Interventions	N at baseline	Gestational age (weeks)	Birth weight (grams)	Race n(%)	Mode of Ventilation, n(%)	Participant age at enrollment	Oxygenation Index	iNO Dose	iNO Duration
of Schreiber, 2003[18] Mestan, 2005[19]			SD: 2.6	SD: 356	B: 52 (76) Other:: 8 (12)		Units: Months	Range: IQR 4.5-14.3		
	iNO	70	Mean: 27.5 SD: 2.4	Mean: 1026 SD: 366	W: 14 (20) B: 44 (63), Other:: 12 (17)	NA	Mean: 24.9 SD: 7.9 Units: Months	Median: 6.6 Range: IQR 4-11.5	10ppm x24hours: decrease to 5ppm and hold 6d or 1hours before extubation	
Srisuparp, 2002[20]	Control	18	Mean: 27.2 SD: 0.5	Mean: 901 SD: 73	B: 16 (89)	HFV: 7 (38.9)	NA	Mean:11.9 SD: 2.2		
	iNO	16	Mean: 26.8 SD: 0.5	Mean: 874 SD: 70	B: 16 (100)	HFV: 7 (43.8)	NA	Mean:10.8 SD: 1.5	20ppm x6-12hours: decrease to 10ppm x12hours decrease to 5ppm x12hours decrease by 1ppm every 12hours	
Su, 2008[21]	Received inhaled oxygen placebo only	33	Mean: 27.9 SD: 1.8	Mean: 1050 SD: 210	NA	NA	Mean:2.5 SD: 1.8 Units: Days	Mean: 30.5 SD: 4.7		
	iNO	32	Mean: 27.4 SD: 2.3	Mean: 1020 SD: 230	NA	CMV : 32(100)	Mean: 2.45 SD: 1.7 Units: Days	Mean:30.3 SD: 3.5	5ppm x6hours: if + response, decrease 1ppm every 6hours to min 1ppm if – response,	Mean: 4.9 SD: 2.3 Unit: days

Appendix E. Evidence Tables

Evidence Table 4. Participant Characteristics (continued)

Author, year	Control Interventions	N at baseline	Gestational age (weeks)	Birth weight (grams)	Race n(%)	Mode of Ventilation, n(%)	Participant age at enrollment	Oxygenation Index	iNO Dose	iNO Duration
									increase 5ppm every 6hours to max. 20ppm	
Subhedar, 1997[22]	Dexamethasone and standard of care	22	Median: 27 Range: 22-31	Median: 750 Range: 520-1400	NA	NA	Median: 104 Range: 96-120 Units: Hours	Median: 3.9 Range: 1.2-11.5		
	iNO + iNO and dexamethasone)	20	Median: 27 Range: 24-30	Median: 882 Range: 416-1354	NA	NA	Median: 99 Range: 96-113 IQR Units: Hours	Median: 7.9 Range: 1.6-46.7	20ppm: iNo started at 20ppm, given for 2 hours, if responsive weaned by 5 ppm every 15 minutes until 5ppm then continued for 72 hours, then discontinued.	
	Dexamethasone alone AND dex + iNO)	21	Median: 27 Range: 22-31	Median: 870 Range: 530-1400	NA	NA	Median: 104 Range: 96-120 Units: Hours	Median: 7.9 Range: 1.2-46.7	20ppm: iNo started at 20ppm, given for 2 hours, if responsive weaned by 5 ppm every 15 minutes until 5ppm then continued for 72 hours, then discontinued.	
	iNO AND	21	Median: 27	Median:	NA	NA	Median: 98	Median: 4.1	20ppm: iNo	

Appendix E. Evidence Tables

Evidence Table 4. Participant Characteristics (continued)

Author, year	Control Interventions	N at baseline	Gestational age (weeks)	Birth weight (grams)	Race n(%)	Mode of Ventilation, n(%)	Participant age at enrollment	Oxygenation Index	iNO Dose	iNO Duration
	standard of care		Range: 22-31	818 Range: 520-1222			Range: 96-114 Units: Hours	Range: 1.4-28	started at 20ppm, given for 2 hours, if responsive weaned by 5 ppm every 15 minutes until 5ppm then continued for 72 hours, then discontinued.	
Follow-up of Subhedar, 1997[22] Bennett, 2001[23]	Control	22	NA	NA	NA	CMV :22 (100)	Mean: 96 Units: Hours	NA		
	iNO	20	NA	NA	NA	CMV :20 (100)	Mean: 96 Units: Hours	NA	5-20ppm iNO x 72hours or until extubated	
Tanaka, 2007[24]	Control	15	Median: 26 Range: 24-30	Median: 818 Range: 720-1400 IQR	NA	HFV: 9 (60)	NA	Median: 23.3 Range:16-45		
	iNO	16	Median: 25.5 Range: 25-28.8	Median: 838 Range: 628-1144 IQR	NA	HFV: 14 (87.5)	NA	Median: 23.3 Range: 16-45 IQR	10ppm: Increase 10ppm every 30min to max 30ppm	
Uga, 2004[25]	Control	10	Mean: 25.8 SD: 2.4 Range: 24-30	Mean: 809 SD: 316 Range: 426-1453	NA	NA	NA	Mean: 13.9 SD: 10.2		
	iNO	8	Mean: 27.2 SD: 2.2 Range: 24-30	Mean: 996 SD: 294 Range: 570-1317	NA	NA	NA	Mean: 28.8 SD: 18.3	30-40ppm	

Appendix E. Evidence Tables

Evidence Table 4. Participant Characteristics (continued)

Author, year	Control Interventions	N at baseline	Gestational age (weeks)	Birth weight (grams)	Race n(%)	Mode of Ventilation, n(%)	Participant age at enrollment	Oxygenation Index	iNO Dose	iNO Duration
Van Meurs, 2005[26]	Control	210	Mean: 26 SD: 2	Mean: 837 SD: 260	W: 96 (46) B: 78 (37) H: 32 (15) Other: 4 (2)	HFV: 124 (59) CMV: 86 (41)	Mean:28 SD: 22 Units: Hours	Mean:22 SD:17		
	iNO	210	Mean: 26 SD: 2	Mean: 840 SD: 264	W: 95 (45) B: 69 (33) H: 36 (17) Other: 10 (5)	HFV: 125 (59) CMV : 85 (40)	Mean:26 SD: 23 Units: Hours	Mean:23 SD:17	5ppm: Hold if PaO2 increases >=20mmHg or increase to 10ppm	Mean: 76 SD: 73 Unit: hours
Sub analysis of Van Meurs, 2005[26] Chock, 2009[27]	Control	6	Mean: 29 SD: 3	Mean: 1179 SD: 369	W: 4 (67) B: 1 (17) H: 0 (0) Other: 1 (17)	HFV: 6 (100)	Mean:11 SD: 4 Units: Hours	Mean:44 SD: 30 Median:39 Range:10-100		
	iNO	6	Mean: 27 SD: 2	Mean: 1039 SD: 355	W: 2 (33) B: 1 (17) H: 2 (33) Other: 1 (17)	HFV: 6 (100)	Mean:12 SD: 8 Units: Hours	Mean:20 SD:27 Median: 19 Range: 11-64	5ppm x30min: increase 5ppm if PaO2 did not increase >20mmHg	Mean: 1 SD: 0.2 Unit: hours
Follow-up of Van Meurs, 2005[26] Hintz, 2007[28]	Placebo	102	Mean: 26.2 SD: 2.2	Mean: 864 SD: 271	W: 46 (45) B: 35 (34) H: 18 (18) Other: 1 (1)	HFV: 57 (56)	NA	Mean: 18.1 SD:11.3 Median: 14.9 Range:.5 - 21.6		Median: 2 Range: 1-75 IQR Unit: hours

Appendix E. Evidence Tables

Evidence Table 4. Participant Characteristics (continued)

Author, year	Control Interventions	N at baseline	Gestational age (weeks)	Birth weight (grams)	Race n(%)	Mode of Ventilation, n(%)	Participant age at enrollment	Oxygenation Index	iNO Dose	iNO Duration
	iNO Follow-up of group	91	Mean: 26.8 SD: 2.3	Mean: 958 SD: 276	W: 43 (47) B: 27 (30) H: 17 (19)	HFV: 61 (67)	NA	Mean: 20 SD:12.9 Median: 16.3 Range: 12-24	5ppm titrated	Median:72 Range: 42-115IQR
Van Meurs, 2007[29]	Control	15	Mean: 31.4 SD: 1.1	Mean: 2168 SD: 441	W: 5 (33) B: 4 (27) H: 6 (40)	HFV: 11 (73) CMV : 2(13) HFFI: 2 (13)	NA	Mean: 28.2 SD:17.3		
	iNO	14	Mean: 31.1 SD: 1.2	Mean: 1970 SD: 391	W: 7 (50) B: 5 (36) H: 1 (7) Other:1 (7)	HFV: 6 (43) CMV : 8 (57) HFFI 0 (0)	NA	Mean:25.1 SD:19.4	5ppm x30min: Increase to 10ppm	
Yadav, 1999[30]	iNO	41	Mean:27 SD:2.6	Mean: 1000 SD: 46	NA	NA	NA	Mean: 40 SD: 17	10ppm	

B:Non-hispanic black; H:Hispanic; W:non-hispanic white; HFV: High-frequency ventilation; CMV: Conventional mechanical ventilation; CPAP: Continuous Positive Airway Pressure; HFFI: High-frequency flow interruption; mmHg: millimeters of mercury; ppm: parts per million; iNO: inhaled nitric oxide

Reference List

1. Ballard RA, Truog WE, Cnaan A *et al*. Inhaled nitric oxide in preterm infants undergoing mechanical ventilation. New Engl. J. Med. 2006; 355(4):343-53.
2. Hibbs AM, Walsh MC, Martin RJ *et al*. One Year Respiratory Outcomes of the Preterm Infants Enrolled in the NO CLD Trial of Inhaled Nitric Oxide (iNO). N/A 2007.
3. Walsh MC, Hibbs AM, Martin CR *et al*. Two-year neurodevelopmental outcomes of ventilated preterm infants treated with inhaled nitric oxide. J Pediatr 2010; 156(4):556-61.e1.
4. Banks BA, Seri I, Ischiropoulos H, Merrill J, Rychik J, Ballard RA. Changes in oxygenation with inhaled nitric oxide in severe bronchopulmonary dysplasia. Pediatrics 1999; 103(3):610-8.
5. Cheung P-Y, Peliowski A, Robertson CMT. The outcome of very low birth

weight neonates ((less-than or equal to)1500 g) rescued by inhaled nitric oxide: Neurodevelopment in early childhood. J. Pediatr. 1998; 133(6):735-9.
6. Clark PL, Ekekezie II, Kaftan HA, Castor CA, Truog WE. Safety and efficacy of nitric oxide in chronic lung disease. Arch Dis Child Fetal Neonatal Ed 2002; 86(1):F41-5.
7. Dani C, Bertini G, Pezzati M, Filippi L, Cecchi A, Rubaltelli FF. Inhaled nitric oxide in very preterm infants with severe respiratory distress syndrome. Acta Paediatr 2006; 95(9):1116-23.
8. Dewhurst C, Ibrahim H, Gothberg S, Jonsson B, Subhedar N. Use of inhaled nitric oxide in the new born period: Results from the European inhaled nitric oxide registry. Acta Paediatr. Int. J. Paediatr. 2010; 99(6):854-60.
9. Field D, Elbourne D, Truesdale A *et al*. Neonatal Ventilation With Inhaled Nitric Oxide Versus Ventilatory Support Without Inhaled Nitric Oxide for Preterm Infants With Severe Respiratory Failure: the INNOVO multicentre randomised controlled trial (ISRCTN 17821339). Pediatrics 2005; 115(4):926-36.
10. Huddy CL, Bennett CC, Hardy P *et al*. The INNOVO multicentre randomised controlled trial: neonatal ventilation with inhaled nitric oxide versus ventilatory support without nitric oxide for severe respiratory failure in preterm infants: follow up at 4-5 years. Arch Dis Child Fetal Neonatal Ed 2008; 93(6):F430-5.
11. Franco-Belgium Collaborative NO Trial Group. Early compared with delayed inhaled nitric oxide in moderately hypoxaemic neonates with respiratory failure: a randomised controlled trial. The Franco-Belgium Collaborative NO Trial Group. Lancet 1999; 354(9184):1066-71.
12. Hascoet JM, Fresson J, Claris O *et al*. The safety and efficacy of nitric oxide therapy in premature infants. J. Pediatr. 2005; 146(3):318-23.
13. Hamon I, Fresson J, Nicolas MB, Buchweiller MC, Franck P, Hascoet JM. Early inhaled nitric oxide improves oxidative balance in very preterm infants. Pediatr Res 2005; 57(5 Pt 1):637-43.
14. Kinsella JP, Walsh WF, Bose CL *et al*. Inhaled nitric oxide in premature neonates with severe hypoxaemic respiratory failure: A randomised controlled trial. Lancet 1999; 354(9184):1061-5.
15. Kinsella JP, Cutter GR, Walsh WF *et al*. Early inhaled nitric oxide therapy in premature newborns with respiratory failure. N Engl J Med 2006; 355(4):354-64.
16. Watson RS, Clermont G, Kinsella JP *et al*. Clinical and economic effects of iNO in premature newborns with respiratory failure at 1 year. Pediatrics 2009; 124(5):1333-43.
17. Mercier JC, Hummler H, Durrmeyer X *et al*. Inhaled nitric oxide for prevention of bronchopulmonary dysplasia in premature babies (EUNO): a randomised controlled trial. Lancet 2010.
18. Schreiber MD, Gin-Mestan K, Marks JD, Huo D, Lee G, Srisuparp P. Inhaled Nitric Oxide in Premature Infants with the Respiratory Distress Syndrome. New Engl. J. Med. 2003; 349(22):2099-107.
19. Mestan KK, Marks JD, Hecox K, Huo D, Schreiber MD. Neurodevelopmental outcomes of premature infants treated with inhaled nitric oxide. N Engl J Med 2005; 353(1):23-32.
20. Srisuparp P, Heitschmidt M, Schreiber MD. Inhaled nitric oxide therapy in premature infants with mild to moderate respiratory distress syndrome. J Med Assoc Thai 2002; 85 Suppl 2:S469-78.
21. Su PH, Chen JY. Inhaled nitric oxide in the management of preterm infants with severe respiratory failure. J Perinatol 2008; 28(2):112-6.
22. Subhedar NV, Ryan SW, Shaw NJ. Open randomised controlled trial of inhaled nitric oxide and early dexamethasone in high risk preterm infants. Arch Dis Child Fetal Neonatal Ed 1997; 77(3):F185-90.
23. Bennett AJ, Shaw NJ, Gregg JE, Subhedar NV. Neurodevelopmental outcome in high-risk preterm infants treated with inhaled nitric oxide. Acta Paediatr 2001; 90(5):573-6.
24. Tanaka Y, Hayashi T, Kitajima H, Sumi K, Fujimura M. Inhaled nitric oxide therapy decreases the risk of cerebral palsy in preterm infants with persistent pulmonary hypertension of the newborn. Pediatrics 2007; 119(6):1159-64.
25. Uga N, Ishii T, Kawase Y, Arai H, Tada H. Nitric oxide inhalation therapy in very low-birthweight infants with hypoplastic lung due to oligohydramnios. Pediatr. Int. 2004; 46(1):10-4.
26. Van Meurs KP, Wright LL, Ehrenkranz RA *et al*. Inhaled nitric oxide for premature infants with severe respiratory failure. N Engl J Med 2005; 353(1):13-22.
27. Chock VY, Van Meurs KP, Hintz SR *et al*. Inhaled nitric oxide for preterm premature rupture of membranes, oligohydramnios, and pulmonary hypoplasia. Am J Perinatol 2009; 26(4):317-22.
28. Hintz SR, Van Meurs KP, Perritt R *et al*. Neurodevelopmental outcomes of premature infants with severe respiratory failure enrolled in a randomized controlled trial of inhaled nitric oxide. J Pediatr 2007; 151(1):16-22, 22.e1-3.
29. Van Meurs KP, Hintz SR, Ehrenkranz RA *et al*. Inhaled nitric oxide in infants >1500 g and <34 weeks gestation with severe respiratory failure. J Perinatol 2007; 27(6):347-52.
30. Yadav M, Emmerson AJ. Inhaled nitric oxide in premature neonates. Lancet 1999; 354(9196):2162-3

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Appendix E. Evidence Tables

Evidence Table 5. Death and survival outcomes for KQ1.

Author, Year	Outcome	Time of outcome measure	Arm Description	N (Number of Participants Measured)	Participants with Outcome n (%)	Relative Effect (95% CI) OR (95% CI)	Adjusted Relative Effect (95% CI) Adjusted OR (95% CI)	Adjustments
Ballard, 2006[1]	Death	36 weeks PMA	Control	288	18 (6.3)			
			iNO	294	16 (5.4)			
		40 weeks PMA	Control	288	19 (6.6)			
			iNO	294	19 (6.5)			
		44 wks PMA	Control	288	20 (6.9)			
			iNO	294	20 (6.8)			
Dani, 2006[2]		NICU	Control	20	6 (30)		P-value: 0.494	birth weight
			iNO	20	4 (20)			
			Nonresponders	6	4 (66)	P-value: 0.078		
			Responders	14	3 (21)			
Field, 2005[3]		1 year	Control	53	34 (64)			
			iNO	55	30 (55)			
Franco-Belgium Collaborative NO Trial Group, 1999[4]		in NICU	Control	45	16 (35)	P-value: Not significant		
			iNO	40	11 (27)			
Hascoet, 2005[5]		7 days of life	Control with HRF	84	14 (17)	P-value: 0.58	1	
			iNO with HRF	61	8 (13)			
		28 days of life	Control with HRF	84	26 (31)	P-value: Not significant		

Appendix E. Evidence Tables

Evidence Table 5. Death and survival outcomes for KQ1 (continued)

Author, Year	Outcome	Time of outcome measure	Arm Description	N (Number of Participants Measured)	Participants with Outcome n (%)	Relative Effect (95% CI) OR (95% CI)	Adjusted Relative Effect (95% CI) Adjusted OR (95% CI)	Adjustments
			iNO with HRF	61	25 (41)			
Kinsella, 1999[6]		Discharge	Control	32	17 (53)	P-value: 0.65 RR: 1.11(0.7-1.8)		
			iNO	48	23 (48)			
Kinsella, 2006[7]		36 wks PMA	Control	392	98 (25)		P-value: 0.08 RR: 0.79 (0.61-1.03)	randomization strata, study sight
			iNO, Total sample)	394	78 (19.8)			
Mercier, 2010 [8]		24-28 weeks	Control	401	42 (10.5)			
			iNO	399	56 (14)			
Schreiber, 2003[9]		NICU	Control	102	23 (22.5)	P-value: 0.18 RR: 0.68 (0.38-1.20)	RR: 0.68 (0.38-1.20)	type of ventilation
			iNO	105	16 (15.2)			
Srisuparp, 2002[10]		7 days	Control	22	2 (11.1)	P-value: 1		
			iNO	16	2 (12.5)			
Su, 2008[11]		During Study (9 death within 96 hours)	Control	33	10 (30.3)			
			iNO	32	6 (18.8)			

Appendix E. Evidence Tables

Evidence Table 5. Death and survival outcomes for KQ1 (continued)

Author, Year	Outcome	Time of outcome measure	Arm Description	N (Number of Participants Measured)	Participants with Outcome n (%)	Relative Effect (95% CI) OR (95% CI)	Adjusted Relative Effect (95% CI) Adjusted OR (95% CI)	Adjustments
			groups 1&3; iNO + iNO and dexamethasone)	20	10 (50)			
Van Meurs, 2005[13]		death before discharge to home or within 365	Control	208	93 (45)		P-value: 0.11 RR:1.16 (0.96-1.39)	Birthweight, study center, OI
			iNO)	210	109 (52)			
Van Meurs, 2007[14]		Death before discharge to home or within 365	Control	15	4 (27)	P-value: 0.7 RR: 1.34 (0.45-4.0)	p-value: 0.65 RR: 1.26 (0.47-3.41)	OI Stratum
			iNO	14	5 (36)			
Ballard, 2006[1]	Survival without BPD	36 weeks PMA	Control	288	105 (36.5)	p-value:0.04 RR: 1.26 (1.02-1.55)	RR: 1.45 (1.03-2.04)	cluster (multiples) using GEE; from the letter to the editor correction
			iNO	294	129 (43.9)			

Appendix E. Evidence Tables

Evidence Table 5. Death and survival outcomes for KQ1 (continued)

Author, Year	Outcome	Time of outcome measure	Arm Description	N (Number of Participants Measured)	Participants with Outcome n (%)	Relative Effect (95% CI) OR (95% CI)	Adjusted Relative Effect (95% CI) Adjusted OR (95% CI)	Adjustments
Hascoet, 2005[5]		28 days	Control with HRF	84	18 (21.4)	p-value:NS		
			iNO with HRF	61	14 (23)	p-value:NS		
Schreiber, 2003[9]		Survived NICU	iNO	89	54 (60.7)			
			Control	79	37 (46.8)			
Schreiber, 2003[9]	Survival with BPD	Survived NICU	Control	102	42 (53.2)	p-value:0.07 RR:0.74 (0.53-1.03)		
			iNO	105	35 (39.3)			
Subhedar, 1997[12]		Not Specified	Control dexamethasone and standard of care	22	14 (64)	RR: 1.07 (0.71-1.37) RR: 0.92 (0.67-1.28)		
			Groups 1&3; iNO + iNO and dexamethasone	10	10 (100)			
			Dexamethasone alone AND dex + iNO	21	11 (52)			
			iNO AND standard of care	21	13 (62)			
Schreiber, 2003[9]	Survival, BPD not specific	Survived NICU	Control	102	79 (77.5)			
			iNO	105	89 (84.8)			

Appendix E. Evidence Tables

BPD: Bronchopulmonary Dysplasia, CI: Confidence Interval, GEE: Generalized estimating equation, HRF: Hypoxemic Respiratory Failure , iNO: Inhaled nitric oxide, NICU: Neonatal intensive care unit, NS: Not significant, OI: Oxygenation Index, OR: Odds ratio, PMA: Post-menstrual age , RR: Relative risk

Reference List

1. Ballard RA, Truog WE, Cnaan A *et al*. Inhaled nitric oxide in preterm infants undergoing mechanical ventilation. New Engl. J. Med. 2006; 355(4):343-53.
2. Dani C, Bertini G, Pezzati M, Filippi L, Cecchi A, Rubaltelli FF. Inhaled nitric oxide in very preterm infants with severe respiratory distress syndrome. Acta Paediatr 2006; 95(9):1116-23.
3. Field D, Elbourne D, Truesdale A *et al*. Neonatal Ventilation With Inhaled Nitric Oxide Versus Ventilatory Support Without Inhaled Nitric Oxide for Preterm Infants With Severe Respiratory Failure: the INNOVO multicentre randomised controlled trial (ISRCTN 17821339). Pediatrics 2005; 115(4):926-36.
4. Franco-Belgium Collaborative NO Trial Group. Early compared with delayed inhaled nitric oxide in moderately hypoxaemic neonates with respiratory failure: a randomised controlled trial. The Franco-Belgium Collaborative NO Trial Group. Lancet 1999; 354(9184):1066-71.
5. Hascoet JM, Fresson J, Claris O *et al*. The safety and efficacy of nitric oxide therapy in premature infants. J. Pediatr. 2005; 146(3):318-23.
6. Kinsella JP, Walsh WF, Bose CL *et al*. Inhaled nitric oxide in premature neonates with severe hypoxaemic respiratory failure: A randomised controlled trial. Lancet 1999; 354(9184):1061-5.
7. Kinsella JP, Cutter GR, Walsh WF *et al*. Early inhaled nitric oxide therapy in premature newborns with respiratory failure. N Engl J Med 2006; 355(4):354-64.
8. Mercier JC, Hummler H, Durrmeyer X *et al*. Inhaled nitric oxide for prevention of bronchopulmonary dysplasia in premature babies (EUNO): a randomised controlled trial. Lancet 2010.
9. Schreiber MD, Gin-Mestan K, Marks JD, Huo D, Lee G, Srisuparp P. Inhaled Nitric Oxide in Premature Infants with the Respiratory Distress Syndrome. New Engl. J. Med. 2003; 349(22):2099-107.
10. Srisuparp P, Heitschmidt M, Schreiber MD. Inhaled nitric oxide therapy in premature infants with mild to moderate respiratory distress syndrome. J Med Assoc Thai 2002; 85 Suppl 2:S469-78.
11. Su PH, Chen JY. Inhaled nitric oxide in the management of preterm infants with severe respiratory failure. J Perinatol 2008; 28(2):112-6.
12. Subhedar NV, Ryan SW, Shaw NJ. Open randomised controlled trial of inhaled nitric oxide and early dexamethasone in high risk preterm infants. Arch Dis Child Fetal Neonatal Ed 1997; 77(3):F185-90.
13. Van Meurs KP, Wright LL, Ehrenkranz RA *et al*. Inhaled nitric oxide for premature infants with severe respiratory failure. N Engl J Med 2005; 353(1):13-22.
14. Van Meurs KP, Hintz SR, Ehrenkranz RA *et al*. Inhaled nitric oxide in infants >1500 g and <34 weeks gestation with severe respiratory failure. J Perinatol 2007; 27(6):347-52.

