Medical Coverage Policy

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Inhaled Nitric Oxide (INO)

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Overview

This Coverage Policy addresses the use of inhaled nitric oxide (INO), a minimally invasive therapy, proposed for the treatment of conditions associated with reversible pulmonary vasoconstriction and pulmonary hypertension in children and adults.

Coverage Policy

Inhaled nitric oxide is considered medically necessary for ANY of the following indications:

- hypoxic respiratory failure in a term or near-term infant (i.e., born at more than 34 weeks gestation) in the absence of an unrepaired congenital diaphragmatic hernia when there is failure, contraindication or intolerance to conventional therapy (e.g., high concentrations of oxygen, hyperventilation, sedation)
- postoperative management of pulmonary hypertension following repair of congenital heart disease
- postoperative management of pulmonary hypertensive crisis following pediatric heart or lung surgery
- pulmonary hypertension during heart catheterization to determine pulmonary vasoreactivity

Inhaled nitric oxide for any other indication, including but not limited to acute respiratory distress syndrome and adult heart and/or lung transplantation, is considered experimental, investigational or unproven.

General Background

Nitric oxide (NO) is a lipophilic, endogenous compound, naturally produced in numerous cells in the body and synthesized by an enzyme called NO synthase (NOS). NO is involved in numerous physiologic functions and aids in pulmonary vasodilatation, inhibition of platelet aggregation, renal perfusion, erection, fertilization, peristalsis and neurotransmission. It is found in neurons, macrophages and in the endothelial cells in the lining of the lumen of blood vessels. With each systole, the endothelial cells within the blood vessels release NO, causing the vessels to relax and dilate, enhancing blood flow through the vessels. During metabolism, NO binds to hemoglobin and is converted to nitrites and nitrates, which are then excreted in the urine (Mosby's, 2006; Klinger, 2002).

NO is commercially available as a colorless, nonflammable, almost odorless gas used for therapeutic administration by inhalation (i.e., inhaled nitric oxide). Inhaled nitric oxide (INO), a pulmonary vasodilator, has been proposed for the treatment of conditions associated with reversible vasoconstriction and pulmonary hypertension. The administration of INO is a minimally invasive treatment involving the inhalation of NO in conjunction with ventilatory support. Absorbed systemically after inhalation, NO combines with hemoglobin and enters circulation as methemoglobin and nitrate. INO vasodilates only those areas that are ventilated and results in improvement of perfusion and oxygenation. Nitric oxide, unstable in air, undergoes spontaneous oxidation to nitrogen dioxide (NO_2). NO_2 is known to be directly toxic to the respiratory tract. Due to this instability and potential toxicity, continuous, in-line monitoring of the administration of INO is the standard of care during therapeutic administration (Ryan and Tobias, 2007; Mosby's, 2006; Griffiths and Evans, 2005).

U.S. Food and Drug Administration (FDA)
A complete nitric oxide delivery system is comprised of a nitric oxide administration apparatus, a nitric oxide gas analyzer, and a nitrogen dioxide gas analyzer. INOmax® (INO Therapeutics Inc., Clinton, NJ) is the only commercially available brand of INO and was initially approved by the FDA New Drug Application (NDA) process in 1999. INOmax, a gaseous blend of nitric oxide (0.8%) and nitrogen (99.2%), is supplied in aluminum cylinders as a compressed gas under high pressure.

INOmax, in conjunction with ventilatory support and other appropriate agents (e.g., surfactant), is approved by the FDA "for the treatment of term and near-term (i.e., > 34 weeks gestation) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, where it improves oxygenation and reduces the need for extracorporeal membrane oxygenation". PaO2, methemoglobin, and inspired NO2 should be monitored during INOmax administration. The apparatuses for administration of INO are regulated by the FDA as Class II devices. An example of a delivery device is the INOvent (Ohmeda Medical, Laurel, MD).

In 2009, the FDA updated the INOmax safety labeling stating that "in patients with pre-existing left ventricular dysfunction, inhaled nitric oxide may increase pulmonary capillary wedge pressure leading to pulmonary edema. Patients who had pre-existing left ventricular dysfunction treated with inhaled nitric oxide, even for short durations, experienced serious adverse events (e.g., pulmonary edema)".