Appendix E. Evidence Tables

Evidence Table 6. BPD for KQ1

Author, Year	Time of outcome measure	Study Arm	N (number of participants measured)	Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments	Duration (days)	Difference in Duration (p-value)
Ballard, 2006[1]	36 weeks PMA	Control	288	164 (56.9)					
		iNO	294	149 (50.7)					
Dani, 2006[2]	36 weeks PMA	Control	20	12 (60)	P-value: 0.067			Mean: 69.4 SD: 30.2	0.054
		iNO	20	6 (30)				Mean: 47.3 SD: 39.4	
		Nonresponders	6	2 (33)				Mean: 19.8 SD: 11.5	0.084
		Responders	14	7 (50)				Mean: 48.6 SD: 37.3	
Field, 2005[3]	36 weeks PMA	Control	55	15 (27)				Mean: 6 IQR:1.0-17.0	
		iNO	53	26 (49)				Mean: 15 IQR:2-71	

Appendix E. Evidence Tables

Evidence Table 6. BPD for KQ1 (continued)

Author, Year	Time of outcome measure	Study Arm	N (number of participants measured)	Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments	Duration (days)	Difference in Duration (p-value)
Franco-Belgium Collaborative NO Trial Group, 1999[4]	during hospitalization	Control	29	8 (29)	p-value: NS			Median: 23 IQR:41	0.38
		iNO	29	7 (24)	p-value: NS OR: 0.95 (0.44–2.04)			Median: 14 IQR:43	
Kinsella, 2006[5]	36 weeks PMA	Control	309	210 (68)	P-value: 0.43	RR:0.96 (0.86–1.09)	randomization strata, study sight		
		iNO	326	212 (65)					
Kinsella, 1999[6]	36 weeks PMA	Control	15	12 (80)	p-value: 0.3 RR: 0.75(0.5-1.13)				
		iNO	25	15 (60)					
Mercier, 2010 [7]	24-28 weeks	Control	358	96 (27)					
		iNO	339	81(24)					
Schreiber, 2003[8]	36 weeks PMA	Control	102	42 (53.2)		P-value: 0.07 RR: 0.74 (0.53–1.03)	type of ventilation		
		iNO	105	35 (39.3)					
Su, 2008[9]	36 weeks PMA	Control	33	11 (33.3)					

Appendix E. Evidence Tables

Evidence Table 6. BPD for KQ1 (continued)

Author, Year	Time of outcome measure	Study Arm	N (number of participants measured)	Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments	Duration (days)	Difference in Duration (p-value)
		iNO	32	10 (31.3)					
Subhedar, 1997[10]	36 weeks PMA	Dexamethasone and standard of care	22	14 (64)					
		Groups 1&3; iNO + iNO and dexamethasone	20	10 (50)					
		Dexamethasone alone AND dex + iNO	21	11 (52)					
		iNO AND standard of care	21	13 (62)					
Van Meurs, 2007[11]	36 weeks PMA	Control	11	5 (45)	p-value: 0.66 RR: 0.66 (0.21-2.08)	p-value: 0.21 RR: 0.40 (0.09-1.71)	OI stratum	Mean: 32 SD: 23	0.45
		iNO	10	3 (30)				Mean: 23.8 SD: 24.4	
Van Meurs, 2005[12]	36 weeks PMA	Control	127	86 (68)	P-value: 0.26	RR: 0.90 (0.75–1.08)			
		iNO	109	65 (60)					
Ballard, 2006[1]	40 weeks PMA	Control	288	84 (29.2)					
		iNO	294	66 (22.4)					
	44 weeks PMA	Control	288	35 (12.2)					
		iNO	294	27 (9.2)					
Dani, 2006[2]	Duration of supplement	Control	20	69.4 days*					
		iNO	20	47.3 days*					

Appendix E. Evidence Tables

Evidence Table 6. BPD for KQ1 (continued)

Author, Year	Time of outcome measure	Study Arm	N (number of participants measured)	Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments	Duration (days)	Difference in Duration (p-value)
	al oxygen	Nonresponders	6	19.8 days*					
		Responders	14	48.6 days*					
Field, 2005[3]	1 year corrected age	Control	18 survivors	1 (6)					
		iNO	20 survivors	3 (15)					
	At term (EDC)	Control	53	12 (23)				Median: 81 IQR:14-100	
		iNO	55	16 (29)				Median: 59 IQR:30-78	
Franco-Belgium Collaborative NO Trial Group, 1999[4]	28 days	Control	29	14 (48)	p-value: NS				
		iNO	29	13 (45)					
Kinsella, 1999[6]	Hospital discharge	Control	15	12 (80)	p-value: 0.1				
					RR: 0.65 (0.41-1.02)				
		iNO	25	13 (54)	p-value: 0.1 1.02)				
					RR: 0.65(0.41-				
Kinsella, 2006 [5]	Post-natal corticosteroids	Control	365	204 (56)	p-value: 0.24				
		iNO	369	222 (60)					
Schreib	Duration of	Control	102	28.5 days*					

Appendix E. Evidence Tables

Evidence Table 6. BPD for KQ1 (continued)

Author, Year	Time of outcome measure	Study Arm	N (number of participants measured)	Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments	Duration (days)	Difference in Duration (p-value)
er, 2003[8]	Mechanical Ventilation	iNO	105	16 days					
Su, 2008[9]	Duration of Mechanical Ventilation	Control	33	14.2 days*					
		iNO	32	12.8 days *					
Van Meurs, 2005[12]	Days on Mechanical Ventilation	Control	210	47 days*					
		iNO	210	39 days*					
Van Meurs, 2007 [11]	Physiologic BPD as per Walsh criteria	Control	10	4 (40)	p-value: 1 RR: 0.91 (0.31-2.70)	p-value: 0.61 RR: 0.74 (0.26-2.09)			
		iNO	11	4 (36)					
Ballard, 2006[1]	40 weeks PMA, severe	Control	288	30 (10.4)					
		iNO	294	18 (6.1)					
	44 weeks PMA, severe	Control	288	12 (4.2)					
		iNO	294	6 (2)					
Dani, 2006[2]	In NICU, severe	Control	20	20 (100)				14.9 (Mean) 18.1 (SD)	
		iNO	20	20 (100)	1			12.5 (Mean)	0.608

Appendix E. Evidence Tables

Evidence Table 6. BPD for KQ1 (continued)

Author, Year	Time of outcome measure	Study Arm	N (number of participants measured)	Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments	Duration (days)	Difference in Duration (p-value)
								10.1 (SD)	
		Nonresponders	6	6 (100)				19 (Mean) 12.7 (SD)	
		Responders	14	14 (100)	1			15.8 (Mean) 17.3 (SD)	0.69
Field, 2005[3]	During hospitalization, severe	Control	53					4 (Mean) 1.0-9.0 IQR	
		iNO	55					7 (Median) 2-26 IQR	
Hascoet, 2005[13]	48 hours of life, severe	Control with HRF	84	30 (35.7)	0.024				
		iNO with HRF	61	49 (80.3)	0.024				
Franco-Belgium, 1999[4]	during hospitalization, severe	Control	29					16 (Median) 14 IQR	ns
		iNO	29					12 (Median) 32 IQR	0.78

Appendix E. Evidence Tables

Evidence Table 6. BPD for KQ1 (continued)

Author, Year	Time of outcome measure	Study Arm	N (number of participants measured)	Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments	Duration (days)	Difference in Duration (p-value)
Schreiber, 2003[8]	Before Discharge, severe	Control	79 survivors					28.5 (Median) IQR 8-48	
		iNO	89 survivors					16 (Median) IQR 8-37	0.19
Subhedar, 1997[10]	Before Discharge, severe	Dexamethasone and standard of care	22					19 (Median) 5-39 range	
		Groups 1&3; iNO + iNO and dexamethasone	20					11 (Median) 5-44 range	
		Dexamethasone alone AND dex + iNO	21					23 (Median) 6-44 range	
		iNO AND standard of care	21					13 (Median) 5-39 range	
	Time to extubation, severe	Dexamethasone and standard of care	22					11 (Median) range 5-	

Appendix E. Evidence Tables

Evidence Table 6. BPD for KQ1 (continued)

Author, Year	Time of outcome measure	Study Arm	N (number of participants measured)	Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments	Duration (days)	Difference in Duration (p-value)
								35	
		Groups 1&3; iNO + iNO and dexamethasone	20					6.5 (Median) range 5-28	
		Dexamethasone alone AND dex + iNO	21					8.5 (Median) 5-35 range	
		iNO AND standard of care	21					11 (Median) 5-28 range	
Van Meurs, 2005[12]	NICU, severe	Control	117					Mean:47 SD: 53	
		iNO	101					Mean:39 SD:45	0.56

* Measure given in days, not number of participants

BPD: Bronchopulmonary Dysplasia, EDC: Estimated date of confinement, HFOV: High-frequency oscillatory ventilation, HRF: Hypoxemic respiratory failure, iNO: Inhaled Nitric Oxide, IQR: Inter-quartile range, NICU: Neonatal Intensive Care Unit, NS: Not significant, PMA: Post-menstrual age, SD: Standard Deviation

Appendix E. Evidence Tables

Reference List

1. Ballard RA, Truog WE, Cnaan A *et al*. Inhaled nitric oxide in preterm infants undergoing mechanical ventilation. New Engl. J. Med. 2006; 355(4):343-53.
2. Dani C, Bertini G, Pezzati M, Filippi L, Cecchi A, Rubaltelli FF. Inhaled nitric oxide in very preterm infants with severe respiratory distress syndrome. Acta Paediatr 2006; 95(9):1116-23.
3. Field D, Elbourne D, Truesdale A *et al*. Neonatal Ventilation With Inhaled Nitric Oxide Versus Ventilatory Support Without Inhaled Nitric Oxide for Preterm Infants With Severe Respiratory Failure: the INNOVO multicentre randomised controlled trial (ISRCTN 17821339). Pediatrics 2005; 115(4):926-36.
4. Franco-Belgium Collaborative NO Trial Group. Early compared with delayed inhaled nitric oxide in moderately hypoxaemic neonates with respiratory failure: a randomised controlled trial. The Franco-Belgium Collaborative NO Trial Group. Lancet 1999; 354(9184):1066-71.
5. Kinsella JP, Cutter GR, Walsh WF *et al*. Early inhaled nitric oxide therapy in premature newborns with respiratory failure. N Engl J Med 2006; 355(4):354-64.
6. Kinsella JP, Walsh WF, Bose CL *et al*. Inhaled nitric oxide in premature neonates with severe hypoxaemic respiratory failure: A randomised controlled trial. Lancet 1999; 354(9184):1061-5.
7. Mercier JC, Hummler H, Durrmeyer X *et al*. Inhaled nitric oxide for prevention of bronchopulmonary dysplasia in premature babies (EUNO): a randomised controlled trial. Lancet 2010.
8. Schreiber MD, Gin-Mestan K, Marks JD, Huo D, Lee G, Srisuparp P. Inhaled Nitric Oxide in Premature Infants with the Respiratory Distress Syndrome. New Engl. J. Med. 2003; 349(22):2099-107.
9. Su PH, Chen JY. Inhaled nitric oxide in the management of preterm infants with severe respiratory failure. J Perinatol 2008; 28(2):112-6.
10. Subhedar NV, Ryan SW, Shaw NJ. Open randomised controlled trial of inhaled nitric oxide and early dexamethasone in high risk preterm infants. Arch Dis Child Fetal Neonatal Ed 1997; 77(3):F185-90.
11. Van Meurs KP, Hintz SR, Ehrenkranz RA *et al.* Inhaled nitric oxide in infants >1500 g and <34 weeks gestation with severe respiratory failure. J Perinatol 2007; 27(6):347-52.
12. Van Meurs KP, Wright LL, Ehrenkranz RA *et al.* Inhaled nitric oxide for premature infants with severe respiratory failure. N Engl J Med 2005; 353(1):13-22.
13. Hascoet JM, Fresson J, Claris O *et al*. The safety and efficacy of nitric oxide therapy in premature infants. J. Pediatr. 2005; 146(3):318-23.

Appendix E. Evidence Tables

Evidence Table 7. Death of BPD outcomes for KQ1

Author, Year	Time of outcome measure	Arm Description	N (Number of Participants Measured)	Participants with Outcome n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments
					OR (95% CI)	Adjusted OR (95% CI)	
Ballard, 2006[1]	36 weeks PMA	Control	288	182 (63.2)			
		iNO	294	165 (56.1)			
Dani, 2006[2]	NICU	Control	20	18 (90)	P-value: 0.016 OR: 0.111 (0.02-0.610)		
		iNO	20	10 (50)			
		Nonresponders	6	6 (100)	P-value: 0.035		
		Responders	14	10 (71)			
Field, 2005[3]	36 weeks PMA	Control	53	48 (91)			
		iNO	55	49 (89)			
Franco-Belgium Collaborative NO Trial Group, 1999[4]	In NICU	Control	45	24 (53)			
		iNO	40	18 (45)			
Kinsella, 1999[5]	Discharge	Control	32	29 (91)	P-value: 0.14 RR: 0.85(0.7-1.03)		
		iNO	48	37 (77)			
Kinsella, 2006[6]	36 wks PMA	Control	392	295 (75.3)		P-value: 0.24 RR: 0.95 (0.87-1.03)	Study sight, randomization strata
		iNO	394	282 (71.6)			
Mercier, 2010[7]	24-28 weeks	Control	400	138 (35)			

Appendix E. Evidence Tables

Evidence Table 7. Death of BPD outcomes for KQ1 (continued)

Author, Year	Time of outcome measure	Arm Description	N (Number of Participants Measured)	Participants with Outcome n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments
					OR (95% CI)	Adjusted OR (95% CI)	
		iNO	395	137 (35)			
Schreiber, 2003[8]	NICU	Control	102	65 (63.7)	P-value: 0.03 RR: 0.76 (0.60-0.97)	RR: 0.77 (0.60-0.98)	type of ventilation
		iNO	105	51 (48.6)			
Su, 2008 [9]	36 weeks PMA	Control	33	21 (64)			
		iNO	32	16 (50)			
Subhedar, 1997 [10]	Before Discharge	Control	22	21 (95)	RR = 1.05 (0.84-1.25)		
		iNO	20	20 (100)			
Van Meurs, 2007[11]	Death before discharge to home or within 365	Control	15	9 (60)	P-value: 0.87 RR: 0.83 (0.43-1.62)	p-value: 0.5 RR: 0.80 (0.43-1.48)	OI Stratum
		iNO	14	7 (50)			
Van Meurs, 2005[12]	before discharge to home or within 365 days among hospitalized infants	Control	208	170 (82)		P-value: 0.52 RR: 0.97 (0.86-1.06)	Birth weight, study site, Oxygenation index
		iNO	210	167 (80)			

BPD: Bronchopulmonary Dysplasia, iNO: Inhaled nitric oxide, NICU: Neonatal intensive care unit, OI: Oxygenation Index, OR: Odds ratio, PMA: Post-menstrual age , RR: Relative risk

Appendix E. Evidence Tables

Reference List

1. Ballard RA, Truog WE, Cnaan A *et al*. Inhaled nitric oxide in preterm infants undergoing mechanical ventilation. New Engl. J. Med. 2006; 355(4):343-53.
2. Dani C, Bertini G, Pezzati M, Filippi L, Cecchi A, Rubaltelli FF. Inhaled nitric oxide in very preterm infants with severe respiratory distress syndrome. Acta Paediatr 2006; 95(9):1116-23.
3. Field D, Elbourne D, Truesdale A *et al*. Neonatal Ventilation With Inhaled Nitric Oxide Versus Ventilatory Support Without Inhaled Nitric Oxide for Preterm Infants With Severe Respiratory Failure: the INNOVO multicentre randomised controlled trial (ISRCTN 17821339). Pediatrics 2005; 115(4):926-36.
4. Franco-Belgium Collaborative NO Trial Group. Early compared with delayed inhaled nitric oxide in moderately hypoxaemic neonates with respiratory failure: a randomised controlled trial. The Franco-Belgium Collaborative NO Trial Group. Lancet 1999; 354(9184):1066-71.
5. Kinsella JP, Walsh WF, Bose CL *et al*. Inhaled nitric oxide in premature neonates with severe hypoxaemic respiratory failure: A randomised controlled trial. Lancet 1999; 354(9184):1061-5.
6. Kinsella JP, Cutter GR, Walsh WF *et al*. Early inhaled nitric oxide therapy in premature newborns with respiratory failure. N Engl J Med 2006; 355(4):354-64.
7. Mercier JC, Hummler H, Durrmeyer X *et al*. Inhaled nitric oxide for prevention of bronchopulmonary dysplasia in premature babies (EUNO): a randomised controlled trial. Lancet 2010.
8. Schreiber MD, Gin-Mestan K, Marks JD, Huo D, Lee G, Srisuparp P. Inhaled Nitric Oxide in Premature Infants with the Respiratory Distress Syndrome. New Engl. J. Med. 2003; 349(22):2099-107.
9. Su PH, Chen JY. Inhaled nitric oxide in the management of preterm infants with severe respiratory failure. J Perinatol 2008; 28(2):112-6.
10. Subhedar NV, Ryan SW, Shaw NJ. Open randomised controlled trial of inhaled nitric oxide and early dexamethasone in high risk preterm infants. Arch Dis Child Fetal Neonatal Ed 1997; 77(3):F185-90.
11. Van Meurs KP, Hintz SR, Ehrenkranz RA *et al.* Inhaled nitric oxide in infants >1500 g and <34 weeks gestation with severe respiratory failure. J Perinatol 2007; 27(6):347-52.
12. Van Meurs KP, Wright LL, Ehrenkranz RA *et al*. Inhaled nitric oxide for premature infants with severe respiratory failure. N Engl J Med 2005; 353(1):13-22.

Appendix E. Evidence Tables

Evidence Table 8. Brain injury outcomes for KQ2.

Author, Year	Outcomes	Time of outcome measure	Arm Description	N (number of participants measured)	Participants with outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments
Dani, 2006[1]	Brain injury, any IVH	before discharge	Control	20	4 (20)	P-value: 0.725		
			iNO	20	5 (25)			
Hascoet, 2005[2]		28 days	Control	84	6 (7)	P-value: NS		
			iNO	61	4 (6)			
Kinsella, 1999[3]		7 days or 36 weeks postconceptional age	iNO	32	18 (56)	P-value: NS		
			Control	17	10 (59)			
Su, 2008[4]		Not specified	Control	33	12 (36.3)			
			iNO	32	8 (25)			
Dani, 2006[1]	Brain injury, IVH grades 3 and 4	Before discharge	Control	20	2 (10)	P-value: 1		
			iNO	20	2 (10)			
			Nonresponders	6	3 (50)	P-value: 0.225		
			Responders	14	3 (21)			
Kinsella, 1999 [3]		7 days	Control	43	16 (37)			
			iNO	26	10 (40)			
Kinsella, 2006[5]		7 to 14 days of age and / or at more than 30 days of age	Control	394	63 (16)		p-value 0.14 RR: 0.77 (0.54-1.09)	study sight, randomization strata
			iNO	398	49 (12.3)			
Mercier, 2010 [6]		24-28 weeks	Control	397	32 (8)			
			iNO	395	24 (6.1)			
Srisuparp, 2002[7]		72 hours	Control	18	5 (27.8)			
			iNO	16	4 (25.1)			
Su, 2008[4]		Not specified	Control	33	8 (24.2)			
			iNO	32	4 (12.5)			

Appendix E. Evidence Tables

Evidence Table 8. Brain injury outcomes for KQ2 (continued)

Author, Year	Outcomes	Time of outcome measure	Arm Description	N (number of participants measured)	Participants with outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments
Ballard, 2006[8]	Brain Injury, IVH Grades 3 or 4 and / or PVL	after study entry	Control	288	10 (4.1)	P-value: 0.67 RR:1.21(0.53-2.76)		
			iNO	294	13 (5)			
Franco-Belgium Collaborative NO Trial Group, 1999[9]		during hospitalization	Control	45	12 (27)	P-value: NS		
			iNO	40	13 (32)			
Kinsella, 2006 [5]		21 days until extubation	Control	364	87 (24)			
			iNO	366	64 (17)			
Schreiber, 2003[10]		NICU	Control	102	24 (23.5)	P-value: 0.04 RR: 0.53 (0.28-0.98)		
			iNO	105	13 (12.4)			
Van Meurs, 2007[11]		28 +/- 3 days	Control	9 (HUS available)	2 (22)	P-value: 0.47		
			iNO	9	0 (0)			
Van Meurs, 2005[12]		Not specified	Control	155	50 (32)	P-value: 0.11 RR: 1.25 (0.95-1.66)		
			iNO	170	69 (39)			
Dani, 2006[1]	Brain Injury, PVL	Before discharge	Control	20	1 (5)	P-value: 0.5		
			iNO	20	0 (0)			
			Nonresponders	6	0 (0)	P-value: 1		
			Responders	14	0 (0)			
Kinsella, 2006[5]		7 to 14 days of age and / or at more than 30 days of age	Control	356	32 (9)		P-value: 0.048 RR: 0.58 (0.33-1.00)	study site, randomization strata
			iNO	365	19 (5.2)			
Kinsella,		7 days or 36 weeks	Control	15	2 (13)	P-value: 0.62		
			iNO	25	2 (8)			

Appendix E. Evidence Tables

Evidence Table 8. Brain injury outcomes for KQ2 (continued)

Author, Year	Outcomes	Time of outcome measure	Arm Description	N (number of participants measured)	Participants with outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments
1999[3]		postconceptional age						
Mercier, 2010 [6]		24-28 weeks	Control	397	1 (0.2)			
			iNO	395	7 (1.7)			
Su, 2008[4]		Not specified	Control	33	4 (12.1)			
			iNO	32	3 (9.4)			

CI: Confidence Interval, iNO: Inhaled nitric oxide, IVH: Intraventricular hemorrhage, NS: Not significant, PVL: Periventricular leukomalacia, RR: Relative risk

Reference List

1. Dani C, Bertini G, Pezzati M, Filippi L, Cecchi A, Rubaltelli FF. Inhaled nitric oxide in very preterm infants with severe respiratory distress syndrome. Acta Paediatr 2006; 95(9):1116-23.
2. Hascoet JM, Fresson J, Claris O *et al*. The safety and efficacy of nitric oxide therapy in premature infants. J. Pediatr. 2005; 146(3):318-23.
3. Kinsella JP, Walsh WF, Bose CL *et al*. Inhaled nitric oxide in premature neonates with severe hypoxaemic respiratory failure: A randomised controlled trial. Lancet 1999; 354(9184):1061-5.
4. Su PH, Chen JY. Inhaled nitric oxide in the management of preterm infants with severe respiratory failure. J Perinatol 2008; 28(2):112-6.
5. Kinsella JP, Cutter GR, Walsh WF *et al*. Early inhaled nitric oxide therapy in premature newborns with respiratory failure. N Engl J Med 2006; 355(4):354-64.
6. Mercier JC, Hummler H, Durrmeyer X *et al*. Inhaled nitric oxide for prevention of bronchopulmonary dysplasia in premature babies (EUNO): a randomised controlled trial. Lancet 2010.
7. Srisuparp P, Heitschmidt M, Schreiber MD. Inhaled nitric oxide therapy in premature infants with mild to moderate respiratory distress syndrome. J Med Assoc Thai 2002; 85 Suppl 2:S469-78.
8. Ballard RA, Truog WE, Cnaan A *et al*. Inhaled nitric oxide in preterm infants undergoing mechanical ventilation. New Engl. J. Med. 2006; 355(4):343-53.
9. Franco-Belgium Collaborative NO Trial Group. Early compared with delayed inhaled nitric oxide in moderately hypoxaemic neonates with respiratory failure: a randomised controlled trial. The Franco-Belgium Collaborative NO Trial Group. Lancet 1999; 354(9184):1066-71.
10. Schreiber MD, Gin-Mestan K, Marks JD, Huo D, Lee G, Srisuparp P. Inhaled Nitric Oxide in Premature Infants with the Respiratory Distress Syndrome. New Engl. J. Med. 2003; 349(22):2099-107.
11. Van Meurs KP, Hintz SR, Ehrenkranz RA *et al*. Inhaled nitric oxide in infants >1500 g and <34 weeks gestation with severe respiratory failure. J Perinatol 2007; 27(6):347-52.
12. Van Meurs KP, Wright LL, Ehrenkranz RA *et al*. Inhaled nitric oxide for premature infants with severe respiratory failure. N Engl J Med 2005; 353(1):13-22.

Appendix E. Evidence Tables

Evidence Table 9. Other short term outcomes addressing KQ2 including PDA, sepsis, NEC, ROP, Pulmonary outcomes, and methemoglobinemia.

Author, Year	Outcomes	Time of outcome measure	Arm Description	N (number of participants measured)	Participants with outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments
Ballard, 2006[1]	Cardiac Outcomes, PDA Requiring Medical or Surgical Treatment	after study entry	Control	288	55 (19.1)	P-value: 0.85 RR: 0.96 (0.68-1.35)		
			iNO	294	54 (18.4)			
Field, 2005[2]		during hospitalization	Control	**53**	13 (25)			
			iNO	**55**	9 (16)			
Schreiber, 2003[3]		Before discharge	Control	**102**	26 (25.5)	P-value: 0.27 RR: 0.75 (0.45-1.25)		
			iNO	**105**	20 (19)			
Kinsella, 2006[4]	Cardiac Outcomes, PDA Requiring Medical Treatment	Before discharge	Control	395	212 (53.7)		P-value: 0.92	study sight, randomization strata
			iNO	398	215 (54)			
Srisuparp, 2002[5]		Before discharge	Control	18	1 (5.6)	P-value: 1		
			iNO	16	0 (0)			
Su, 2008[6]		Before discharge	Control	33	8 (24.2)			
			iNO	32	9 (28.1)			
Subhedar, 1997[7]		Before discharge	Control dexamethasone and standard of care	22	1 (5)			

Appendix E. Evidence Tables

Evidence Table 9. Other short term outcomes addressing KQ2 including PDA, sepsis, NEC, ROP, Pulmonary outcomes, and methemoglobinemia (continued)

Author, Year	Outcomes	Time of outcome measure	Arm Description	N (number of participants measured)	Participants with outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments
			Groups 1&3; iNO + iNO and dexamethasone	20	3 (15)			
			Dexamethasone alone AND dex + iNO	21	1 (5)			
			iNO AND standard of care	21	2 (10)			
Kinsella, 2006[4]	Cardiac Outcomes, PDA requiring surgical treatment	Before discharge	Control	395	86 (21.8)		P-value: 0.96	study sight, randomization strata
			iNO	398	86 (21.6)			
Mercier, 2010 [8]		24-28 weeks	Control	397	45 (11.3)			
			iNO	395	59 (14.9)			
Srisuparp, 2002[5]		Before discharge	Control	18	0 (0)	P-value: 0.47		
			iNO	16	1 (6.3)			
Subhedar, 1997[7]		Before discharge	Control dexamethasone and standard of care	22	2 (10)			
			Groups 1&3; iNO + iNO and dexamethasone	20	1 (5)			
			Dexamethasone alone AND	21	2 (10)			

Appendix E. Evidence Tables

Evidence Table 9. Other short term outcomes addressing KQ2 including PDA, sepsis, NEC, ROP, Pulmonary outcomes, and methemoglobinemia (continued)

Author, Year	Outcomes	Time of outcome measure	Arm Description	N (number of participants measured)	Participants with outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments
			dex + iNO					
			iNO AND standard of care	21	2 (10)			
Dani, 2006[9]	Cardiac Outcomes, Incidence of PDA	Before discharge	Control	20	18 (90)	P-value: 0.421		
			iNO	20	16 (80)			
			Nonresponders	6	5 (60)	P-value: 0.657		
			Responders	14	11 (80)			
Kinsella, 1999[10]	Cardiac Outcomes, Symptomatic PDA	Before discharge	Control	Unclear	Unclear (19)	P-value: NS		
			iNO		Unclear (21)			
Subhedar, 1997[7]		Before discharge	Control dexamethasone and standard of care	22	3 (15)			
			Groups 1&3; iNO + iNO and dexamethasone	20	4 (20)			
			Dexamethasone alone AND dex + iNO	21	3 (14)			
			iNO AND standard of care	21	4 (19)			
Hascoet, 2005[11]	Cardiac Outcomes, Undefined PDA	28 days	Control with Hypoxemic Respiratory Failure	84	31 (37)	P-value: NS		
			iNO with Hypoxemic Respiratory	61	20.74 (34)			

Appendix E. Evidence Tables

Evidence Table 9. Other short term outcomes addressing KQ2 including PDA, sepsis, NEC, ROP, Pulmonary outcomes, and methemoglobinemia (continued)

Author, Year	Outcomes	Time of outcome measure	Arm Description	N (number of participants measured)	Participants with outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments
			Failure					
Dani, 2006 [9]	Sepsis Defined by Positive Culture	before discharge	Control	20	**10 (50)**			
			iNO	20	**8 (40)**	0.751		
			Responders	6	**2 (33)**			
			Nonresponders	14	**6 (43)**	0.545		
Field, 2005 [2]		during hospitalization	Control	53	**21 (40)**			
			iNO	55	**23 (42)**			
Srisuparp, 2002 [5]		Unspecified	Control	18	**7 (38.9)**	1		
			iNO	16	**7 (43.8)**	1		
Field, 2005 [2]	Sepsis Defined by Clinician	during hospitalization	Control	53				
			iNO	55	**12 (22)**			
Su, 2008 {#200)	Undefined Sepsis	Unspecified	Control	33	**2 (6.1)**			
			iNO	32	**3 (9.4)**			
Kinsella, 2006 [4]		Unspecified	Control	369	**118 (32)**			
			iNO	381	**139 (0.365)**		0.19	randomization strata, study sight
Ballard, 2006 [1]		after study entry	Control	288	**118 (41)**	0.91 0.98(0.80-1.20)		
			iNO	294	**121 (41.2)**	0.91 0.98(0.80-1.20)		
Schreiber, 2003 [3]		After 24 hours of age	Control	102	**50 (49)**			
			iNO	105	**54 (51.5)**	0.73 1.05 (0.80-1.38)		
Ballard,	Cardiac	after study	Control	288	19 (6.6)	P-value: 0.63		

Appendix E. Evidence Tables

Evidence Table 9. Other short term outcomes addressing KQ2 including PDA, sepsis, NEC, ROP, Pulmonary outcomes, and methemoglobinemia (continued)

Author, Year	Outcomes	Time of outcome measure	Arm Description	N (number of participants measured)	Participants with outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments
2006[1]	Outcomes, NEC requiring surgical treatment	entry	iNO	294	23 (7.8)	RR: 1.17(0.64-2.13)		
Ballard, 2006[1]	Cardiac Outcomes, NEC requiring medical treatment	after study entry	Control	288	8 (2.8)	P-value: 0.84 RR:1.20(0.46-3.13)		
			iNO	294	10 (3.4)			
Dani, 2006[9]	Cardiac Outcomes, NEC diagnosed by clinical criteria	Before discharge	Control	20	0 (0)	P-value: 0.5		
			iNO	20	1 (5)			
		Before discharge	Nonresponders	6	0 (0)	P-value: 0.7		
			Responders	14	1 (7)			
Hascoet, 2005[11]	Cardiac Outcomes, NEC undefined	28 days of life	Control with Hypoxemic Respiratory Failure	84	(6)	NS		
			iNO with Hypoxemic Respiratory Failure	61	(8)			
Kinsella, 2006[4]		Before discharge	Control	369	46 (12.5)		0.54	study site, randomization strata
			iNO	379	53 (14)			
Mercier, 2010 [8]		Before discharge	Control	397	7 (1.8)			
			iNO	395	11 (2.8)			
Schreiber,		before	Control	102	6 (5.9)	P-value: 0.11		

Appendix E. Evidence Tables

Evidence Table 9. Other short term outcomes addressing KQ2 including PDA, sepsis, NEC, ROP, Pulmonary outcomes, and methemoglobinemia (continued)

Author, Year	Outcomes	Time of outcome measure	Arm Description	N (number of participants measured)	Participants with outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments
2003[3]		discharge	iNO	105	13 (12.4)	RR: 2.10 (0.83-5.32)		
Su, 2008[6]		Before discharge	Control	33	2 (6.1)			
			iNO	32	2 (6.3)			
Subhedar, 1997[7]		before discharge	Control dexamethasone and standard of care	22	2 (10)			
			Groups 1&3; iNO + iNO and dexamethasone	20	1 (5)			
			Dexamethasone alone AND dex + iNO	21	2 (10)			
			iNO AND standard of care	21	1 (5)			
Ballard, 2006 [1]	ROP requiring treatment by cryo or laser	After study entry	Control	288	68 (23.6)	p-value: 0.95 RR = 0.97 (0.72-1.31)		
			iNO	294	72 (24.5)			
Field, 2005[2]		Before hospital discharge	Control	49	4 (8)			
			iNO	50	8 (16)			
Kinsella, 1999[10]		Before hospital discharge	Control	15	3 (20)	P-value: 0.1		
			iNO	25	1 (4)			
Kinsella, 2006[4]		Before Discharge	Control	395	60 (15.2)	P-value: 0.59		
			iNO	398	66 (16.6)			
Schreiber,		Before	Control	102	10 (9.8)	P-value: 0.27		

Appendix E. Evidence Tables

Evidence Table 9. Other short term outcomes addressing KQ2 including PDA, sepsis, NEC, ROP, Pulmonary outcomes, and methemoglobinemia (continued)

Author, Year	Outcomes	Time of outcome measure	Arm Description	N (number of participants measured)	Participants with outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments
2003[3]		hospital discharge	iNO	105	6 (5.7)			
Subhedar, 1997[7]		Before Hospital Discharge	Control dexamethasone and standard of care	22	0 (0)			
			Groups 1&3; iNO + iNO and dexamethasone	20	2 (10)			
			Dexamethasone alone AND dex + iNO	21	2 (10)			
			iNO AND standard of care	21	0 (0)			
Van Meurs, 2007[12]		Before Discharge	Control	5	2 (40)	P-value: 0.44		
			iNO	5	0 (0)			
Van Meurs, 2005[13]		before hospital discharge	Control	112	36 (32)		P-value: 0.42	Study center, Oxygenation index, birth weight
			iNO	98	29 (30)			
Field, 2005[2]	Pulmonary Hemorrhage	Hospital discharge	Control	53	5 (9)			
			iNO	55	4 (7)			
Kinsella, 2006[4]		Before discharge	Control	395	26 (6.6)		0.75	study sight, randomization strata
			iNO	398	24 (6)			
Mercier, 2010 [8]		Discharge	Control	397	14 (3.5)			
			iNO	395	12 (3)			
Schreiber,		Before	Control	102	4 (3.8)	P-value: 0.37		

Appendix E. Evidence Tables

Evidence Table 9. Other short term outcomes addressing KQ2 including PDA, sepsis, NEC, ROP, Pulmonary outcomes, and methemoglobinemia (continued)

Author, Year	Outcomes	Time of outcome measure	Arm Description	N (number of participants measured)	Participants with outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments
2003[3]		discharge	iNO	105	7 (6.9)	RR:0.56 (0.17-1.84)		
Su, 2008[6]		Before discharge	Control	33	2 (6.1)			
			iNO	32	3 (9.4)			
Field, 2005[2]	Air Leak	Hospital discharge	Control	53	20 (38)			
			iNO	55	20 (36)			
Kinsella, 1999 [10]								
Kinsella, 2006[4]		Before discharge	Control	395	24 (6.1)		P-value: 0.94	study sight, randomization strata
			iNO, Total sample)	398	25 (6.3)			
Mercier, 2010 [8]		24-28 weeks	Control	397	13(3)			
			iNO	395	12 (2)			
Schreiber, 2003[3]		Before discharge	Control	102	16 (15.7)	P-value: 0.27 RR: 0.67 (0.33-1.37)		
			iNO	105	11 (10.5)			
		Before discharge	Control	102	Pulmonary interstitial emphysema 35 (34.3)	P-value: 0.23 RR: 0.78 (0.51-1.18)		
			iNO	105	Pulmonary interstitial emphysema 28 (26.7)			
Srisuparp, 2002 [5]		72 hours	Control	18	1 (5.6)	p-value: 0.59		
			iNO	16	2 (12.5)			
Su, 2008[6]		Before discharge	Control	33	2 (6.1)			
			iNO	32	2 (6.3)			

Appendix E. Evidence Tables

Evidence Table 9. Other short term outcomes addressing KQ2 including PDA, sepsis, NEC, ROP, Pulmonary outcomes, and methemoglobinemia (continued)

Author, Year	Outcomes	Time of outcome measure	Arm Description	N (number of participants measured)	Participants with outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments
Subhedar, 1997[7]		Before discharge	Control dexamethasone and standard of care	22	1 (5)			
			Groups 1&3; iNO + iNO and dexamethasone	20	3 (15)			
			Dexamethasone alone AND dex + iNO	21	3 (14)			
			iNO AND standard of care	21	1 (5)			
Van Meurs, 2005[13]		Before discharge	Control	117	37 (32)		P-value: 0.55 RR: 1.12 (0.78-1.61)	center, Oxygenation index, birth weight
			iNO	101	35 (35)			
Van Meurs, 2007[12]		discharge	Control	11	2 (18)	P-value:0.48		
			iNO	9	0 (0)			
Schreiber, 2003[3]	Cardiac Outcomes, Methemoglobinemia >4%	Before discharge	Control	102	0 (0)			
			iNO	105	3 (2.9)			
Van Meurs, 2007[12]		Before discharge	Control	14	0 (0)			
			iNO	14	0 (0)			
Van Meurs, 2005[13]		Before discharge	Control	210	2 (1)			center, Oxygenation index
			iNO	210	2 (1)			

Appendix E. Evidence Tables

Evidence Table 9. Other short term outcomes addressing KQ2 including PDA, sepsis, NEC, ROP, Pulmonary outcomes, and methemoglobinemia (continued)

Author, Year	Outcomes	Time of outcome measure	Arm Description	N (number of participants measured)	Participants with outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments
Schreiber, 2003[3]	Cardiac Outcomes, Methemoglobinemia >8%	Before discharge	Control	102	0 (0)			
			iNO	105	0 (0)			
Van Meurs, 2005[13]		Before discharge	Control	210	0 (0)		P-value: 0.99	center, Oxygenation index

CI: Confidence Interval; HRF: Hypoxemic respiratory failure; iNO: Inhaled nitric oxide; NEC: Necrotizing enterocolitis; NS: Not significant,: Relative risk; PDA: Patent Ductus Arteriosis; ROP: Retinopathy of Prematurity; RR: Relative risk;

Reference List

1. Ballard RA, Truog WE, Cnaan A *et al*. Inhaled nitric oxide in preterm infants undergoing mechanical ventilation. New Engl. J. Med. 2006; 355(4):343-53.
2. Field D, Elbourne D, Truesdale A *et al*. Neonatal Ventilation With Inhaled Nitric Oxide Versus Ventilatory Support Without Inhaled Nitric Oxide for Preterm Infants With Severe Respiratory Failure: the INNOVO multicentre randomised controlled trial (ISRCTN 17821339). Pediatrics 2005; 115(4):926-36.
3. Schreiber MD, Gin-Mestan K, Marks JD, Huo D, Lee G, Srisuparp P. Inhaled Nitric Oxide in Premature Infants with the Respiratory Distress Syndrome. New Engl. J. Med. 2003; 349(22):2099-107.
4. Kinsella JP, Cutter GR, Walsh WF *et al*. Early inhaled nitric oxide therapy in premature newborns with respiratory failure. N Engl J Med 2006; 355(4):354-64.
5. Srisuparp P, Heitschmidt M, Schreiber MD. Inhaled nitric oxide therapy in premature infants with mild to moderate respiratory distress syndrome. J Med Assoc Thai 2002; 85 Suppl 2:S469-78.
6. Su PH, Chen JY. Inhaled nitric oxide in the management of preterm infants with severe respiratory failure. J Perinatol 2008; 28(2):112-6.
7. Subhedar NV, Ryan SW, Shaw NJ. Open randomised controlled trial of inhaled nitric oxide and early dexamethasone in high risk preterm infants. Arch Dis Child Fetal Neonatal Ed 1997; 77(3):F185-90.
8. Mercier JC, Hummler H, Durrmeyer X *et al*. Inhaled nitric oxide for prevention of bronchopulmonary dysplasia in premature babies (EUNO): a randomised controlled trial. Lancet 2010.
9. Dani C, Bertini G, Pezzati M, Filippi L, Cecchi A, Rubaltelli FF. Inhaled nitric oxide in very preterm infants with severe respiratory distress syndrome. Acta Paediatr 2006; 95(9):1116-23.
10. Kinsella JP, Walsh WF, Bose CL *et al*. Inhaled nitric oxide in premature neonates with severe hypoxaemic respiratory failure: A randomised controlled trial. Lancet 1999; 354(9184):1061-5.
11. Hascoet JM, Fresson J, Claris O *et al*. The safety and efficacy of nitric oxide therapy in premature infants. J. Pediatr. 2005; 146(3):318-23.
12. Van Meurs KP, Hintz SR, Ehrenkranz RA *et al*. Inhaled nitric oxide in infants >1500 g and <34 weeks gestation with severe respiratory failure. J Perinatol 2007; 27(6):347-52.
13. Van Meurs KP, Wright LL, Ehrenkranz RA *et al*. Inhaled nitric oxide for premature infants with severe respiratory failure. N Engl J Med 2005; 353(1):13-22.

Appendix E. Evidence Tables

Evidence Table 10. Death and survival beyond the NICU for KQ3.