Additional warnings and precautions were added in 2013 including rebound hypertension following abrupt discontinuation, hypoxia from methemoglobinemia, and airway injury from nitrous dioxide. Patients with left ventricular dysfunction treated with INOmax may experience pulmonary increased pulmonary capillary wedge pressure, worsening of left ventricular dysfunction, systemic hypotension, bradycardia and cardiac arrest. In

October 2015 a warning was added for the use of INO regarding the formation of nitrogen dioxide (NO2) when nitric oxide and oxygen are mixed. NO2 may cause airway inflammation and damage to lung tissue. The warning states that if "there is an unexpected change in NO2 concentration, or if the NO2 concentration reaches 3 ppm when measured in the breathing circuit, then the delivery system should be assessed in accordance with the

Nitric Oxide Delivery System O&M Manual troubleshooting section, and the NO2 analyzer should be recalibrated. The dose of INOmax and/or FiO2 should be adjusted as appropriate".

Hypoxic Respiratory Failure
The primary clinical indication for INO, in conjunction with ventilatory support and other treatment modalities (e.g., surfactant), is hypoxic respiratory failure secondary to pulmonary hypertension in the neonate born at more than 34 weeks gestation. Persistent pulmonary hypertension (PPHN) may occur as a primary developmental defect or as a condition secondary to morbidities such as respiratory distress syndrome (i.e., hyaline membrane disease), meconium aspiration syndrome, pneumonia, sepsis, congenital diaphragmatic hernia, cardiac malformations and pulmonary hypoplasia (American Academy of Pediatrics [AAP] 2014; Weinberger, et al., 2001; Hintz, et al., 2000; Oliveira, et al., 2000).

The goal of therapy for PPHN is to maximize the amount of oxygen transported by the lungs and, in turn, to systemic circulation. Conventional therapies include high concentrations of oxygen, hyperventilation, high-frequency ventilation, induction of alkalosis, neuromuscular blockade, and sedation. When conventional therapies fail, INO may be indicated. INO improves oxygenation, decreases the need for extracorporeal membrane oxygenation (ECMO) and decreases mortality. In addition to pulmonary vasodilatation and a reduction in extrapulmonary right-to-left shunting, INO also improves ventilation/perfusion matching, decreases lung inflammation, and enhances growth in the immature lung (Kinsella, 2006; Walsh-Sukys, et al., 2000).

The recommended initial dose of INO is 20 parts per million (ppm). Studies have included treatment with 5–80 ppm of INO. Toxicity is typically seen in doses ≥ 80 ppm; however, the occurrence of toxicity has also been seen at lower doses. The duration of therapy is normally less than five days, but may be maintained for up to 14 days, or until the underlying oxygen desaturation has been resolved, and the neonate is ready to be weaned from therapy. To avoid rebound vasospasm, the infant should be slowly weaned off of INO. Abrupt withdrawal of INO may lead to worsening oxygenation and increased pulmonary artery pressure. According to AAP, INO is indicated when ventilatory therapy has failed, and ECMO is usually initiated only after INO fails due to the significant morbidity and mortality rates associated with ECMO. Because hypoxic respiratory failure often progresses rapidly, it is suggested that ECMO be available at facilities that have INO. If the infant must be transferred for ECMO, INO should not be discontinued (Ikaria, 2013; Stoll and Kliegman, 2004; Hintz, et al., 2000; Walsh-Sukys, et al., 2000).