Study, year	Outcomes	Time of outcome measure	Study Arm	N (Participant Measured)	Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted. Relative Effect (95% CI)	Adjustments
Bennett, 2001[1]	Death	30 months corrected age	Control	22	7 (32)	P-value: 0.13 RR: 1.65 (0.87–3.3)		
			iNO	20	10 (50)			
Hintz, 2007 [2]		18-22 months	Control	98	210 (47)			
			iNO	109	210 (52)			
Huddy, 2008[3]		4-5 years, median 4.52 (IQR 0.9)	Control	19	0 (0)			
		4-5 years, median 4.63, IQR 0.84)	iNO	25	1 (4)			
Walsh, 2010[4]		2 years	Control	288	23 (8)	RR: 1.02 (0.59-1.77)		
			iNO	294	24 (8.2)			
Watson, 2009[5]		1 year corrected age	Control	384	98 (25.5)	P-value: 0.12		
			iNO	385	80 (20.8)			
Mestan KK, 2005[6]	Survival	25.2+/-8.4 months corrected age	Control	102	79 (0.775)			
		24.9 +/-7.9 months corrected age	iNO	105	89 (84.8)			

CP: Cerebral palsy, iNO: Inhaled nitric oxide, IQR: Inter-quartile range, MDI: Mental developmental index, NDI: Neurodevelopmental impairment, NS: Not significant,OI: Oxygenation index, PDI: Physical developmental index

Appendix E. Evidence Tables

Reference List

1. Bennett AJ, Shaw NJ, Gregg JE, Subhedar NV. Neurodevelopmental outcome in high-risk preterm infants treated with inhaled nitric oxide. Acta Paediatr 2001; 90(5):573-6.
2. Hintz SR, Van Meurs KP, Perritt R *et al*. Neurodevelopmental outcomes of premature infants with severe respiratory failure enrolled in a randomized controlled trial of inhaled nitric oxide. J Pediatr 2007; 151(1):16-22, 22.e1-3.
3. Huddy CL, Bennett CC, Hardy P *et al*. The INNOVO multicentre randomised controlled trial: neonatal ventilation with inhaled nitric oxide versus ventilatory support without nitric oxide for severe respiratory failure in preterm infants: follow up at 4-5 years. Arch Dis Child Fetal Neonatal Ed 2008; 93(6):F430-5.
4. Walsh MC, Hibbs AM, Martin CR *et al*. Two-year neurodevelopmental outcomes of ventilated preterm infants treated with inhaled nitric oxide. J Pediatr 2010; 156(4):556-61.e1.
5. Watson RS, Clermont G, Kinsella JP *et al*. Clinical and economic effects of iNO in premature newborns with respiratory failure at 1 year. Pediatrics 2009; 124(5):1333-43.
6. Mestan KK, Marks JD, Hecox K, Huo D, Schreiber MD. Neurodevelopmental outcomes of premature infants treated with inhaled nitric oxide. N Engl J Med 2005; 353(1):23-32.

Evidence Table 11. Cerebral palsy outcomes in KQ3.

Refid	Outcome	Time of Outcome Measure	Study Arm	N (Participants Measured)	Number of Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments
Bennett, 2001[1]	Moderate / Severe CP	18 to 22 months	Control	14	2 (14.3)			
			iNO	7	0 (0)			
Hintz SR, 2007[2]	Moderate / Severe CP	3 years	Control	102	11 (11)	P-value; 0.11 RR: 1.85 (0.93-3.71)	P-value: Model #1: 0.0453; Model #2: 0.048 RR: Model #1: 2.01 (1.01-3.98); Model #2: 2.41 (1.01-5.75)	Model #1: adjusted for BWt, center, sex, and OI entry criterion, birth weight, Model #2: adjusted for BWt, center, OI entry criterion, sex, BPD, IVH gr 3 or 4 or PVL, length of iNO exposure, postnatal steroids
			iNO	90	18 (20)			
Huddy, 2008[3]	Mild CP	4-5 years	iNO	16	4 (25)			
			Control	22	6 (27.3)			
	Moderate / Severe CP	4-5 years	Control	16	2 (12.5)			
			iNO	22	3 (13.6)			
Mestan KK, 2005[4]	Any CP	25.2+/-8.4 months corrected age 24.9+/-7.9 months corrected age	Control	68	7 (10)	P-value: 0.78		
			iNO	70	6 (9)			

Evidence Table 11. Cerebral palsy outcomes in KQ3 (continued)

Author, Year	Outcome	Time of Outcome Measure	Study Arm	N (Participants Measured)	Number of Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments
Tanaka, 2007 5	Any CP	3 years	Control	15	7 (46.7)			
			iNO	16	2 (12.5)			
Van Meurs, 2007 6	Moderate/Severe CP	18-22 months	Control	0	8 (0)			
			iNO	0	9 (0)			
Walsh, 20107	Moderate / Severe CP	2 years	Control	234	12 (5.1)	RR: 1.23 (0.59-2.55)		
		24.9+/-7.9 months corrected age	iNO	243	15 (6.2)			

CI: Confidence Interval, CP: Cerebral Palsy, iNO: Inhaled Nitric Oxide, OI: Oxygenation Index, RR: Risk Ratio

Reference List

1. Bennett AJ, Shaw NJ, Gregg JE, Subhedar NV. Neurodevelopmental outcome in high-risk preterm infants treated with inhaled nitric oxide. Acta Paediatr 2001; 90(5):573-6.
2. Hintz SR, Van Meurs KP, Perritt R *et al*. Neurodevelopmental outcomes of premature infants with severe respiratory failure enrolled in a randomized controlled trial of inhaled nitric oxide. J Pediatr 2007; 151(1):16-22, 22.e1-3.
3. Huddy CL, Bennett CC, Hardy P *et al*. The INNOVO multicentre randomised controlled trial: neonatal ventilation with inhaled nitric oxide versus ventilatory support without nitric oxide for severe respiratory failure in preterm infants: follow up at 4-5 years. Arch Dis Child Fetal Neonatal Ed 2008; 93(6):F430-5.
4. Mestan KK, Marks JD, Hecox K, Huo D, Schreiber MD. Neurodevelopmental outcomes of premature infants treated with inhaled nitric oxide. N Engl J Med 2005; 353(1):23-32.
5. Tanaka Y, Hayashi T, Kitajima H, Sumi K, Fujimura M. Inhaled nitric oxide therapy decreases the risk of cerebral palsy in preterm infants with persistent pulmonary hypertension of the newborn. Pediatrics 2007; 119(6):1159-64.
6. Van Meurs KP, Hintz SR, Ehrenkranz RA *et al*. Inhaled nitric oxide in infants >1500 g and <34 weeks gestation with severe respiratory failure. J Perinatol 2007; 27(6):347-52.
7. Walsh MC, Hibbs AM, Martin CR *et al*. Two-year neurodevelopmental outcomes of ventilated preterm infants treated with inhaled nitric oxide. J Pediatr 2010; 156(4):556-61.e1.

Evidence Table 12. Cognitive outcomes for KQ3

Author, year	Outcome	Time of Outcome Measure	Study Arm	N (Participants Measured)	Number of Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments
Hintz, 2007[1]	NDI: any of the following: mod-severe CP, blind, deaf, MDI<70 or PDI<70	18-22 months	Control	102	48 (47)	P-value:0.74 RR: 1.07 (0.80 - 1.44)		Model #1: BW, center, OI entry criterion strata, sex, Model #2: same as model #1 + BPD, IVH gr 3 or 4 or PVL, length of iNO exposure, postnatal steroids
			iNO	89	45 (51)			
	Isolated delay = MDI<70 or PDI<70 in absence of mod-severe CP, deafness or blindness		Control	102	35 (34)	P-value:0.37 RR:0.79 (0.51-1.23)	P-value: Model #1: 0.78: Model #2 0.37 RR: Model #1: 1.04 (0.79-1.36); Model #2: 1.19 (0.81-1.73)	Model #1: BW, center, OI entry criterion strata, sex
			iNO	88	24 (27)			
Huddy, 2008[2]	Any cognitive disability (GCAS<85)	4-5 yrs, median 4.52 (IQR 0.9)	Control	16	9 (56.2)			
		4-5 yrs, median 4.63, IQR 0.84)	iNO	22	11 (50)			

Evidence Table 12. Cognitive outcomes for KQ3 (continued)

Author, year	Outcome	Time of Outcome Measure	Study Arm	N (Participants Measured)	Number of Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments
	Moderate or severe cognitive disability (GCAS<70)	4-5 yrs, median 4.52 (IQR 0.9)	Control	16	6 (37.5)			
		4-5 yrs, median 4.63, IQR 0.84)	iNO	22	6 (27.3)			
	Severe cognitive disability (GCAS <50)	4-5 yrs, median 4.52 (IQR 0.9)	Control	16	3 (18.7)			
		4-5 yrs, median 4.63, IQR 0.84)	iNO	22	3 (13.6)			
	GCAS>84	4-5 yrs, median 4.52 (IQR 0.9)	Control	16	7 (43.7)			
		4-5 yrs, median 4.63, IQR 0.84)	iNO	22	11 (50)			
	Overall outcome: severe disability	4-5 yrs, median 4.52 (IQR 0.9)	Control	16	3 (18.7)			
		4-5 yrs, median 4.63, IQR 0.84)	iNO	22	3 (13.6)			
	Overall outcome: Moderate disability	4-5 yrs, median 4.52	Control	16	4 (25)			

Evidence Table 12. Cognitive outcomes for KQ3 (continued)

Author, year	Outcome	Time of Outcome Measure	Study Arm	N (Participants Measured)	Number of Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments
		(IQR 0.9)						
		4-5 yrs, median 4.63, IQR 0.84)	iNO	22	5 (22.7)			
	Overall outcome: Normal	4-5 yrs, median 4.52 (IQR 0.9)	Control	16	3 (18.7)			
		4-5 yrs, median 4.63, IQR 0.84)	iNO	22	5 (22.7)			
	Overall outcome: mild disability	4-5 yrs, median 4.52 (IQR 0.9)	Control	16	4 (25)			
		4-5 yrs, median 4.63, IQR 0.84)	iNO	22	6 (27.3)			
Mestan, 2005[3]	Abnormal neurodevelopmental outcome (any disability or any BSID II score <70)	25.2+/- 8.4 months corrected age 24.9 +/- 7.9 months corrected age	Control	67	31 (46)	P-value:0.01 RR: 0.53 (0.33-0.87)	P-value: Model #1: 0.50: Model #2: 0.79 RR: Model #1: 0.85 (0.54-1.35); Model #2: 0.91 (0.46-1.81)	
			iNO	70	17 (24)			
	Abnormal neurodevelopmental outcome (any disability or any BSID II score <70)	25.2+/- 8.4 months corrected age	Control	67				birth weight
		24.9 +/-	iNO	70				

Evidence Table 12. Cognitive outcomes for KQ3 (continued)

Author, year	Outcome	Time of Outcome Measure	Study Arm	N (Participants Measured)	Number of Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments
		7.9 months corrected age						
	Abnormal neurodevelopmental outcome (any disability or any BSID II score <70)	25.2+/-8.4 months corrected age	Control	67			P-value:0.002 RR:0.57(0.35-0.93	sex
		24.9 +/-7.9 months corrected age	iNO	70				
	Abnormal neurodevelopmental outcome (any disability or any BSID II score <70)	25.2+/-8.4 months corrected age	Control	67			P-value:0.006 RR:0.52 (0.32-0.82)	Mother graduation from high school
		24.9 +/-7.9 months corrected age	iNO	70				
	Abnormal neurodevelopmental outcome (any disability or any BSID II score <70)	25.2+/-8.4 months corrected age	Control	67			P-value:0.007 RR:0.48 (0.28-0.82)	household without employed person
		24.9 +/-7.9 months corrected age	iNO	70				
	Abnormal neurodevelopmental outcome	25.2+/-8.4 months	Control	67			P-value:0.006 RR:0.49 (0.29-0.82)	type of ventilation

Evidence Table 12. Cognitive outcomes for KQ3 (continued)

Author, year	Outcome	Time of Outcome Measure	Study Arm	N (Participants Measured)	Number of Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments
	(any disability or any BSID II score <70)	corrected age						
		24.9 +/- 7.9 months corrected age	iNO	70				
	Abnormal neurodevelopmental outcome (any disability or any BSID II score <70)	25.2+/- 8.4 months corrected age	Control	67			P-value:0.01 RR:0.53 (0.33-0.87)	chronic lung disease and severe IVH or PVL
		24.9 +/- 7.9 months corrected age	iNO	70				
	Abnormal neurodevelopmental outcome (any disability or any BSID II score <70)	25.2+/- 8.4 months corrected age	Control	67			P-value:0.03 RR:0.6 (0.38-0.96)	prolonged postnatal exposure to corticosteroids
		24.9 +/- 7.9 months corrected age	iNO	70				
	Abnormal neurodevelopmental outcome (any disability or any BSID II score <70)	25.2+/- 8.4 months corrected age	Control	67			P-value:0.01 RR:0.53 (0.33-0.87)	birth weight and sex
		24.9 +/- 7.9 months corrected age	iNO	70				

Evidence Table 12. Cognitive outcomes for KQ3 (continued)

Author, year	Outcome	Time of Outcome Measure	Study Arm	N (Participants Measured)	Number of Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments
	Abnormal neurodevelopmental outcome (any disability or any BSID II score <70)	25.2+/- 8.4 months corrected age	Control	67			P-value:0.01 RR:0.55 (0.35-0.99)	severe intraventricular hemorrhage or periventricular leukomalacia
		24.9 +/- 7.9 months corrected age	iNO	70				
	Abnormal neurodevelopmental outcome (any disability or any BSID II score <70)	25.2+/- 8.4 months corrected age	Control	67			P-value:0.01 RR:0.55 (0.34-0.89)	chronic lung disease
		24.9 +/- 7.9 months corrected age	iNO	70				
	Delay without disability	25.2+/- 8.4 months corrected age	Control	67	23 (34)		P-value:0.03 RR:0.59 (0.36-0.95)	
		24.9 +/- 7.9 months corrected age	iNO	69	11 (16)			
	Disability (CP, bilateral blindness or bilateral hearing loss)	25.2+/- 8.4 months corrected age	Control	68	8 (12)			
		24.9 +/- 7.9	iNO	67	6 (9)			

Evidence Table 12. Cognitive outcomes for KQ3 (continued)

Author, year	Outcome	Time of Outcome Measure	Study Arm	N (Participants Measured)	Number of Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments
		months corrected age						
	MDI or PDI < 70	25.2+/- 8.4 months corrected age	Control	67	28 (42)	P-value: 0.03		
		24.9 +/- 7.9 months corrected age	iNO	69	16 (23)			
	MDI and PDI < 70	25.2+/- 8.4 months corrected age	Control	67	8 (12)	P-value: 0.58		
		24.9 +/- 7.9 months corrected age	iNO	69	6 (9)			
Van Meurs, 2007[4]	NDI = any one of the following: moderate to severe CP, blind, deaf, MDI <70, or PDI <70	18 to 22 months	Control	8	2 (25)	P-value:0.58 RR: 0.44 (0.05-4,02)		OI stratum
			iNO	9	1 (11)			
Walsh, 2010[5]	MDI>85	2 years	Control	214	83 (35)			
		24.9 +/- 7.9 months corrected age	iNO	210	95 (45.2)			
	PDI>85	2 years	Control	212	73 (31)			

Evidence Table 12. Cognitive outcomes for KQ3 (continued)

Author, year	Outcome	Time of Outcome Measure	Study Arm	N (Participants Measured)	Number of Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments
			iNO	207	75 (36.2)			
	NDI in subset with complete evaluations	2 years	Control	212	(51)	RR:0.93 (0.76-1.14)		
			iNO	207	(48)			
	Neurodevelopmental Impairment (NDI = MDI<70, PDI<70, unable to crawl or walk (GMFCS>=2), bilateral blindness, or bilateral deafness requiring amplification).	2 years	Control	234	114 (49)	RR: 0.92 (0.75-1.12)		
			iNO	243	109 (44.8)			

BSID: Bayley Scale of Infant Development**,** BW: Birth weight, CP: Cerebral Palsy, GCAS: General conceptual ability score, GMFCS: Gross Motor Function Classification System, iNO: Inhaled Nitric Oxide, IQR: Inter-quartile range, IVH: Intravascular hemorrhage, MDI: Mental Development Index, NDI: Neurodevelopmental Impairment, OI: Oxygenation Index, PDI: Psychomotor Development Index, PVL: Periventricular leukomalacia, RR: Relative Risk

Reference List

1. Hintz SR, Van Meurs KP, Perritt R *et al*. Neurodevelopmental outcomes of premature infants with severe respiratory failure enrolled in a randomized controlled trial of inhaled nitric oxide. J Pediatr 2007; 151(1):16-22, 22.e1-3.
2. Huddy CL, Bennett CC, Hardy P *et al*. The INNOVO multicentre randomised controlled trial: neonatal ventilation with inhaled nitric oxide versus ventilatory support without nitric oxide for severe respiratory failure in preterm infants: follow up at 4-5 years. Arch Dis Child Fetal Neonatal Ed 2008; 93(6):F430-5.
3. Mestan KK, Marks JD, Hecox K, Huo D, Schreiber MD. Neurodevelopmental outcomes of premature infants treated with inhaled nitric oxide. N Engl J Med 2005; 353(1):23-32.

4. Van Meurs KP, Hintz SR, Ehrenkranz RA *et al*. Inhaled nitric oxide in infants >1500 g and <34 weeks gestation with severe respiratory failure. J Perinatol 2007; 27(6):347-52.
5. Walsh MC, Hibbs AM, Martin CR *et al*. Two-year neurodevelopmental outcomes of ventilated preterm infants treated with inhaled nitric oxide. J Pediatr 2010; 156(4):556-61.e1.

Evidence Table 13. Sensory impairment for KQ3.

Author, year	Outcome	Time of Outcome Measure	Study Arm	N (Participants Measured)	Number of Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments
Bennett, 2001 [1]	Sensorineural Impairment		Control	22	1 (5)			
			iNO	20	0 (0)			
Field, 2005 [2]	Visual Impairment	1 year corrected age	Control	53	0 (0)			
			iNO	55	1 (2)			
	Hearing Impairment		Control	53	0 (0)			
			iNO	55	3 (5)			
Huddy, 2008[3]	Visual Impairment	4-5 years	Control	16	7 (43.7)			
			iNO	22	13 (59.1)			
	Hearing Impairment	4-5 years	Control	16	0 (0)			
			iNO	22	2 (9.1)			
Mestan KK, 2005[4]	Hearing Aid	25.2+/-8.4 months corrected age 24.9+/-7.9 months corrected age	Control	68	1 (1)	P-value: 0.49		
			iNO	70	0 (0)			
	Blindness	25.2+/-8.4 months corrected age 24.9+/-7.9	Control	68	2 (3)	P-value: 0.24		
			iNO	70	0 (0)			
Van Meurs, 2007[5]	Deafness	4-5 years	Control	16	0 (0)			
			iNO	22	1 (4.5)			

Evidence Table 13. Sensory impairment for KQ3 (continued)

Author, year	Outcome	Time of Outcome Measure	Study Arm	N (Participants Measured)	Number of Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments
	No recognizable speech	4-5 years	Control	16	0 (0)			
			iNO	22	3 (13.6)			
	Any disability of hearing or communication	4-5 years	Control	16	3 (18.7)			
			iNO	22	3 (13.6)			
	Deafness	18 to 22 months	Control	8	0 (0)			
			iNO	9	0 (0)			
Walsh, 2010[6]	Deafness	2 years	Control	234	3 (1)	RR: 2.56 (0.68-9.52)		
		24.9+/-7.9 months corrected age	iNO	243	8 (3.2)			
	Blindness	2 years	Control	234	9 (4)	RR: 0.97 (0.40-2.40)		
		24.9+/-7.9	iNO	243	9 (3.7)			
Watson, 2009 [7]	Sensory impairment included in NDI but not individually.							

CI: Confidence Interval, iNO: Inhaled nitric oxide, NDI: Neurodevelopmental Impairment, RR: Relative Risk

Reference List

1. Bennett AJ, Shaw NJ, Gregg JE, Subhedar NV. Neurodevelopmental outcome in high-risk preterm infants treated with inhaled nitric oxide. Acta Paediatr 2001; 90(5):573-6.
2. Field D, Elbourne D, Truesdale A *et al*. Neonatal Ventilation With Inhaled Nitric Oxide Versus Ventilatory Support Without Inhaled Nitric Oxide for Preterm Infants With Severe Respiratory Failure: the INNOVO multicentre randomised controlled trial (ISRCTN 17821339). Pediatrics 2005; 115(4):926-36.
3. Huddy CL, Bennett CC, Hardy P *et al*. The INNOVO multicentre randomised controlled trial: neonatal ventilation with inhaled nitric oxide versus ventilatory support without nitric oxide for severe respiratory failure in preterm infants: follow up at 4-5 years. Arch Dis Child Fetal Neonatal Ed 2008; 93(6):F430-5.
4. Mestan KK, Marks JD, Hecox K, Huo D, Schreiber MD. Neurodevelopmental outcomes of premature infants treated with inhaled nitric oxide. N Engl J Med 2005; 353(1):23-32.
5. Van Meurs KP, Hintz SR, Ehrenkranz RA *et al*. Inhaled nitric oxide in infants >1500 g and <34 weeks gestation with severe respiratory failure. J Perinatol 2007; 27(6):347-52.
6. Walsh MC, Hibbs AM, Martin CR *et al*. Two-year neurodevelopmental outcomes of ventilated preterm infants treated with inhaled nitric oxide. J Pediatr 2010; 156(4):556-61.e1.
7. Watson RS, Clermont G, Kinsella JP *et al*. Clinical and economic effects of iNO in premature newborns with respiratory failure at 1 year. Pediatrics 2009; 124(5):1333-43.

Evidence Table 13. Sensory impairment for KQ3.

Author, year	Outcome	Time of Outcome Measure	Study Arm	N (Participants Measured)	Number of Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments
Bennett, 2001 [1]	Sensorineural Impairment		Control	22	1 (5)			
			iNO	20	0 (0)			
Field, 2005 [2]	Visual Impairment	1 year corrected age	Control	53	0 (0)			
			iNO	55	1 (2)			
	Hearing Impairment		Control	53	0 (0)			
			iNO	55	3 (5)			
Huddy, 2008[3]	Visual Impairment	4-5 years	Control	16	7 (43.7)			
			iNO	22	13 (59.1)			
	Hearing Impairment	4-5 years	Control	16	0 (0)			
			iNO	22	2 (9.1)			
Mestan KK, 2005[4]	Hearing Aid	25.2+/-8.4 months corrected age 24.9+/-7.9 months corrected age	Control	68	1 (1)	P-value: 0.49		
			iNO	70	0 (0)			
	Blindness	25.2+/-8.4 months corrected age 24.9+/-7.9	Control	68	2 (3)	P-value: 0.24		
			iNO	70	0 (0)			
Van Meurs, 2007[5]	Deafness	4-5 years	Control	16	0 (0)			
			iNO	22	1 (4.5)			

Evidence Table 13. Sensory impairment for KQ3 (continued)

Author, year	Outcome	Time of Outcome Measure	Study Arm	N (Participants Measured)	Number of Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments
No	recognizable speech	4-5 years	Control	16	0 (0)			
			iNO	22	3 (13.6)			
	Any disability of hearing or communication	4-5 years	Control	16	3 (18.7)			
			iNO	22	3 (13.6)			
	Deafness	18 to 22 months	Control	8	0 (0)			
			iNO	9	0 (0)			
Walsh, 2010[6]	Deafness	2 years	Control	234	3 (1)	RR: 2.56 (0.68-9.52)		
		24.9+/-7.9 months corrected age	iNO	243	8 (3.2)			
	Blindness	2 years	Control	234	9 (4)	RR: 0.97 (0.40-2.40)		
		24.9+/-7.9	iNO	243	9 (3.7)			
Watson, 2009 [7]	Sensory impairment included in NDI but not individually.							

CI: Confidence Interval, iNO: Inhaled nitric oxide, NDI: Neurodevelopmental Impairment, RR: Relative Risk

Reference List

1. Bennett AJ, Shaw NJ, Gregg JE, Subhedar NV. Neurodevelopmental outcome in high-risk preterm infants treated with inhaled nitric oxide. Acta Paediatr 2001; 90(5):573-6.
2. Field D, Elbourne D, Truesdale A *et al*. Neonatal Ventilation With Inhaled Nitric Oxide Versus Ventilatory Support Without Inhaled Nitric Oxide for Preterm Infants With Severe Respiratory Failure: the INNOVO multicentre randomised controlled trial (ISRCTN 17821339). Pediatrics 2005; 115(4):926-36.
3. Huddy CL, Bennett CC, Hardy P *et al*. The INNOVO multicentre randomised controlled trial: neonatal ventilation with inhaled nitric oxide versus ventilatory support without nitric oxide for severe respiratory failure in preterm infants: follow up at 4-5 years. Arch Dis Child Fetal Neonatal Ed 2008; 93(6):F430-5.
4. Mestan KK, Marks JD, Hecox K, Huo D, Schreiber MD. Neurodevelopmental outcomes of premature infants treated with inhaled nitric oxide. N Engl J Med 2005; 353(1):23-32.
5. Van Meurs KP, Hintz SR, Ehrenkranz RA *et al*. Inhaled nitric oxide in infants >1500 g and <34 weeks gestation with severe respiratory failure. J Perinatol 2007; 27(6):347-52.
6. Walsh MC, Hibbs AM, Martin CR *et al*. Two-year neurodevelopmental outcomes of ventilated preterm infants treated with inhaled nitric oxide. J Pediatr 2010; 156(4):556-61.e1.
7. Watson RS, Clermont G, Kinsella JP *et al*. Clinical and economic effects of iNO in premature newborns with respiratory failure at 1 year. Pediatrics 2009; 124(5):1333-43.

Evidence Table 14. NDI and death or NDI outcomes for KQ3.

Author, year	Outcome	Time of Outcome Measure	Study Arm	N (Participants Measured)	Number of Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments
Bennett, 2001[1]	Severe neurodisability - one or more of: moderate or severe developmental delay; CP; sensorineural impairment (hearing loss requiring hearing aids and blindness)	30 months corrected age	Control	14	5 (36)	P-value: 0.12		
			iNO	7	0 (0)			
Hintz SR, 2007[2]	NDI: any of the following: mod-severe CP, blind, deaf, MDI<70 or PDI<70	18-22 months	Control	102	48 (47)	P-value:0.74 RR: 1.07 (0.80 - 1.44)		Model #1: BWt, center, OI entry criterion strata, sex, Model #2: same as model #1 + BPD, IVH gr 3 or 4 or PVL, length of iNO exposure, postnatal steroids
			iNO	89	45 (51)			

Evidence Table 14. NDI and death or NDI outcomes for KQ3 (continued)

Author, year	Outcome	Time of Outcome Measure	Study Arm	N (Participants Measured)	Number of Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments
	Isolated delay = MDI<70 or PDI<70 in absence of mod-severe CP, deafness or blindness		Control	102	35 (34)	P-value:0.37 RR:0.79 (0.51-1.23)	P-value: Model #1: 0.78: Model #2 0.37 RR: Model #1: 1.04 (0.79-1.36); Model #2: 1.19 (0.81-1.73)	Model #1: BWt, center, OI entry criterion strata, sex
			iNO	88	24 (27)			
	Unimpaired = MDI & PDI>85, no mod-severe CP, and not blind or deaf		Control	102	26 (25)	P-value:0.86 RR:0.92 (0.56 - 1.51)	P-value: Model #1: 0.10; Model #2: 0.43 RR: Model #1: 0.72 (0.48-1.07); Model #2: 0.79 (0.44-1.42)	Model #1: BWt, center, OI entry criterion strata, sex
Huddy, 2008[3]	Overall outcome: severe disability	4-5 yrs, median 4.52 (IQR 0.9)	Control	16	3 (18.7)			
		4-5 yrs, median 4.63, IQR 0.84)	iNO	22	3 (13.6)			
	Overall outcome: Moderate disability	4-5 yrs, median 4.52 (IQR 0.9)	Control	16	4 (25)			
		4-5 yrs, median 4.63, IQR 0.84)	iNO	22	5 (22.7)			
	Overall outcome: Normal	4-5 yrs, median	Control	16	3 (18.7)			

Evidence Table 14. NDI and death or NDI outcomes for KQ3 (continued)

Author, year	Outcome	Time of Outcome Measure	Study Arm	N (Participants Measured)	Number of Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments
		4.52 (IQR 0.9)						
		4-5 yrs, median 4.63, IQR 0.84)	iNO	22	5 (22.7)			
	Overall outcome: mild disability	4-5 yrs, median 4.52 (IQR 0.9)	Control	16	4 (25)			
		4-5 yrs, median 4.63, IQR 0.84)	iNO	22	6 (27.3)			
Mestan, 2005[4]	Abnormal neurodevelopmental outcome (any disability or any BSID II score <70)	25.2+/-8.4 months corrected age 24.9 +/-7.9 months corrected age	Control	68	31 (46)	P-value:0.01 RR: 0.53 (0.33-0.87)	P-value: Model #1: 0.50: Model #2: 0.79 RR: Model #1: 0.85 (0.54-1.35); Model #2: 0.91 (0.46-1.81))	
			iNO	70	17 (24)			
	Abnormal neurodevelopmental outcome (any disability or any BSID II score <70)	25.2+/-8.4 months corrected age	Control	68				birth weight
		24.9 +/-7.9 months corrected age	iNO	70				
	Abnormal neurodevelopment	25.2+/-8.4 months	Control	68			P-value:0.002 RR:0.57(0.35-0.93	sex

Evidence Table 14. NDI and death or NDI outcomes for KQ3 (continued)

Author, year	Outcome	Time of Outcome Measure	Study Arm	N (Participants Measured)	Number of Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments
	al outcome (any disability or any BSID II score <70)	corrected age						
		24.9 +/-7.9 months corrected age	iNO	70				
	Abnormal neurodevelopmental outcome (any disability or any BSID II score <70)	25.2+/-8.4 months corrected age	Control	68			P-value:0.006 RR:0.52 (0.32-0.82)	Mother graduation from high school
		24.9 +/-7.9 months corrected age	iNO	70				
	Abnormal neurodevelopmental outcome (any disability or any BSID II score <70)	25.2+/-8.4 months corrected age	Control	68			P-value:0.007 RR:0.48 (0.28-0.82)	household without employed person
		24.9 +/-7.9 months corrected age	iNO	70				
	Abnormal neurodevelopmental outcome (any disability or any BSID II score <70)	25.2+/-8.4 months corrected age	Control	68			P-value:0.006 RR:0.49 (0.29-0.82)	type of ventilation
		24.9 +/-7.9 months corrected age	iNO	70				
	Abnormal neurodevelopmental outcome (any disability or any BSID II score <70)	25.2+/-8.4 months corrected age	Control	68			P-value:0.01 RR:0.53 (0.33-0.87)	chronic lung disease and severe IVH or PVL
		24.9 +/-7.9 months corrected	iNO	70				

Evidence Table 14. NDI and death or NDI outcomes for KQ3 (continued)

Author, year	Outcome	Time of Outcome Measure	Study Arm	N (Participants Measured)	Number of Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments
		age						
	Abnormal neurodevelopmental outcome (any disability or any BSID II score <70)	25.2+/-8.4 months corrected age	Control	68			P-value:0.03 RR:0.6 (0.38-0.96)	prolonged postnatal exposure to corticosteroids
		24.9 +/-7.9 months corrected age	iNO	70				
	Abnormal neurodevelopmental outcome (any disability or any BSID II score <70)	25.2+/-8.4 months corrected age	Control	68			P-value:0.01 RR:0.53 (0.33-0.87)	birth weight and sex
		24.9 +/-7.9 months corrected age	iNO	70				
	Abnormal neurodevelopmental outcome (any disability or any BSID II score <70)	25.2+/-8.4 months corrected age	Control	68			P-value:0.01 RR:0.55 (0.35-0.99)	severe intraventricular hemorrhage or periventricular leukomalacia
		24.9 +/-7.9 months corrected age	iNO	70				
	Abnormal neurodevelopmental outcome (any disability or any BSID II score <70)	25.2+/-8.4 months corrected age	Control	68			P-value:0.01 RR:0.55 (0.34-0.89)	chronic lung disease
		24.9 +/-7.9 months corrected age	iNO	70				
Van Meurs, 2007[5]	NDI = any one of the following: moderate to severe CP, blind,	18 to 22 months	Control	8	2 (25)	P-value:0.58 RR: 0.44 (0.05-4.02)		OI stratum
			iNO	9	1 (11)			

Evidence Table 14. NDI and death or NDI outcomes for KQ3 (continued)

Author, year	Outcome	Time of Outcome Measure	Study Arm	N (Participants Measured)	Number of Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments
	deaf, MDI <70, or PDI <70							
Walsh, 2010[6]	NDI in subset with complete evaluations	2 years	Control	212	(51)	RR:0.93 (0.76-1.14)		
		24.9 +/-7.9 months corrected age	iNO	207	(48)			
	Neurodevelopmental Impairment (NDI = MDI<70, PDI<70, unable to crawl or walk (GMFCS>=2), bilateral blindness, or bilateral deafness requiring amplification).	2 years	Control	234	114 (49)	RR: 0.92 (0.75-1.12)		
			iNO	243	109 (44.8)			
Watson, 2009[7]	NDI (CP, severe hearing loss, MDI or PDI< 70,or blindness)	1 year corrected age	Control	218	73 (33.5)	P-value: 0.66		
			iNO	237	84 (35.4)			
Van Meurs, 2007[5]	Death or NDI, Death and/or NDI	18 to 22 months	Control	12	6 (50)	P-value: 1 RR: 0.86 (0.37-1.96)	P-value: 0.8 RR: 0.90 (0.40-2.02)	OI Strata
			iNO	14	6 (43)			
Van Meurs, 2007[5]	Death or NDI, Death and/or moderate to severe CP	18 to 22 months	Control	12	4 (33)	P-value: 1 RR: 1.07 (0.37-3.11)	P-value: 0.88 RR: 1.08 (0.39-3.03)	OI Strata
			iNO	14	5 (36)			
Bennett, 2001[1]	Death or NDI, Death or severe neurodisability	30 months corrected age	Control	22	13 (59)	P-value: 0.79 RR: 1.1 (0.57-2.3)		
			iNO	19	12 (63)			
Watson, 2009[7]	Death or NDI, Death or NDI (CP, severe hearing	1 year corrected age	Control	384	171 (44.5)	P-value: 0.55		
			iNO	387	164 (42.4)			

Evidence Table 14. NDI and death or NDI outcomes for KQ3 (continued)

Author, year	Outcome	Time of Outcome Measure	Study Arm	N (Participants Measured)	Number of Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments
	loss, MDI or PDI< 70,or blindness)							
Watson, 2009[7]	Death or NDI, Death, on oxygen, or NDI (CP, severe hearing loss, MDI or PDI< 70,or blindness)	1 year corrected age	Control	384	175 (45.6)	P-value: 0.65		
			iNO	387	170 (43.9)			
Hintz SR, 2007[2]	Death or NDI, Death or NDI:any of the following: mod-severe CP, blind, deaf, MDI<70 or PDI<70	18-22 months	Control	200	146 (73)	P-value: 0.32 RR:1.07 (0.95-1.19)	P-value: 0.3 RR: Model #1: 1.06 (0.95-1.17)	Model #1: BWt, center, OI entry criterion strata, sex
			iNO	198	154 (78)			
Hintz SR, 2007[2]	Death or NDI, Death or moderate to severe CP	18-22 months	Control	200	109 (54)	P-value: 0.07 RR:1.17 (0.99-1.38)	P-value: 0.07 RR: Model #1: 1.15 (0.99-1.34)	Model #1: BWt, center, OI entry criterion strata, sex
			iNO	199	127 (64)			

CI: Confidence Interval; CP: Cerebral Palsy; GMFCS: Gross motor function classification system; iNO: Inhaled nitric oxide; IQR: Inter-quartile range; MDI: Mental developmental index; NDI: Neurodevelopmental impairment; NS: Not significant,OI: Oxygenation index; OI: Oxygenation Index; PDI: Physical developmental index;

Reference List

1. Bennett AJ, Shaw NJ, Gregg JE, Subhedar NV. Neurodevelopmental outcome in high-risk preterm infants treated with inhaled nitric oxide. Acta Paediatr 2001; 90(5):573-6.
2. Hintz SR, Van Meurs KP, Perritt R *et al*. Neurodevelopmental outcomes of premature infants with severe respiratory failure enrolled in a randomized controlled trial of inhaled nitric oxide. J Pediatr 2007; 151(1):16-22, 22.e1-3.
3. Huddy CL, Bennett CC, Hardy P *et al*. The INNOVO multicentre randomised controlled trial: neonatal ventilation with inhaled nitric oxide

versus ventilatory support without nitric oxide for severe respiratory failure in preterm infants: follow up at 4-5 years. Arch Dis Child Fetal Neonatal Ed 2008; 93(6):F430-5.
4. Mestan KK, Marks JD, Hecox K, Huo D, Schreiber MD. Neurodevelopmental outcomes of premature infants treated with inhaled nitric oxide. N Engl J Med 2005; 353(1):23-32.
5. Van Meurs KP, Hintz SR, Ehrenkranz RA *et al*. Inhaled nitric oxide in infants >1500 g and <34 weeks gestation with severe respiratory failure. J Perinatol 2007; 27(6):347-52.
6. Walsh MC, Hibbs AM, Martin CR *et al*. Two-year neurodevelopmental outcomes of ventilated preterm infants treated with inhaled nitric oxide. J Pediatr 2010; 156(4):556-61.e1.
7. Watson RS, Clermont G, Kinsella JP *et al*. Clinical and economic effects of iNO in premature newborns with respiratory failure at 1 year. Pediatrics 2009; 124(5):1333-43.

Evidence Table 15. Other long term outcomes included in KQ3 including seizures, growth, oral feeding, pulmonary outcomes.

Refid	Outcome	Time of Outcome Measure	Study Arm	N (Participants Measured)	Number of Participants with Outcome—n (%)	Z-score	Measurement	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)
Field, 2005[1]	Seizures	1 year corrected age	Control	18	0 (0)				
			iNO	25	3 (12)				
Huddy, 2008[2]	Seizures	4-5 years	Control	16	2 (9.1)				
			iNO	22	3 (13.6)				
Field, 2005[1]	Oral feeding	1 year corrected	Control	53	20 (38)				
			iNO	55	28 (51)				
Huddy, 2008[2]	Steroids, Inhaled	4-5 years	Control	16	3 (18.8)				
			iNO	22	4 (18.2)				
Field, 2005[1]	Steroids, Unspecified	1 year corrected age	Control	18	5 (28)				
			iNO	25	5 (20)				
Hibbs, 2007[3]		12 +/- 3 months	Control	225	(17.7)			OR: 0.5 (0.32-0.77)	

Evidence Table 15. Other long term outcomes included in KQ3 including seizures, growth, oral feeding, pulmonary outcomes (continued)

Refid	Outcome	Time of Outcome Measure	Study Arm	N (Participants Measured)	Number of Participants with Outcome—n (%)	Z-score	Measurement	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)
			iNO	230	(11)				
		12 +/- 3 months	Control	225	(32.4)			OR: 0.56 (0.32-0.97)	
			iNO	230	(19.8)				
Cheung, 1998[4]	Bronchodilators		iNO	10	1 (10)				
Field, 2005[1]		1 year corrected age	Control	18	7 (39)				
		1 year corrected age	iNO	25	10 (40)				
Hibbs, 2007[3]		12 +/- 3 months	Control	225	(54.1)			OR:0.53(0.36-0.78)	
			iNO	230	(40.1)				
Huddy, 2008[2]		4-5 years	Control	16	4 (25)				
			iNO	22	7 (31.8)				
Hibbs AM, 2007[3]	Diuretics	12 +/- 3 months	Control	225	(28.4)			OR: 0.54 (0.34-0.85)	
			iNO	230	(18.6)				
Huddy, 2008[2]	Long-Term Pulmonary Outcomes, Asthma	4-5 yrs, median 4.52 (IQR 0.9)	Control	16	4 (25)				
		4-5 yrs, median 4.63,	iNO	22	9 (40.9)				

Evidence Table 15. Other long term outcomes included in KQ3 including seizures, growth, oral feeding, pulmonary outcomes (continued)

Refid	Outcome	Time of Outcome Measure	Study Arm	N (Participants Measured)	Number of Participants with Outcome—n (%)	Z-score	Measurement	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)
		IQR 0.84)							
Huddy, 2008[2]	Long-Term Pulmonary Outcomes, Respiratory Disability	4-5 yrs	Control	16	1 (6.2)				
			iNO	22	2 (9.1)				
Field, 2005[1]	Long-Term Pulmonary Outcomes, Feeding tube	1 year corrected age	Control	18	1 (6)				
			iNO	25	1 (4)				
Cheung, 1998[4]	Long-Term Pulmonary Outcomes, Wheezing	> 1 year corrected age	iNO	10	4 (40)				
Field, 2005[1]		1 year corrected age	Control	18	5 (28)				
			iNO	25	13 (52)				
Hibbs, 2007[3]		12 +/- 3 months	Control	225	(56.4)			OR: 0.7 (0.48-1.03)	
			iNO	230	(49.6)				
Huddy, 2008[2]		4-5 yrs, median 4.52 (IQR 0.9)	Control	16	6 (50)				
		4-5 yrs, median 4.63, IQR 0.84)	iNO	22	9 (40.9)				
Cheung, 1998[4]	Long-Term Pulmonary Outcomes, Recurrent Aspiration Pneumonia	> 1 year corrected age	iNO	10	1 (10)				
Clark, 2002 [5]	Long-Term Pulmonary Outcomes, Supplemental Oxygen	6 months PCA	iNO	25	10 (40)				
Field, 2005 [1]		1 year corrected age	Control	18	1 (6)				
			iNO	25	3 (12)				
Hibbs, 2007		Any Home	Control	225	(49.5)				

Evidence Table 15. Other long term outcomes included in KQ3 including seizures, growth, oral feeding, pulmonary outcomes (continued)

Refid	Outcome	Time of Outcome Measure	Study Arm	N (Participants Measured)	Number of Participants with Outcome—n (%)	Z-score	Measurement	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)
[3]		Oxygen Use	iNO	230	(38.4)				
		Persistent Oxygen use at time of followup	Control	225	(9.4)				
			iNO	230	(3)				
Huddy, 2008 [2]		4-5 years (Oxygen discontinued prior to follow-up)	Control	16	4 (25)				
			iNO	22	4 (18)				
Watson, 2009 [6]		1 year corrected age 500-749g	Control	192	3 (2)				
			iNO	192	13 (7)				
		1 year corrected age 750-999g	Control	139	5 (4)				
			iNO	141	4 (3)				
		1 year corrected age 1000-1250g	Control	64	3 (5)				
			iNO	65	0 (0)				
Huddy, 2008[2]	Height	4-5 years	Control	16		-0.68			
			iNO	22		-0.9			
Mestan KK, 2005[7]		2 years	Control	79	68 (86)	-0.59 (IQR -1.25 to 0.41)	Median:83.9 cm IQR 81-88.3 cm	0.55	0.32
			iNO	138	70 (51)	-0.23 (IQR -0.83 to 0.36)	Median:84.5 cm IQR 81.2-88.5		
Walsh, 2010[8]		2 Years	Control	234			Mean: 85.3 cm SD:6 cm		

Evidence Table 15. Other long term outcomes included in KQ3 including seizures, growth, oral feeding, pulmonary outcomes (continued)

Refid	Outcome	Time of Outcome Measure	Study Arm	N (Participants Measured)	Number of Participants with Outcome—n (%)	Z-score	Measurement	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)
			iNO	243			Mean: 85.2 cm SD:5.2 cm		
Hintz SR, 2007[9]	Weight	2 Years	Control	102			Mean 10.6 kg SD:1.7 kg	0.72	
			iNO	91			Mean:10.6 kg SD:1.4 kg		
Huddy, 2008[2]		4-5 years	Control	16		-1.02			
			iNO	22		-0.86			
Mestan KK, 2005[7]		2 years	Control	79	68 (.86)	-1.07 (IQR -2.25 to -0.38)	Median:10.8 kg IQR 9.5-12.2 kg	0.04	0.02
			iNO	138	70 ()	-0.49 (IQR -1.51 to 0.61	Median:1.17 kg IQR 1.05-1.35 k g		
Walsh, 2010[8]		2 Years	Control	234			Mean:11.5 kg SD:1.7 kg		
			iNO	243			Mean:11.4 kg SD:1.7		
513 Field, 2005[1]	Head Circumferance	1 year	Control	18	15 (83)		Mean:45.2 cm SD:1.6 cm		
			iNO	25	23 (92)		45.5 SD:1.8 cm		
Hintz SR, 2007[9]		18-22 Months	Control	102			Mean:46.7 cm SD:1.9 cm	0.64	

Evidence Table 15. Other long term outcomes included in KQ3 including seizures, growth, oral feeding, pulmonary outcomes (continued)

Refid	Outcome	Time of Outcome Measure	Study Arm	N (Participants Measured)	Number of Participants with Outcome—n (%)	Z-score	Measurement	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)
			iNO	91			Mean:46.8 cm SD:1.7 cm		
160 Huddy, 2008[2]		4-5 years	Control	16		-1.53			
			iNO	22		-1.48			
Walsh, 2010[8]		2 Years	Control	234			Mean:47.8 cm SD:1.9 cm		
			iNO	243			Mean:47.6 cm SD:2.1 cm		
Cheung, 1998 [4]	Slow Weight, Height or Head Circumference Development	1 year	iNO	10	4				

CI: Confidence Interval; CP: Cerebral Palsy; iNO: Inhaled Nitric Oxide; IQR: Inter-quartile range; OI: Oxygenation Index; RR: Risk Ratio

Reference List

1. Field D, Elbourne D, Truesdale A *et al*. Neonatal Ventilation With Inhaled Nitric Oxide Versus Ventilatory Support Without Inhaled Nitric Oxide for Preterm Infants With Severe Respiratory Failure: the INNOVO multicentre randomised controlled trial (ISRCTN 17821339). Pediatrics 2005; 115(4):926-36.
2. Huddy CL, Bennett CC, Hardy P *et al*. The INNOVO multicentre randomised controlled trial: neonatal ventilation with inhaled nitric oxide versus ventilatory support without nitric oxide for severe respiratory failure in preterm infants: follow up at 4-5 years. Arch Dis Child Fetal Neonatal Ed 2008; 93(6):F430-5.
3. Hibbs AM, Walsh MC, Martin RJ *et al*. One Year Respiratory Outcomes of the Preterm Infants Enrolled in the NO CLD Trial of Inhaled Nitric Oxide (iNO). N/A 2007.
4. Cheung P-Y, Peliowski A, Robertson CMT. The outcome of very low birth weight neonates ((less-than or equal to)1500 g) rescued by inhaled nitric oxide: Neurodevelopment in early childhood. J. Pediatr. 1998; 133(6):735-9.
5. Clark PL, Ekekezie II, Kaftan HA, Castor CA, Truog WE. Safety and efficacy of nitric oxide in chronic lung disease. Arch Dis Child Fetal Neonatal Ed 2002; 86(1):F41-5.
6. Watson RS, Clermont G, Kinsella JP *et al*. Clinical and economic effects of iNO in premature newborns with respiratory failure at 1 year. Pediatrics 2009; 124(5):1333-43.
7. Mestan KK, Marks JD, Hecox K, Huo D, Schreiber MD. Neurodevelopmental outcomes of premature infants treated with inhaled

nitric oxide. N Engl J Med 2005; 353(1):23-32.
8. Walsh MC, Hibbs AM, Martin CR *et al*. Two-year neurodevelopmental outcomes of ventilated preterm infants treated with inhaled nitric oxide. J Pediatr 2010; 156(4):556-61.e1.
9. Hintz SR, Van Meurs KP, Perritt R *et al*. Neurodevelopmental outcomes of premature infants with severe respiratory failure enrolled in a randomized controlled trial of inhaled nitric oxide. J Pediatr 2007; 151(1):16-22, 22.e1-3.