Studies have demonstrated that INO was ineffective or had minimal effect in newborns with an unrepaired congenital diaphragmatic hernia, even when INO treatment was combined with surfactant. The cause of hypoxic respiratory failure in these infants is complex and includes pulmonary hypoplasia, surfactant dysfunction, functional and structural abnormalities of the pulmonary vascular bed and left ventricular dysfunction. Response is low due to the possible combination of lung hypoplasia and immaturity and PPHN aggravated by left ventricular underdevelopment. Some infants with congenital diaphragmatic hernia have prolonged pulmonary hypertension despite improvements in pulmonary function and gas exchange. The incidence of death or requiring ECMO for newborns with congenital diaphragmatic hernias was not statistically different in infants who received INO compared to infants who did not receive INO. The lack of efficacy of INO has been proposed to be due to the complexity of the disease. INO has not been proven to be beneficial in the treatment of hypoxic respiratory failure in the infant less than birth age 34 weeks gestation or in the treatment of other conditions, such as acute respiratory distress syndrome (Finer and Barrington, 2006; Kinsella, 2006; Kinsella and Abman, 2005; Weinberger, et al., 2001; Clark, et al., 2000).

Literature Review: Systematic reviews, meta-analysis, randomized controlled trials and case series have reported that INO improved systematic oxygenation and that fewer term and near-term infants with birth age greater than 34 weeks gestation required ECMO and/or developed chronic lung disease. Some studies reported a higher survival rate following INO therapy. The studies consistently demonstrated the ineffectiveness of INO when used in the treatment of infants with congenital diaphragmatic hernia (CDH) (Wang, et al., 2019; Barrington, et al., 2017a; Wang, et al., 2011; Rosenberg, et al., 2010; Hoskote, et al., 2008; Field, et al., 2007; Konduri, et al., 2004; Clark, et al., 2000; Oleira, et al., 2000; Neonatal Inhaled Nitric Oxide Study Group, 1997).

Postoperative Management of Pulmonary Hypertension with Congenital Heart Disease (CHD)

Depending on the severity of the disease, CHD can increase pulmonary blood flow or cause pulmonary venous obstruction, leading to pulmonary artery smooth muscle hypertrophy, vasoconstriction, vascular obliteration and pulmonary hypertension. At this point, surgical intervention may be indicated to reverse the condition and ward off impending death. Following surgical intervention, children and adults can experience life-threatening reactive or persistent elevated pulmonary arterial pressure, or pulmonary hypertension. Due to its specificity for the pulmonary vascular bed, INO acts directly on pulmonary vascular smooth muscle. It is inactivated when exposed to hemoglobin, therefore avoiding side effects of systemic vasodilation that may be encountered with the use of other available vasodilators. Alternatives to the use of INO include ECMO and ventricular assist devices. Because of its ability to decrease pulmonary vascular resistance (PVR) and intrapulmonary shunting, and increase oxygenation, INO is an established treatment option for pulmonary hypertension following surgical repair of congenital heart disease (Kliegman, et al., 2007; Carroll, et al., 2005; Ichinose, et al., 2004; Kawakami and Ichinose, 2004; Hermon, et al., 2003).

Literature Review: Randomized controlled trials, non-randomized comparative studies and case series reported that INO effectively lowered pulmonary vascular resistance and pulmonary artery pressure in children and adults with pulmonary hypertension after open heart surgery. However, it did not appear to increase the survival rate in those with severe pulmonary hypertension (Sharma, et al., 2001; Miller, et al., 2000; Morris, et al., 2000).

Postoperative Management of Pulmonary Hypertensive Crisis (PHC) Following Pediatric Heart or Lung Surgery: According to the 2015 American Heart Association and American Thoracic Society pediatric guidelines on the treatment of pulmonary hypertension, studies of pathophysiology and management of acute PHCs have been in the critical care setting primarily focused on the perioperative period after cardiac and lung surgery. PHC is sudden, potentially lethal, and can be triggered by various stimuli (e.g., pain, anxiety, tracheal suction, hypoxia, acidosis). The diagnosis of postoperative PHC may include a sudden increase in pulmonary artery pressure, followed by an increase in right atrial and right ventricular end-diastolic pressures, decreased systemic and mixed venous oxygen saturations, decreased systemic pressure, and decreased cardiac output. Bronchoconstriction or increased airway resistance may accompany these hemodynamic changes. PHC can prolong hospitalization and the need for mechanical ventilation. It can also increase postoperative mortality. Respiratory management plays a critical role in the treatment of pulmonary hypertension and avoidance of PHCs. Although there are a limited number of well-designed published studies on the outcomes of INO for the treatment of postoperative management of PHC following pediatric heart or lung surgery, INO is an established treatment option for this subpopulation. The AHA/ATS guideline made a class I, level B recommendation (i.e., the treatment should be performed and is effective) for the use of INO as an initial adjunctive therapy with conventional postoperative care for this subpopulation of children (Abman, et al., 2015).