Evidence Table 16. All outcomes addressing the KQ4 populations subgroups including death, BPD at 36 weeks PMA, death or BPD, Survival without BPD, Survival with BPD, NDI, death or NDI, Dath, ICH, and PVL, death or disability, cerebral palsy.

Author, Year	Outcomes	Time of outcome measure	Study Arm	N (number of participants measured)	Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments
Chock, 2009[1]	BPD at 36 weeks	36 weeks PMA	Control	2	2 (100)	P-value: 0.43		
			iNO	5	2 (40)			
Field, 2005[2]		36 weeks PMA	Control	55	15 (27)			
			iNO	53	26 (49)			
Kinsella, 2006[3]		36 weeks PMA	Control	309	210 (68)	P-value: 0.43	RR:0.96 (0.86–1.09)	randomization strata, study sight
			iNO	326	212 (65)			
		36 weeks PMA	Control Birth weight of 500–749 g	189	66 (34.9)		P-value: 0.20 RR: 0.82 (0.61-1.11)	randomization strata, study sight
			iNO Birth weight of 500–749 g	191	55 (28.8)			
		36 weeks PMA	Control Birth weight of 750–999 g	139	24 (17.3)		P-value: 0.19 RR: 0.63 (0.35-1.15)	randomization strata, study sight
			iNO Birth weight of 750–999 g	138	15 (10.9)			
		36 weeks PMA	Control Birth weight of 1000–1250 g	64	8 (12.5)		P-value: 0.97 RR: 0.98 (0.39-2.46)	randomization strata, study sight
			iNO Birth weight of 1000–1250 g	65	8 (12.3)			

Evidence Table 16. All outcomes addressing the KQ4 populations subgroups including death, BPD at 36 weeks PMA, death or BPD, Survival without BPD, Survival with BPD, NDI, death or NDI, Dath, ICH, and PVL, death or disability, cerebral palsy (continued)

Author, Year	Outcomes	Time of outcome measure	Study Arm	N (number of participants measured)	Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments
Schreiber, 2003[4]		36 weeks PMA	Control	102	42 (53.2)		P-value: 0.07 RR: 0.74 (0.53–1.03)	type of ventilation
			iNO	105	35 (39.3)			
Van Meurs, 2005[5]		36 weeks PMA	Control	127	86 (68)	P-value: 0.26	RR: 0.90 (0.75–1.08)	center, birth-weight group, and oxygenation-index stratum
			iNO	109	65 (60)			
			Control BW<=1000g	88	64 (73)	P-value: 0.84	RR: 1.02 (0.85–1.23)	center, birth-weight group, and oxygenation-index stratum
			Arm B BW<=1000 g	67	49 (73)			
			Control BW>1000 g	37	21(57)	P-value: 0.08	RR: 0.68 (0.45–1.05)	center, birth-weight group, and oxygenation-index stratum
			iNO BW>1000g	42	16 (38)			
			Control OI<=17	76	50 (66)	P-value: 0.12	RR: 0.80 (0.61–1.06)	center, birth-weight group, and oxygenation-index stratum
			iNO OI<=17	59	30 (51)			
			Control OI>17	49	36 (72)	P-value: 0.85	RR: 0.98 (0.77–1.24)	center, birth-weight group, and oxygenation-index stratum
			iNO OI>17	50	35 (70)			
Ballard, 2006[6]	Survival without BPD	36 weeks PMA	Control	288	105 (36.5)	P-value: 0.04 RR: 1.45 (1.03-2.04)		
			iNO	294	129 (43.9)			
		36 weeks PMA	Control 500-799 g)	197	74 (37.6)	P-value: 0.07 RR: 1.20 (0.94–1.54)		
			iNO 500-799 g	197	85 (43.1)			
		36 weeks PMA	Control 800-	91	32 (35.2)	P-value: 0.14		

Evidence Table 16. All outcomes addressing the KQ4 populations subgroups including death, BPD at 36 weeks PMA, death or BPD, Survival without BPD, Survival with BPD, NDI, death or NDI, Dath, ICH, and PVL, death or disability, cerebral palsy (continued)

Author, Year	Outcomes	Time of outcome measure	Study Arm	N (number of participants measured)	Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments
			1250 grams birth weight)			RR: 1.30 (0.91-1.87)		
			iNO 800-1250 grams birth weight	97	44 (45.4)			
		36 weeks PMA	Control OI at study entry < 3.5	149	68 (45.6)	RR: 1.28(1.02-1.61)		
			iNO OI at study entry < 3.5	162	92 (56.8)			
		36 weeks PMA	Control OI at study entry >= 3.5)	139	37 (26.6)	RR: 1.11(0.74-1.66)		
			iNO OI at study entry >= 3.5	132	37 (28)			
Schreiber, 2003[4]		Survived NICU	Control	79	37 (46.8)			
			iNO	89	54 (60.7)			
		Survived NICU	Control BW<=750 g	40	4 (10)			
			iNO BW<=750 g	32	7 (21.9)			
		Survived NICU	iNO BW 751-1000 g	28	14 (50)			
			Control BW 751-1000 g	29	11 (37.9)			
		Survived NICU	Control BW 1001-1500 g	21	12 (57.1)			
			iNO BW 1001-1500 g	30	18 (60)			
		Survived NICU	Control BW	12	10 (83.3)			

Evidence Table 16. All outcomes addressing the KQ4 populations subgroups including death, BPD at 36 weeks PMA, death or BPD, Survival without BPD, Survival with BPD, NDI, death or NDI, Dath, ICH, and PVL, death or disability, cerebral palsy (continued)

Author, Year	Outcomes	Time of outcome measure	Study Arm	N (number of participants measured)	Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments
			>1500 g					
			iNO BW >1500 g	15	15 (100)			
		Survived NICU	Control OI <6.94 (median)	49	16 (32.7)			
			iNO OI <6.94 (median)	50	32 (64)			
		Survived NICU	Control OI>=6.94 (median)	48	20 (41.7)			
			iNO 0I>=6.94 (median))	51	21 (41.2)			
Schreiber, 2003 [4]	Survival with BPD	Survived NICU	Control	102	42 (53.2)	p-value = 0.07 RR = 0.74 (0.53-1.03)	0.75 (0.54-1.05)	
			iNO	105	35 (39.3)			
Banks, 1999[7]	Death	3-24 months from enrollment	iNO	16	7 (44)			
			iNO responders	11	4 (36)			
			iNO non-responders	5	3 (60)			
Chock, 2009[1]		Death prior to discharge home or within 365 days	Control	6	4 (67)	P-value: 0.57		
			iNO	6	2 (33)			
Field, 2005 [2]		36 weeks	Control	53	34 (64)			
			iNO	55	30 (55)			
Hintz SR,		18-22 months	Control Birth	152	79 (52)	P-value: 0.04	RR: 1.22 (1.10-	OI criterion, birth

Evidence Table 16. All outcomes addressing the KQ4 populations subgroups including death, BPD at 36 weeks PMA, death or BPD, Survival without BPD, Survival with BPD, NDI, death or NDI, Dath, ICH, and PVL, death or disability, cerebral palsy (continued)

Author, Year	Outcomes	Time of outcome measure	Study Arm	N (number of participants measured)	Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments
2007[8]			weight </=1000g, F/U cohort					weight, study center, sex
			iNO tx, Birth weight </= 1000gm	152	98 (64)			
			Control Birth weight >1000g, F/U Cohort	48	19 (40)	P-value: 0.08 1.46)	RR: 0.58 (0.31-1.07)	OI criterion, birth weight, study center, sex
			iNO Tx, Birth weight >1000g	48	11 (23)			
			Control Placebo, Birth weight 401-750grams	99	55 (56)	P-value: 0.01		OI criterion, birth weight, study center, sex
			iNO tx, Birth weight 401-750grams	94 / 400 (for analysis cohort)	69 (73)			
			Control Placebo, Birth weight 751-1000grams	53	24 (45)	P-value: 0.63		OI criterion, birth weight, study center, sex
			iNO tx, Birth weight 751-1000grams)	58 / 400 (analysis cohort)	29 (50)			
			Control Placebo, Birth weight 1001 -1500 grams	48 / 400 (analysis cohort)	19 (40)	P-value: 0.07		OI criterion, birth weight, study center, sex
			iNO tx. Birth weight 1001-1500grams	48 / 400 (analysis cohort)	11 (23)			

Evidence Table 16. All outcomes addressing the KQ4 populations subgroups including death, BPD at 36 weeks PMA, death or BPD, Survival without BPD, Survival with BPD, NDI, death or NDI, Dath, ICH, and PVL, death or disability, cerebral palsy (continued)

Author, Year	Outcomes	Time of outcome measure	Study Arm	N (number of participants measured)	Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments
Kinsella, 2006[3]		36 wks PMA	Control	392	98 (25)		P-value: 0.08 RR: 0.79 (0.61-1.03)	randomization strata, study sight
			iNO	394	78 (19.8)			
		36 wks PMA	Control BW 500-749 g; mean 639, SD 71	189	66 (34.9)		P-value:0.2 RR: 0.82 (0.61-1.11)	randomization strata, study sight
			iNO BW 500-749 g; mean 642, SD 76	191	55 (28.8)			
		36 wks PMA	Control BW 750-999 g; mean 843, SD 71	139	24 (17.3)		P-value: 0.13 RR: 0.63 (0.35-1.15)	randomization strata, study sight
			iNO BW 750-999 g; mean 851, SD 71	138	15 (10.9)			
		36 wks PMA	Control BW 1000-1250 g; mean 1113 g, SD 77g	64	8 (12.5)		P-value: 0.97 RR: 0.98 (0.39-2.46)	randomization strata, study sight
			iNO BW 1000-1250 g; mean 1129 g, SD 68g	65	8 (12.3)			
Kumar, 2007[9]			Control					
			iNO	23				

Evidence Table 16. All outcomes addressing the KQ4 populations subgroups including death, BPD at 36 weeks PMA, death or BPD, Survival without BPD, Survival with BPD, NDI, death or NDI, Dath, ICH, and PVL, death or disability, cerebral palsy (continued)

Author, Year	Outcomes	Time of outcome measure	Study Arm	N (number of participants measured)	Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments
Schreiber, 2003[4]		NICU	Control	102	23 (22.5)		P-value: 0.18 RR: 0.68 (0.38-1.20)	type of ventilation
			iNO	105	16 (15.2)			
Van Meurs, 2005[5]		Death before discharge to home or within 365 days among hospitalized infants	Control	208	93 (44)		P-value: 0.11 RR: 1.16 (0.96-1.39)	birth weight, study center, Oxygenation index
			iNO	210	109 (52)			
		Death before discharge to home or within 365 days among hospitalized infants	Control BW<=1000g	158	76 (48)		P-value: 0.01 RR: 1.28 (1.06-1.54)	birth weight, study center, Oxygenation index
			iNO BW<=1000 g	158	98 (62)			
		Death before discharge to home or within 365 days among hospitalized infants	Control BW>1000 g)	52	17 (33)		P-value: 0.16 RR: 0.65 (0.36-1.18)	birth weight, study center, Oxygenation index
			iNO BW>1000g	52	11 (21)			
		Death before	Control OI<=17	110	40 (36)		P-value: 0.09	birth weight, study center,

Evidence Table 16. All outcomes addressing the KQ4 populations subgroups including death, BPD at 36 weeks PMA, death or BPD, Survival without BPD, Survival with BPD, NDI, death or NDI, Dath, ICH, and PVL, death or disability, cerebral palsy (continued)

Author, Year	Outcomes	Time of outcome measure	Study Arm	N (number of participants measured)	Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments
		discharge to home or within 365 days among hospitalized infants	iNO OI<=17	100	45 (45)		RR: 1.27 (0.96-1.68)	Oxygenation index
		Death before discharge to home or within 365 days among hospitalized infants	Control OI>17	100	53 (53)		P-value: 0.39 RR: 1.11 (0.88-1.4)	birth weight, study center, Oxygenation index
			iNO OI>17	110	64 (58)			
Yadav, 1999[10]		Prior to hospital discharge	iNO	41	25 (61)			
			iNO responders to iNO based on decrease in IO by 10 in first 60 minutes of treatment	26	11 (42)			
			iNO noesponders based on failure to decrease OI by 10 in 60 minutes of	15	14 (93)			

Evidence Table 16. All outcomes addressing the KQ4 populations subgroups including death, BPD at 36 weeks PMA, death or BPD, Survival without BPD, Survival with BPD, NDI, death or NDI, Dath, ICH, and PVL, death or disability, cerebral palsy (continued)

Author, Year	Outcomes	Time of outcome measure	Study Arm	N (number of participants measured)	Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments
			treatment					
Chock, 2009[1]	Death or BPD	Death prior to discharge home or within 365 days	Control	6	6 (100)	P-value: 0.18		
			iNO	6	3 (50)			
Field, 2005[2]		36 weeks PMA	Control	53	48 (91)			Diagnosis, OI severity
			iNO	55	49(89)			
		36 weeks PMA	Control acute diagnosis at study entry(lung disease immediately after birth and randomizing at <= 3 days)	36	32 (89)		RR: 0.98(0.87-1.11)	Diagnosis, OI severity
			iNO acute diagnosis at study entry(lung disease immediately	35	30 (86)			

Evidence Table 16. All outcomes addressing the KQ4 populations subgroups including death, BPD at 36 weeks PMA, death or BPD, Survival without BPD, Survival with BPD, NDI, death or NDI, Dath, ICH, and PVL, death or disability, cerebral palsy (continued)

Author, Year	Outcomes	Time of outcome measure	Study Arm	N (number of participants measured)	Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments
			after birth and randomizing at <= 3 days)					
		36 weeks PMA	Control chronic diagnosis (presenting with lung disease immediately after birth with continuing problems and randomizing >3 days))	9	9 (100)			Diagnosis, OI severity
			iNO chronic diagnosis (presenting with lung disease immediately after birth with continuing problems and randomizing >3 days))	10	10 (100)			
		36 weeks PMA	Control other diagnosis (developed lung disease after initial recovery	8	7 (88)		RR: 0.98(0.87-1.12)	Diagnosis, OI severity

Evidence Table 16. All outcomes addressing the KQ4 populations subgroups including death, BPD at 36 weeks PMA, death or BPD, Survival without BPD, Survival with BPD, NDI, death or NDI, Dath, ICH, and PVL, death or disability, cerebral palsy (continued)

Author, Year	Outcomes	Time of outcome measure	Study Arm	N (number of participants measured)	Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments
			from respiratory problems)					
			iNO other diagnosis (developed lung disease after initial recovery from respiratory problems)	10	9 (10)			
		36 weeks PMA	Control OI<=30 at study entry	25	22 (88)			Diagnosis, OI severity
			iNO OI<=30 at study entry	25	22 (88)			
		36 weeks PMA	Control OI>30 at study entry	28	26 (93)		RR: 0.98(0.87-1.12)	Diagnosis, OI severity

Evidence Table 16. All outcomes addressing the KQ4 populations subgroups including death, BPD at 36 weeks PMA, death or BPD, Survival without BPD, Survival with BPD, NDI, death or NDI, Dath, ICH, and PVL, death or disability, cerebral palsy (continued)

Author, Year	Outcomes	Time of outcome measure	Study Arm	N (number of participants measured)	Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments
			iNO OI>30 at study entry	30	27 (90)			
		Term EDC	Control acute diagnosis at study entry(lung disease immediately after birth and randomizing at <= 3 days)	36	29 (81)			
			iNO acute diagnosis at study entry(lung disease immediately after birth and randomizing at <= 3 days)	35	22 (63)			
		Term EDC	Control chronic	9	9 (100)			

Evidence Table 16. All outcomes addressing the KQ4 populations subgroups including death, BPD at 36 weeks PMA, death or BPD, Survival without BPD, Survival with BPD, NDI, death or NDI, Dath, ICH, and PVL, death or disability, cerebral palsy (continued)

Author, Year	Outcomes	Time of outcome measure	Study Arm	N (number of participants measured)	Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments
			diagnosis (presenting with lung disease immediately after birth with continuing problems and randomizing >3 days)					
			iNO chronic diagnosis (presenting with lung disease immediately after birth with continuing problems and randomizing >3 days)	10	10 (100)			
		Term EDC	Control other diagnosis (developed lung disease after initial recovery from respiratory problems)	8	7 (88)			
			iNO other diagnosis (developed lung disease	10	7 (70)			

Evidence Table 16. All outcomes addressing the KQ4 populations subgroups including death, BPD at 36 weeks PMA, death or BPD, Survival without BPD, Survival with BPD, NDI, death or NDI, Dath, ICH, and PVL, death or disability, cerebral palsy (continued)

Author, Year	Outcomes	Time of outcome measure	Study Arm	N (number of participants measured)	Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments
			after initial recovery from respiratory problems)					
		Term EDC	Control OI<=30 at study entry	25	20 (80)			
			iNO OI<=30 at study entry	25	17 (68)			
			Control OI>30 at study entry	28	25 (89)			
			iNO OI>30 at study entry	30	22 (73)			
Kinsella, 2006[3]		36 wks PMA	Control	392	295 (75.3)		P-value: 0.24 RR: 0.95 (0.87-1.03)	study sight, randomization strata
			iNO	394	282 (71.6)			
		36 wks PMA	Control BW 500-749 g; mean 639, SD 71)	189	159 (84.1)		P-value: 0.85 RR: 1.01 (0.92-1.1)	study sight, randomization strata
			iNO BW 500-749 g; mean 642, SD 76	191	162 (84.8)			
		36 wks PMA	Control BW	139	95 (68.3)		P-value: 0.93	study sight,

Evidence Table 16. All outcomes addressing the KQ4 populations subgroups including death, BPD at 36 weeks PMA, death or BPD, Survival without BPD, Survival with BPD, NDI, death or NDI, Dath, ICH, and PVL, death or disability, cerebral palsy (continued)

Author, Year	Outcomes	Time of outcome measure	Study Arm	N (number of participants measured)	Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments
			750-999 g; mean 843, SD 71				RR: 1.01 (0.86-1.18)	randomization strata
			iNO BW 750-999 g; mean 851, SD 71	138	95 (68.8)			
		36 wks PMA	Control BW 1000-1250 g; mean 1113 g, SD 77 g)	64	41 (64.1)		P-value: 0.004 RR: 0.6 (0.42-0.86)	study sight, randomization strata
			BW 1000-1250 g; mean 1129 g, SD 68g	65	25 (38.5)			
Schreiber, 2003 [4]		Survived NICU	Control	102	51 (48.6)	p = 0.03 RR = 0.76 (0.60-0.97)	0.77 (0.60-0.98)	
			iNO	105	65 (63.7)			
Van Meurs, 2007[11]		Death before discharge to home or within 365	Control	15	9 (60)	P-value: 0.87 RR: 0.83 (0.43-1.62)	p-value: 0.5 RR: 0.80 (0.43-1.48)	OI Stratum
			iNO	14	7 (50)			

Evidence Table 16. All outcomes addressing the KQ4 populations subgroups including death, BPD at 36 weeks PMA, death or BPD, Survival without BPD, Survival with BPD, NDI, death or NDI, Dath, ICH, and PVL, death or disability, cerebral palsy (continued)

Author, Year	Outcomes	Time of outcome measure	Study Arm	N (number of participants measured)	Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments
Van Meurs, 2005[5]		Before discharge to home or within 365 days among hospitalized infants	Control	208	170 (82)		P-value: 0.52 RR: 0.97 (0.86-1.06)	Birth weight , study site, Oxygenation index
			iNO	210	167 (80)			
		Before discharge to home or within 365 days among hospitalized infants	Control BW<=1000 g	158	133 (85)		P-value: 0.29 RR: 1.04 (0.96-1.13)	Birth weight , study site, Oxygenation index
			iNO BW<=1000 g	158	141 (89)			
		Before discharge to home or within 365 days among hospitalized infants	Control BW>1000 g	52	35 (69)		P-value: 0.03 RR: 0.72 (0.54-0.96)	Birth weight , study site, Oxygenation index
			iNO BW>1000 g	52	26 (50)			
		Before discharge to home or within 365 days among hospitalized infants	Control OI<=17	110	83 (75)		P-value: 0.37 RR: 0.93 (0.81-1.08)	Birth weight , study site, Oxygenation index
			iNO OI<=17	100	71 (71)			

Evidence Table 16. All outcomes addressing the KQ4 populations subgroups including death, BPD at 36 weeks PMA, death or BPD, Survival without BPD, Survival with BPD, NDI, death or NDI, Dath, ICH, and PVL, death or disability, cerebral palsy (continued)

Author, Year	Outcomes	Time of outcome measure	Study Arm	N (number of participants measured)	Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments
		Before discharge to home or within 365 days among hospitalized infants	Control OI>17	100	85 (86)		P-value: 0.75 RR: 1.02 (0.92-1.12)	Birth weight , study site, Oxygenation index
			iNO OI>17	110	96 (87)			
Watson, 2009[12]		1 year corrected age	Control	383	110 (28.7)	P-value: 0.29		
			iNO	384	97 (25.3)			
		1 year corrected age	Control birth weight 500-749 g	187	70 (37.4)	P-value: 0.99		
			iNO birth weight 500-749 g	187	70 (37.4)			
		1 year corrected age	Control birth weight 750-999 g	133	29 (21.8)	P-value: 0.08		
			iNO birth weight 750-999 g	139	19 (13.7)			
		1 year corrected age	Controlbirth weight 1000-1250 g	64	11 (17.2)	P-value: 0.61		

Evidence Table 16. All outcomes addressing the KQ4 populations subgroups including death, BPD at 36 weeks PMA, death or BPD, Survival without BPD, Survival with BPD, NDI, death or NDI, Dath, ICH, and PVL, death or disability, cerebral palsy (continued)

Author, Year	Outcomes	Time of outcome measure	Study Arm	N (number of participants measured)	Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments
			iNO birth weight 1000-1250 g	58	8 (13.8)			
Van Meurs, 2005 [5]	Brain Injury, Severe IVH (grades 3-4) or PVL	36 weeks	Control	210	50 (32)	p-value = 0.11 RR= 1.25 (0.95-1.66)		
			iNO	210	69 (39)			
Kinsella, 2006[3]	Death or Brain Injury, Death or grade 3 or 4 ICH or PVL	30 days	Control	391	151 (38.6)		P-value: 0.02 RR: 0.79 (0.65-0.96)	study site, randomization
			iNO	392	120 (30.6)			
		30 days	Control BW 500-749 g; mean 639, SD 71	189	89 (47.1)		P-value: 0.18 RR: 0.86 (0.68-1.08)	study site, randomization
			iNO BW 500-749 g; mean 642, SD 76	191	77 (40.3)			
		30 days	Control BW 750-999 g; mean 843, SD 71	139	47 (33.8)		P-value: 0.02 RR: 0.63 (0.42-0.93)	study site, randomization

Evidence Table 16. All outcomes addressing the KQ4 populations subgroups including death, BPD at 36 weeks PMA, death or BPD, Survival without BPD, Survival with BPD, NDI, death or NDI, Dath, ICH, and PVL, death or disability, cerebral palsy (continued)

Author, Year	Outcomes	Time of outcome measure	Study Arm	N (number of participants measured)	Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments
			iNO BW 750-999 g; mean 851, SD 71)	137	29 (21.2)			
		30 days	Control BW 1000-1250 g; mean 1113 g, SD 77 g	63	15 (23.8)		P-value: 0.8 RR: 0.92 (0.48-1.74)	study site, randomization
			iNO BW 1000-1250 g; mean 1129 g, SD 68 g)	64	14 (21.9)			
Field, 2005[2]	Death or NDI	1 year corrected	Control acute diagnosis at study entry(lung disease immediately after birth and randomizing at <= 3 days)	36	24 (67)		RR: 0.99(0.76-1.28)	diagnosis, OI severity
			iNO acute diagnosis at study entry(lung disease immediately	35	23 (66)			

Evidence Table 16. All outcomes addressing the KQ4 populations subgroups including death, BPD at 36 weeks PMA, death or BPD, Survival without BPD, Survival with BPD, NDI, death or NDI, Dath, ICH, and PVL, death or disability, cerebral palsy (continued)

Author, Year	Outcomes	Time of outcome measure	Study Arm	N (number of participants measured)	Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments
			after birth and randomizing at <= 3 days)					
		1 year corrected	Control chronic diagnosis (presenting with lung disease immediately after birth with continuing problems and randomizing >3 days))	9	7 (78)			diagnosis, OI severity
			iNO chronic diagnosis (presenting with lung disease immediately after birth with continuing problems and randomizing >3 days))	10	8 (10)			
		1 year corrected	Control other diagnosis (developed lung disease after initial recovery	8	5 (63)			diagnosis, OI severity

Evidence Table 16. All outcomes addressing the KQ4 populations subgroups including death, BPD at 36 weeks PMA, death or BPD, Survival without BPD, Survival with BPD, NDI, death or NDI, Dath, ICH, and PVL, death or disability, cerebral palsy (continued)

Author, Year	Outcomes	Time of outcome measure	Study Arm	N (number of participants measured)	Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments
			from respiratory problems)					
			iNO other diagnosis (developed lung disease after initial recovery from respiratory problems)	10	6 (60)			
		1 year corrected	Control OI<=30 at study entry	25	15 (60)	RR: 0.99(0.76-1.28)		diagnosis, OI severity
			iNO OI<=30 at study entry	25	16 (64)			
		1 year corrected	Control OI>30 at study entry	28	21 (75)			
			iNO OI>30 at study entry	30	21 (70)			
			iNO	387	164 (42.4)			
Hintz SR, 2007[8]		18-22 months	Control	196	146 (73)	P-value: 0.32 RR: 1.07 (0.95-1.19)	P-value: 0.3 RR: Model #1: 1.06 (0.95-1.17)	Model #1: Birth weight, center, OI entry criterion strata, sex

Evidence Table 16. All outcomes addressing the KQ4 populations subgroups including death, BPD at 36 weeks PMA, death or BPD, Survival without BPD, Survival with BPD, NDI, death or NDI, Dath, ICH, and PVL, death or disability, cerebral palsy (continued)

Author, Year	Outcomes	Time of outcome measure	Study Arm	N (number of participants measured)	Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments
			iNO	198	154 (78)			
		18-22 months	Control Birth weight </=1000g, F/U cohort	152	120 (79)		P-value: 0.12 RR: 1.08 (0.98-1.20)	OI criterion, center, and sex
			iNO tx, Birth weight </= 1000gm	151	131 (87)			
		18-22 months	Control Birth weight >1000g, F/U Cohort	48	26 (54)		P-value: 0.63 RR: 0.91 (0.63-1.33)	OI criterion, center, and sex
			iNO Tx, Birth weight >1000g	47	23 (49)			
		18-22 months	Control Placebo, Birth weight 401-750grams	99 / 400 (analysis cohort)	81 (82)		P-value 0.051	OI criterion, center, and sex Birth weight, center, OI entry criterion strata, sex
			iNO tx, Birth weight 401-750grams	94 / 400 (for analysis cohort)	86 (91)			

Evidence Table 16. All outcomes addressing the KQ4 populations subgroups including death, BPD at 36 weeks PMA, death or BPD, Survival without BPD, Survival with BPD, NDI, death or NDI, Dath, ICH, and PVL, death or disability, cerebral palsy (continued)

Author, Year	Outcomes	Time of outcome measure	Study Arm	N (number of participants measured)	Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments
		18-22 months	Control Placebo, Birth weight 751-1000grams	53	39 (74)		P-value: 0.51	OI criterion, center, and sex Birth weight, center, OI entry criterion strata, sex
			iNO tx, Birth weight 751-1000grams	58 / 400 (analysis cohort)	45 / 57 (79)			
		18-22 months	Control Placebo, Birth weight 1001 -1500 grams	48 / 400 (analysis group)	26 (54)		P-value: 0.54	OI criterion, center, and sex Birth weight, center, OI entry criterion strata, sex
			iNO tx. Birth weight 1001-1500grams	48 / 400 (analysis group)	23 / 47 (49)			
		18-22 months	Control	200	109 (54)	P-value: 0.07 1.17 RR: (0.99-1.38)	P-value: 0.07 RR: Model #1: 1.15 (0.99-1.34)	OI criterion, center, and sex Birth weight, center, OI entry criterion strata, sex
			iNO	199	127 (64)			
		18-22 months	Control Birth weight </=1000g, F/U cohort	152	89 (59)	P-value: 0.01	RR: 1.22 (1.05-1.43)	OI criterion, center, and sex Birth weight, center, OI entry criterion strata, sex
			iNO tx, Birth weight </=	152	111/151 (74)			

Evidence Table 16. All outcomes addressing the KQ4 populations subgroups including death, BPD at 36 weeks PMA, death or BPD, Survival without BPD, Survival with BPD, NDI, death or NDI, Dath, ICH, and PVL, death or disability, cerebral palsy (continued)

Author, Year	Outcomes	Time of outcome measure	Study Arm	N (number of participants measured)	Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments
			1000gm					
		18-22 months	Control Birth weight >1000g, F/U Cohort	48	20 (42)	P-value: 0.39	RR: 0.80 (0.48-1.33)	OI criterion, center, and sex Birth weight, center, OI entry criterion strata, sex
			iNO Tx, Birth weight >1000g	48	16 (33)			
		18-22 months	Control Placebo, Birth weight 401-750grams	99 / 400 (analysis cohort)	61 (62)			Center, and sex
			iNO tx, Birth weight 401-750grams	94 / 400 (for analysis cohort)	75 / 93 (81)			
		18-22 months	Control Placebo, Birth weight 751-1000grams	53	28 (53)			Center, and sex
			iNO tx, Birth weight 751-1000grams)	58 / 400 (analysis cohort)	36 (62)			
		18-22 months	Control Placebo, Birth weight 1001 -1500 grams)	48 / 400 (analysis group)	20 (42)			Center, and sex

Evidence Table 16. All outcomes addressing the KQ4 populations subgroups including death, BPD at 36 weeks PMA, death or BPD, Survival without BPD, Survival with BPD, NDI, death or NDI, Dath, ICH, and PVL, death or disability, cerebral palsy (continued)

Author, Year	Outcomes	Time of outcome measure	Study Arm	N (number of participants measured)	Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments
			iNO tx. Birth weight 1001-1500grams)	48 / 400 (analysis group)	16 (33)			
Watson, 2009[12]		1 year corrected age	Control birth weight 500-749 g	187	96 (51.3)	P-value: 0.57		
			iNO birth weight 500-749 g	188	102 (54.3)			
		1 year corrected age	Control birth weight 750-999 g	133	59 (44.4)	P-value: 0.04		
			iNO birth weight 750-999 g)	140	45 (32.1)			
		1 year corrected age	Control birth weight 1000-1250 g	64	16 (25)	P-value: 0.63		
			iNO birth weight 1000-1250 g	59	17 (28.8)			
		1 year corrected age	Control	384	171 (44.5)	P-value: 0.55		
			iNO	387	164 (42.4)			
		1 year corrected age	Control	384	175 (45.6)	P-value: 0.65		
			iNO	387	170 (43.9)			
		1 year corrected age	Control birth weight 500-749 g	187	98 (52.4)	P-value: 0.38		
			iNO birth weight 500-749 g	188	107 (56.9)			

Evidence Table 16. All outcomes addressing the KQ4 populations subgroups including death, BPD at 36 weeks PMA, death or BPD, Survival without BPD, Survival with BPD, NDI, death or NDI, Dath, ICH, and PVL, death or disability, cerebral palsy (continued)

Author, Year	Outcomes	Time of outcome measure	Study Arm	N (number of participants measured)	Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments
		1 year corrected age	Control birth weight 750-999 g	133	60 (45.1)	P-value: 0.04		
			iNO birth weight 750-999 g	140	46 (32.9)			
		1 year corrected age	Control birth weight 1000-1250 g	64	17 (26.6)	P-value: 0.78		
			iNO birth weight 1000-1250 g)	59	17 (28.8)			
Uga, 2004 [13]	Survival	28 days	Control	5	10 (50)			
			iNO	8	8 (100)			
Field, 2005 [2]	Severe Disability	1 year	Control	53	2 (4)			
			iNO	55	7 (13)			
Yadav, 1999 [10]	Survival to Discharge	27 weeks	Responders	15	26			
			Non-responders	1	15			
Hintz, 2007 [8]	Death or Moderate to severe CP	18-22 months	Control		109 (54)	P = 0.07 RR = 1.17 (0.99-1.38)		
			iNO	199	127 (64)			
Watson, 2009 [12]	Death/Oxygen/NDI	1 year	Control		175 (45.6)	P = 0.65		
			iNO		170 (43.9)			
		BW: 500-749g	Control		98 (52.4)			
			iNO		107 (56.9)			
		BW: 750-999g	Control		60 (45.1)			
			iNO		46 (32.9)			
		BW: 1000-1250g	Control		17 (26.6)			
			iNO		17 (28.8)			

BPD: Bronchopulmonary Dysplasia; BPD: Bronchopulmonary Dysplasia; BSID: Bayley scale of infant development; BW: Birth weight; CI: Confidence Interval; CP: Cerebral palsy; DQ: Developmental quotient; EDC: Estimated date of confinement; F/U: Follow: up; GEE: Generalized estimated equations; HFOV: High-frequency oscillatory ventilation;

HFV: High-frequency ventilation; HRF: Hypoxemic respiratory failure; ICH: Intracranial Hemorrhage; iNO: Inhaled nitric oxide; IQR: Inter-quartile range; IVH: Intraventricular hemorrhage ; MDI: Mental developmental scale; NDI: Neurodevelopmental impairment; NICU: Neonatal intensive care unit; NS: Not significant; OI: Oxygenation index; PMA: Postmenstrual age; PVL: Periventricular leukomalacia; RR: Relative risk; SD: Standard deviation; tx: treatment;

Reference List

1. Chock VY, Van Meurs KP, Hintz SR *et al*. Inhaled nitric oxide for preterm premature rupture of membranes, oligohydramnios, and pulmonary hypoplasia. Am J Perinatol 2009; 26(4):317-22.
2. Field D, Elbourne D, Truesdale A *et al*. Neonatal Ventilation With Inhaled Nitric Oxide Versus Ventilatory Support Without Inhaled Nitric Oxide for Preterm Infants With Severe Respiratory Failure: the INNOVO multicentre randomised controlled trial (ISRCTN 17821339). Pediatrics 2005; 115(4):926-36.
3. Kinsella JP, Cutter GR, Walsh WF *et al*. Early inhaled nitric oxide therapy in premature newborns with respiratory failure. N Engl J Med 2006; 355(4):354-64.
4. Schreiber MD, Gin-Mestan K, Marks JD, Huo D, Lee G, Srisuparp P. Inhaled Nitric Oxide in Premature Infants with the Respiratory Distress Syndrome. New Engl. J. Med. 2003; 349(22):2099-107.
5. Van Meurs KP, Wright LL, Ehrenkranz RA *et al*. Inhaled nitric oxide for premature infants with severe respiratory failure. N Engl J Med 2005; 353(1):13-22.
6. Ballard RA, Truog WE, Cnaan A *et al*. Inhaled nitric oxide in preterm infants undergoing mechanical ventilation. New Engl. J. Med. 2006; 355(4):343-53.
7. Banks BA, Seri I, Ischiropoulos H, Merrill J, Rychik J, Ballard RA. Changes in oxygenation with inhaled nitric oxide in severe bronchopulmonary dysplasia. Pediatrics 1999; 103(3):610-8.
8. Hintz SR, Van Meurs KP, Perritt R *et al*. Neurodevelopmental outcomes of premature infants with severe respiratory failure enrolled in a randomized controlled trial of inhaled nitric oxide. J Pediatr 2007; 151(1):16-22, 22.e1-3.
9. Kumar VH, Hutchison AA, Lakshminrusimha S, Morin FC 3rd, Wynn RJ, Ryan RM. Characteristics of pulmonary hypertension in preterm neonates. J Perinatol 2007; 27(4):214-9.
10. Yadav M, Emmerson AJ. Inhaled nitric oxide in premature neonates. Lancet 1999; 354(9196):2162-3.
11. Van Meurs KP, Hintz SR, Ehrenkranz RA *et al*. Inhaled nitric oxide in infants >1500 g and <34 weeks gestation with severe respiratory failure. J Perinatol 2007; 27(6):347-52.
12. Watson RS, Clermont G, Kinsella JP *et al*. Clinical and economic effects of iNO in premature newborns with respiratory failure at 1 year. Pediatrics 2009; 124(5):1333-43.
13. Uga N, Ishii T, Kawase Y, Arai H, Tada H. Nitric oxide inhalation therapy in very low-birthweight infants with hypoplastic lung due to oligohydramnios. Pediatr. Int. 2004; 46(1):10-4.

Evidence Table 17. All outcomes addressed in the KQ5 subgroups including death, BPD, and NDI

Author, Year	Outcome	Time of outcome measure	Study Arm	N (number of participants measured)	Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments	Duration	Difference in Duration (p-value)
Ballard, 2006[1]	BPD	36 weeks PMA	Control	288	164 (56.9)					
			iNO	294	149 (50.7)					
Dani, 2006[2]		36 weeks PMA	Control	20	12 (60)	P-value: 0.067			Mean: 69.4 SD: 30.2	0.054
			iNO	20	6 (30)				Mean: 47.3 SD: 39.4	
			Nonresponders	6					Mean: 19.8 SD: 11.5	0.084
			Responders	14					Mean: 48.6 SD: 37.3	
Field, 2005[3]		36 weeks PMA	Control	49	15 (28)				Mean: 6 IQR:1.0-17.0	
			iNO	50	26 (47)				Mean: 15 IQR:2-71	
Franco-Belgium Collaborative NO Trial Group, 1999[4]		during hospitalization	Control	29	8 (29)	p-value: NS			Median: 23 IQR:41	0.38
			iNO	29	7 (24)	p-value: NS OR: 0.95 (0.44–2.04)			Median: 14 IQR:43	
Kinsella, 1999[5]		36 weeks PMA	Control	15	12 (80)	p-value: 0.3 RR: 0.75(0.5-1.13)				
			iNO	25	15 (60)					

Evidence Table 17. All outcomes addressed in the KQ5 subgroups including death, BPD, and NDI (continued)

Author, Year	Outcome	Time of outcome measure	Study Arm	N (number of participants measured)	Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments	Duration	Difference in Duration (p-value)
Kinsella, 2006[6]		36 weeks BDP at 36 weeks PMA	Control	309	210 (68)	P-value: 0.43	RR:0.96 (0.86–1.09)	randomization strata, study sight		
			iNO	326	212 (65)					
Mercier, 2010 [7]		36 weeks PMA	Control	358	96 (27)					
			iNO	339	81(24)					
Schreiber, 2003[8]		36 weeks PMA	Control	102	42 (53.2)		P-value: 0.07 RR: 0.74 (0.53–1.03)	type of ventilation		
			iNO	105	35 (39.3)					
Su, 2008[9]		36 weeks PMA	Control	33	11 (33.3)					
			iNO	32	10 (31.3)					
Subhedar, 1997[10]		36 weeks PMA	Control dexamethasone and standard of care	22	14 (64)					
			Groups 1&3; iNO + iNO and dexamethasone	20	10 (50)	RR: 0.79(0.44-1.33)				
			Dexamethasone alone AND dex + iNO	21	11 (52)					
			iNO AND standard of care	21	13 (62)	RR: 0.85(0.48-1.44)				
Van Meurs,		36 weeks PMA	Control	11	5 (45)	p-value: 0.66	p-value: 0.21	OI stratum	Mean: 32 SD: 23	0.45

Evidence Table 17. All outcomes addressed in the KQ5 subgroups including death, BPD, and NDI (continued)

Author, Year	Outcome	Time of outcome measure	Study Arm	N (number of participants measured)	Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments	Duration	Difference in Duration (p-value)
2007[11]			iNO	10	3 (30)	RR: 0.66 (0.21-2.08)	RR: 0.40 (0.09-1.71)		Mean: 23.8 SD: 24.4	
Van Meurs, 2007[12]		36 weeks PMA	Control	127	86 (68)	P-value: 0.26	RR: 0.90 (0.75–1.08)			
			iNO	109	65 (60)					
Ballard, 2006[1]		40 weeks PMA	Control	288	84 (29.2)					
			iNO	294	66 (22.4)					
			Control	288	35 (12.2)					
			iNO	294	27 (9.2)					
Field, 2005[3]		At term (EDC)	Control	53	12 (23)				Median: 81 IQR:14-100	
			iNO	55	16 (29)				Median: 59 IQR:30-78	
Field, 2005[3]		1 year corrected age	Control	18 survivors	1 (6)					
			iNO	20 survivors	3 (15)					
Franco-Belgium Collaborative NO Trial Group, 1999[4]		28 days	Control	29	14 (48)	p-value: NS				
			iNO	29	13 (45)					
Hamon, 2005[13]		28 days	Control Hypoxemic Respiratory Failure, no iNO	29	15 (55.6)					

Evidence Table 17. All outcomes addressed in the KQ5 subgroups including death, BPD, and NDI (continued)

Author, Year	Outcome	Time of outcome measure	Study Arm	N (number of participants measured)	Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments	Duration	Difference in Duration (p-value)
			iNO treated Hypoxemic Respiratory Failure	22	8 (36.4)					
Kinsella, 1999[5]		Hospital discharge	Control	15	12 (80)	p-value: 0.1				
						RR: 0.65 (0.41-1.02)				
			iNO	25	13 (54)	p-value: 0.1 1.02)				
						RR: 0.65(0.41-				
Van Meurs, 2005[12]		Physiologic BPD as per Walsh criteria	Control	115	69 (60)	P-value: 0.17	RR: 0.87 (0.68–1.10)	center, birth-weight group, and oxygenation-index entry stratum		
			iNO	100	50 (50)					
						OR (95% CI)	**Adjusted OR (95% CI)**			
Ballard, 2006[1]	Death	36 weeks PMA	Control	288	18 (6.3)					
			iNO	294	16 (5.4)					
		40 weeks PMA	Control	288	19 (6.6)					
			iNO	294	19 (6.5)					
		44 wks PMA	Control	288	20 (6.9)					
			iNO	294	20 (6.8)					

Evidence Table 17. All outcomes addressed in the KQ5 subgroups including death, BPD, and NDI (continued)

Author, Year	Outcome	Time of outcome measure	Study Arm	N (number of participants measured)	Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments	Duration	Difference in Duration (p-value)
		36 weeks PMA	Control 7-14 days age at study entry	115	**13 (11.3)**					
			7-14 days age at study entry	112	**12 (10.7)**					
		36 weeks PMA	Control 15-21 days age at study entry	173	**10 (5.8)**					
			iNO 15-21 days age at study entry	182	**12 (6.6)**					
Banks, 1999[14]		3-24 months from enrollment	iNO	16	**7 (44)**					
Bennett, 2001[15]		30 months corrected age	Control	22	**7 (32)**	P-value: 0.13 RR: 1.65 (0.87–3.3)				
			iNO	20	**10 (50)**					
		24.9 +/- 7.9 months corrected age	iNO	105	**89 (85)**					

Evidence Table 17. All outcomes addressed in the KQ5 subgroups including death, BPD, and NDI (continued)

Author, Year	Outcome	Time of outcome measure	Study Arm	N (number of participants measured)	Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments	Duration	Difference in Duration (p-value)
Dani, 2006[2]		NICU	Control	20	6 (30)		P-value: 0.494	birth weight		
			iNO	20	4 (20)					
			Nonresponders	6	4 (66)	P-value: 0.078				
			Responders	14	3 (21)					
Field, 2005[3]		1 year	Control	53	34 (64)					
			iNO	55	30 (55)					
Franco-Belgium Collaborative NO Trial Group, 1999[4]		in NICU	Control	45	16 (35)	P-value: Not significant				
			iNO	40	11 (27)					
Hascoet, 2005[16]		7 days of life	Control with Hypoxemic Respiratory Failure	84	14 (17)	P-value: 0.58	1			
			iNO with Hypoxemic Respiratory Failure	61	8 (13)					
		28 days of life	Control with Hypoxemic Respiratory Failure	84	26 (31)	P-value: Not significant				
			iNO with Hypoxemic Respiratory Failure	61	25 (41)					

Evidence Table 17. All outcomes addressed in the KQ5 subgroups including death, BPD, and NDI (continued)

Author, Year	Outcome	Time of outcome measure	Study Arm	N (number of participants measured)	Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments	Duration	Difference in Duration (p-value)
Hintz SR, 2007[17]		18-22 months	Control	210	**98 (47)**		P-value: 0.27	birth weight category, OI strata		
			iNO	210	**109 (52)**					
Huddy, 2008[18]		4-5 years, median 4.52 (IQR 0.9)	Control	19	**0 (0)**					
		4-5 years, median 4.63, IQR 0.84)	iNO	25	**1 (4)**					
Kinsella, 2006[6]		36 wks PMA	Control	392	98 (25)		P-value: 0.08 RR: 0.79 (0.61-1.03)	randomization strata, study sight		
			iNO	394	78 (19.8)					
Kinsella, 1999[5]		Discharge	Control	32	17 (53)	P-value: 0.65 RR: 1.11(0.7-1.8)				
			iNO	48	23 (48)					
Mercier, 2010 [7]			Control	401	42 (10.5)					
			iNO	399	56 (14)					
Schreiber, 2003[8]		NICU	Control	102	23 (22.5)	P-value: 0.18 RR: 0.68 (0.38-1.20)	RR: 0.68 (0.38-1.20)	type of ventilation		
			iNO	105	16 (15.2)					

Evidence Table 17. All outcomes addressed in the KQ5 subgroups including death, BPD, and NDI (continued)

Author, Year	Outcome	Time of outcome measure	Study Arm	N (number of participants measured)	Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments	Duration	Difference in Duration (p-value)
Srisuparp, 2002[19]		7 days	Control	22	2 (11.1)	P-value: 1				
			iNO	16	2 (12.5)					
Su, 2008[9]		During Study (9 death within 96 hours)	Control	33	10 (30.3)					
			iNO	32	6 (18.8)					
Subhedar, 1997[10]		36 wks PMA	Control dexamethasone and standard of care	22	7 (32)	RR: 1.57(0.76-3.38)				
			Groups 1&3; iNO + iNO and dexamethasone	20	10 (50)					
			Dexamethasone alone AND dex + iNO	21	9 (43)	RR: 1.13 (0.54-2.36)				
			iNO AND standard of care	21	8 (38)					
Van Meurs, 2005[12]		death before discharge to home or within 365	Control	208	**93 (45)**		P-value: 0.11 RR:1.16 (0.96-1.39)	Birthweight, study center, Oxygenation index		
			iNO	210	**109 (52)**					

Evidence Table 17. All outcomes addressed in the KQ5 subgroups including death, BPD, and NDI (continued)

Author, Year	Outcome	Time of outcome measure	Study Arm	N (number of participants measured)	Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments	Duration	Difference in Duration (p-value)
Van Meurs, 2007[11]		Death before discharge to home or within 365	Control	15	**4 (27)**	P-value: 0.7 RR: 1.34 (0.45-4.0)	p-value: 0.65 RR: 1.26 (0.47-3.41)	OI Stratum		
			iNO	14	**5 (36)**					
Walsh, 2010[20]		2 years	Control	288	**23 (8)**	RR: 1.02 (0.59-1.77)				
			iNO	294	**24 (8.2)**					
Watson, 2009[21]		1 year corrected age	Control	384	**98 (25.5)**	P-value: 0.12				
			iNO	385	**80 (20.8)**					
Ballard, 2006[1]	Death or BPD	36 weeks PMA	Control	288	182 (63.2)					
			iNO	294	165 (56.1)					
Dani, 2006[2]		NICU	Control	20	18 (90)	P-value: 0.016 OR: 0.111 (0.02-0.610)				
			iNO	20	10 (50)					

Evidence Table 17. All outcomes addressed in the KQ5 subgroups including death, BPD, and NDI (continued)

Author, Year	Outcome	Time of outcome measure	Study Arm	N (number of participants measured)	Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments	Duration	Difference in Duration (p-value)
			Nonresponders	6	6 (100)	P-value: 0.035				
			Responders	14	10 (71)					
Field, 2005[3]		36 weeks PMA	Control	53	48 (91)					
			iNO	55	49 (89)					
		36 weeks PMA	Control trial entry <= 3 days	37	**32 (86)**		RR: 0.98(0.87-1.11)			
			iNO trial entry <= 3 days)	38	**32 (84)**					
		36 weeks PMA	Control trial entry > 3 days	16	**16 (100)**					
			iNO trial entry > 3 days	17	**17 (100)**					
Franco-Belgium Collaborative NO Trial Group, 1999[4]		in NICU	Control	45	24 (53)					
			iNO	40	18 (45)					
Kinsella, 1999[5]		Discharge	Control	32	29 (91)	P-value: 0.14 RR: 0.85(0.7-1.03)				
			iNO	48	37 (77)					

Evidence Table 17. All outcomes addressed in the KQ5 subgroups including death, BPD, and NDI (continued)

Author, Year	Outcome	Time of outcome measure	Study Arm	N (number of participants measured)	Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments	Duration	Difference in Duration (p-value)
Kinsella, 2006[6]		36 wks PMA	Control	392	295 (75.3)		P-value: 0.24 RR: 0.95 (0.87-1.03)	Study sight, randomization strata		
			iNO	394	282 (71.6)					
Schreiber, 2003[8]		NICU	Control	102	65 (63.7)	P-value: 0.03 RR: 0.76 (0.60-0.97)	RR: 0.77 (0.60-0.98)	type of ventilation		
			iNO	105	51 (48.6)					
Subhedar, 1997[10]		36 weeks PMA	Control dexamethasone and standard of care	22	21 (95)	RR: 1.05 (0.84-1.25)				
			Groups 1&3; iNO + iNO and dexamethasone	20	20 (100)					
			Dexamethasone alone AND dex + iNO	21	20 (95)	RR: 0.95 (0.79-1.18)				
			iNO AND standard of care	21	21 (100)					
Van Meurs, 2007[11]		Death before discharge to home or	Control	15	9 (60)	P-value: 0.87 RR: 0.83 (0.43-1.62)	p-value: 0.5 RR: 0.80 (0.43-1.48)	OI Stratum		

Evidence Table 17. All outcomes addressed in the KQ5 subgroups including death, BPD, and NDI (continued)

Author, Year	Outcome	Time of outcome measure	Study Arm	N (number of participants measured)	Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments	Duration	Difference in Duration (p-value)
		within 365	iNO	14	7 (50)					
Van Meurs, 2005[12]		before discharge to home or within 365 days among hospitalized infants	Control	208	170 (82)		P-value: 0.52 RR: 0.97 (0.86-1.06)	birth weight, study site, Oxygenation index		
			iNO	210	167 (80)					
Watson, 2009[21]		1 Year corrected	Control	385	**110 (28.7)**	P-value: 0.29				
			iNO	384	**97 (25.3)**					
Hintz SR, 2007[17]	Death or NDI, Death or moderate to severe CP	18-22 months	Control	200	**109 (54)**	P-value: 0.07 RR:1.17 (0.99-1.38)	P-value: 0.07 RR: Model #1: 1.15 (0.99-1.34)	Model #1: BWt, center, OI entry criterion strata, sex		
			iNO Follow-Up group	199	**127 (64)**					

Evidence Table 17. All outcomes addressed in the KQ5 subgroups including death, BPD, and NDI (continued)

Author, Year	Outcome	Time of outcome measure	Study Arm	N (number of participants measured)	Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments	Duration	Difference in Duration (p-value)
Hintz SR, 2007[17]	Death or NDI, Death or NDI:any of the following: mod-severe CP, blind, deaf, MDI<70 or PDI<70	18-22 months	Control	200	**146 (73)**	P-value: 0.32 RR:1.07 (0.95-1.19)	P-value: 0.3 RR: Model #1: 1.06 (0.95-1.17)	Model #1: BWt, center, OI entry criterion strata, sex		
			iNO Follow-Up group	198	**154 (78)**					
		18-22 months	Control HFV, F/U cohort	119	**93 (78)**	P-value: 0.91	RR: 1.01 (0.88-1.15)	OI criterion, center, and sex Birth weight, center, OI entry criterion strata, sex		
			iNO tx, HFV	115	**90 (78)**					
		18-22 months	Control Conventional vent, F/U cohort	81	**53 (65)**	P-value: 0.12	RR: 1.15(0.97-1.36)	OI criterion, center, and sex Birth weight, center, OI entry criterion		

Evidence Table 17. All outcomes addressed in the KQ5 subgroups including death, BPD, and NDI (continued)

Author, Year	Outcome	Time of outcome measure	Study Arm	N (number of participants measured)	Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments	Duration	Difference in Duration (p-value)
								strata, sex		
			iNO tx, Conventional Vent	83	**64 (77)**					
Field, 2005[3]	Death or Severe Disability	1 year corrected	Control trial entry <= 3 days	37	24 (65)		RR: 0.99(0.76-1.28)	diagnosis, OI severity		
			iNO trial entry <= 3 days	38	25 (66)					
		1 year corrected	Control trial entry > 3 days	16	12 (75)			diagnosis, OI severity		
			iNO trial entry > 3 days	17	12 (71)					
Bennett, 2001[15]	Survival	30 months corrected age	Control	22	14 (63.6)	P-value: 0.13 RR:1.65(0.87-3.3)				
			iNO	20	8 (40)					
Hamon, 2005[13]		28 days	Control Hypoxemic Respiratory Failure, no iNO	39	27 (69.3)					
			iNO treated Hypoxemic Respiratory Failure	37	22 (59.5)					
Mestan, 2005[22]		25.2+/-8.4 months	Control	102	79 (78)					

Evidence Table 17. All outcomes addressed in the KQ5 subgroups including death, BPD, and NDI (continued)

Author, Year	Outcome	Time of outcome measure	Study Arm	N (number of participants measured)	Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments	Duration	Difference in Duration (p-value)
		corrected age								
Schreiber, 2003[8]		Survived NICU	Control	102	79 (77.5)					
			iNO	105	89 (84.8)					
Ballard, 2006[1]	Survival without BPD	36 weeks PMA	Control	288	105 (36.5)	p-value:0.04 RR: 1.26 (1.02-1.55)	RR: 1.45 (1.03-2.04)	cluster (multiples) using GEE; from the letter to the editor correction		
			iNO	294	129 (43.9)					
			Control 7-14 days age at study entry	115	31 (27)	RR: 1.91 (1.31-2.78)				
			iNO 7-14 days age at study entry	112	55 (49.1)					
			Control 15-21 days age at study entry	173	74 (42.8)	RR: 0.99 (0.77-1.28)				
			iNO 15-21 days age at study entry	182	74 (40.7)					
Hamon, 2005 [13]		28 days	Control	39	12 (31)					
			iNO	37	14 (38)					

Evidence Table 17. All outcomes addressed in the KQ5 subgroups including death, BPD, and NDI (continued)

Author, Year	Outcome	Time of outcome measure	Study Arm	N (number of participants measured)	Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments	Duration	Difference in Duration (p-value)
Bennett, 2001[15]	Severe neurodisability - one or more of: moderate or severe developmental delay; CP; sensorineural impairment (hearing loss requiring hearing aids and blindness)	30 months corrected age	Control	14	5 (36)	P-value: 0.12				
			iNO	7	0 (0)					
Field, 2005[3]	Severe disability defined as no /little head control or inability to sit unsupported or no/minimal response to visual stim (equivalent to DQ <50 age	1 year corrected age	Control	18	2 (11)					
			iNO	25	7 (28)					

Evidence Table 17. All outcomes addressed in the KQ5 subgroups including death, BPD, and NDI (continued)

Author, Year	Outcome	Time of outcome measure	Study Arm	N (number of participants measured)	Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments	Duration	Difference in Duration (p-value)
	adjusted)									
Hintz SR, 2007[17]	NDI: any of the following: mod-severe CP, blind, deaf, MDI<70 or PDI<70	18-22 months	Control	102	48 (47)	P-value:0.74 RR: 1.07 (0.80 - 1.44)				
			iNO	89	45 (51)					
Huddy, 2008[18]	Moderate or severe cognitive disability (GCAS<70)	4-5 yrs, median 4.52 (IQR 0.9)	Control	16	**6 (37.5)**					
		4-5 yrs, median 4.63, IQR 0.84)	iNO	22	**6 (27.3)**					
	Moderate / Severe CP	4-5 years	Control	16	**2 (12.5)**					
			iNO	22	**3 (13.6)**					
Mestan, 2005[22]	Abnormal neurodevelopmental outcome (any disability or any BSID II score <70)	25.2+/-8.4 months corrected age 24.9 +/- 7.9 months corrected age	Control	68	31 (46)	P-value:0.01 RR: 0.53 (0.33-0.87)				
			iNO	70	17 (24)					
Van Meurs, 2007[11]	NDI = any one of the following: moderate to severe CP, blind,	18 to 22 months	Control	8	2 (25)					
			iNO	9	1 (11)					

Evidence Table 17. All outcomes addressed in the KQ5 subgroups including death, BPD, and NDI (continued)

Author, Year	Outcome	Time of outcome measure	Study Arm	N (number of participants measured)	Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments	Duration	Difference in Duration (p-value)
	deaf, MDI <70, or PDI <70									
Walsh, 2010[20]	NDI in subset with complete evaluations	2 years	Control	212	**(51)**	RR:0.93 (0.76-1.14)				
			iNO	207	**(48)**					
	Neurodevelopmental Impairment (NDI = MDI<70, PDI<70, unable to crawl or walk (GMFCS>=2), bilateral blindness, or bilateral deafness requiring amplification).	2 years	Control	234	**114 (49)**	RR: 0.92 (0.75-1.12)				
			iNO	243	**109 (44.8)**					
	Moderate / Severe CP	2 years	Control	234	**12 (5.1)**	RR: 1.23 (0.59-2.55)				
			iNO	243	**12 (4.9)**					
Watson, 2009[21]	NDI (CP, severe hearing loss, MDI	1 year corrected age	Control	218	**73 (33.5)**	P-value: 0.66				
			iNO	237	**84 (35.4)**					

Evidence Table 17. All outcomes addressed in the KQ5 subgroups including death, BPD, and NDI (continued)

Author, Year	Outcome	Time of outcome measure	Study Arm	N (number of participants measured)	Participants with Outcome—n (%)	Relative Effect (95% CI)	Adjusted Relative Effect (95% CI)	Adjustments	Duration	Difference in Duration (p-value)
	or PDI< 70,or blindness)									
Van Meurs, 2007[11]	Moderate / Severe CP	18 to 22 months	Control	8	**0 (0)**					
			iNO	9	**0 (0)**					

BPD: Bronchopulmonary Dysplasia; BSID: Bayley scale of infant devleopment; BW: Birth weight; CI: Confidence Interval; CP: Cerebral palsy; DQ: Developmental quotient; EDC: Estimated date of confinement; F/U: Follow: up; HFOV: High-frequency oscillatory ventilation; HFV: High-frequency ventilation; HRF: Hypoxemic respiratory failure; iNO: Inhaled nitric oxide; IQR: Inter-quartile range; IVH: Intraventricular hemorrhage ; MDI: Mental developmental scale; NDI: Neurodevelopmental impairment; NICU: Neonatal intensive care unit; NS: Not significant; OI: Oxygenation index; OR: Odds ratio; PDI: Psychomotor Development Index; PMA: Post-menstrual age; PVL: Periventricular leukomalacia; RR: Relative risk; SD: Standard Deviation; tx: Treatment;

Reference List

1. Ballard RA, Truog WE, Cnaan A *et al*. Inhaled nitric oxide in preterm infants undergoing mechanical ventilation. New Engl. J. Med. 2006; 355(4):343-53.
2. Dani C, Bertini G, Pezzati M, Filippi L, Cecchi A, Rubaltelli FF. Inhaled nitric oxide in very preterm infants with severe respiratory distress syndrome. Acta Paediatr 2006; 95(9):1116-23.
3. Field D, Elbourne D, Truesdale A *et al*. Neonatal Ventilation With Inhaled Nitric Oxide Versus Ventilatory Support Without Inhaled Nitric Oxide for Preterm Infants With Severe Respiratory Failure: the INNOVO multicentre randomised controlled trial (ISRCTN 17821339). Pediatrics 2005; 115(4):926-36.
4. Franco-Belgium Collaborative NO Trial Group. Early compared with delayed inhaled nitric oxide in moderately hypoxaemic neonates with respiratory failure: a randomised controlled trial. The Franco-Belgium Collaborative NO Trial Group. Lancet 1999; 354(9184):1066-71.
5. Kinsella JP, Walsh WF, Bose CL *et al*. Inhaled nitric oxide in premature neonates with severe hypoxaemic respiratory failure: A randomised controlled trial. Lancet 1999; 354(9184):1061-5.
6. Kinsella JP, Cutter GR, Walsh WF *et al*. Early inhaled nitric oxide therapy in premature newborns with respiratory failure. N Engl J Med 2006; 355(4):354-64.
7. Mercier JC, Hummler H, Durrmeyer X *et al*. Inhaled nitric oxide for prevention of bronchopulmonary dysplasia in premature babies (EUNO): a randomised controlled trial. Lancet 2010.
8. Schreiber MD, Gin-Mestan K, Marks JD, Huo D, Lee G, Srisuparp P. Inhaled Nitric Oxide in Premature Infants with the Respiratory Distress Syndrome. New Engl. J. Med. 2003; 349(22):2099-107.
9. Su PH, Chen JY. Inhaled nitric oxide in the management of preterm infants with severe respiratory failure. J Perinatol 2008; 28(2):112-6.
10. Subhedar NV, Ryan SW, Shaw NJ. Open randomised controlled trial of inhaled nitric oxide and early dexamethasone in high risk preterm infants. Arch Dis Child Fetal Neonatal Ed 1997; 77(3):F185-90.

11. Van Meurs KP, Hintz SR, Ehrenkranz RA *et al*. Inhaled nitric oxide in infants >1500 g and <34 weeks gestation with severe respiratory failure. J Perinatol 2007; 27(6):347-52.
12. Van Meurs KP, Wright LL, Ehrenkranz RA *et al*. Inhaled nitric oxide for premature infants with severe respiratory failure. N Engl J Med 2005; 353(1):13-22.
13. Hamon I, Fresson J, Nicolas MB, Buchweiller MC, Franck P, Hascoet JM. Early inhaled nitric oxide improves oxidative balance in very preterm infants. Pediatr Res 2005; 57(5 Pt 1):637-43.
14. Banks BA, Seri I, Ischiropoulos H, Merrill J, Rychik J, Ballard RA. Changes in oxygenation with inhaled nitric oxide in severe bronchopulmonary dysplasia. Pediatrics 1999; 103(3):610-8.
15. Bennett AJ, Shaw NJ, Gregg JE, Subhedar NV. Neurodevelopmental outcome in high-risk preterm infants treated with inhaled nitric oxide. Acta Paediatr 2001; 90(5):573-6.
16. Hascoet JM, Fresson J, Claris O *et al*. The safety and efficacy of nitric oxide therapy in premature infants. J. Pediatr. 2005; 146(3):318-23.
17. Hintz SR, Van Meurs KP, Perritt R *et al*. Neurodevelopmental outcomes of premature infants with severe respiratory failure enrolled in a randomized controlled trial of inhaled nitric oxide. J Pediatr 2007; 151(1):16-22, 22.e1-3.
18. Huddy CL, Bennett CC, Hardy P *et al*. The INNOVO multicentre randomised controlled trial: neonatal ventilation with inhaled nitric oxide versus ventilatory support without nitric oxide for severe respiratory failure in preterm infants: follow up at 4-5 years. Arch Dis Child Fetal Neonatal Ed 2008; 93(6):F430-5.
19. Srisuparp P, Heitschmidt M, Schreiber MD. Inhaled nitric oxide therapy in premature infants with mild to moderate respiratory distress syndrome. J Med Assoc Thai 2002; 85 Suppl 2:S469-78.
20. Walsh MC, Hibbs AM, Martin CR *et al*. Two-year neurodevelopmental outcomes of ventilated preterm infants treated with inhaled nitric oxide. J Pediatr 2010; 156(4):556-61.e1.
21. Watson RS, Clermont G, Kinsella JP *et al*. Clinical and economic effects of iNO in premature newborns with respiratory failure at 1 year. Pediatrics 2009; 124(5):1333-43.
22. Mestan KK, Marks JD, Hecox K, Huo D, Schreiber MD. Neurodevelopmental outcomes of premature infants treated with inhaled nitric oxide. N Engl J Med 2005; 353(1):23-32.