Diagnostic Testing for Pulmonary Hypertension

The initial evaluation for the diagnosis of pulmonary hypertension in adults and children may include conventional therapies, such as chest radiography, electrocardiogram, echocardiogram, doppler echocardiography, pulmonary function studies and arterial blood gases. If the pulmonary hypertension cannot be confirmed by these conventional diagnostic studies, a right-heart catheterization using a pulmonary vasodilator may be indicated. INO may be administered as a vasodilator to assess pulmonary vasoreactivity in the management of pulmonary hypertension. A positive response to a vasodilating agent is indicative of favorable long-term clinical outcomes. A decrease in pulmonary artery pressure or pulmonary vascular resistance (PVR) in response to INO predicts a subsequent beneficial response to oral vasodilators such as nifedipine and identifies candidates who will benefit from long-term calcium channel blockers. INO testing can also help to determine if a patient is a good surgical candidate. Intravenous prostacyclin, adenosine and channel blockers may also be used to assess pulmonary vasoreactivity. Proponents of INO state that due to the potent, short-acting vasodilatory effect of INO and the potential of severe hypotension, increased intrapulmonary right-to-left shunting and death in response to other agents, INO is considered a safer alternative. INO is an established vasodilator for diagnostic testing for pulmonary hypertension (Krasuski RA, et al., 2011; Park, 2008; Bloch, et al., 2007; Minai and Budev, 2007; Ichinose, et al., 2004).

Literature Review: Randomized controlled trials, case series and nonrandomized comparative studies reported a significant decrease in systemic and pulmonary vascular resistance and mean pulmonary artery pressure, as well as an increase in cardiac output following INO therapy. The administration of INO with oxygen compared to oxygen alone resulted in more accurate selection of surgical candidates. When oxygen alone was compared to

oxygen/INO administration, accuracy (68% vs. 90%, respectively) and sensitivity (64% vs. 97%, respectively) were increased with INO administration when the systemic vascular resistance index:systemic vascular resistance index (Rp:Rs) < 0.33 was used as the criterion for operability (Barst, et al., 2010; Cannon, et al., 2005; Leuchte, et al., 2004).

Other Proposed Indications
Due to INO's success in treating persistent pulmonary hypertension (PPHN) in term and near-term neonates and the postoperative management of pulmonary hypertension following repair of congenital heart disease, INO has been proposed for the treatment of other conditions, including: respiratory distress in preterm infants less than birth age 34 weeks gestation; chronic lung disease or bronchopulmonary dysplasia in preterm infants; acute respiratory failure in older children and adults; adult heart and lung transplantation; chronic obstructive pulmonary disease in adults; pulmonary vascular resistance following ventricular assist device insertion; sickle cell disease; chronic pulmonary hypertension; cardiogenic shock; pain associated with coronary artery disease; and other conditions associated with pulmonary hypertension. There is insufficient evidence in the published peer-reviewed scientific literature to support the safety and efficacy of INO for all other indications. Selection criteria for patients who will benefit from INO, dosage and duration of therapy, beneficial clinical outcomes, and long-term outcomes have not been established (Tavare and Tsakok, 2011; Arul and Konduri, 2009; Ichinose, et al., 2009).

Respiratory Distress in Preterm Infants less than Birth Age 34 Weeks Gestation: Studies for the administration of INO in premature infants less than birth age 34 weeks gestation with respiratory distress of various etiologies including bronchopulmonary dysplasia (BPD) are ongoing and inconclusive. Collectively, the results of the studies indicated that INO has not been proven beneficial for the treatment of this subpopulation. The long-term pulmonary and extrapulmonary effects (e.g., pulmonary cell proliferation and differentiation, alveolar and microvascular development) of INO have not been reported. Standard care in preterm infants with RDS may include surfactant replacement therapy, breathing support from a ventilator or nasal continuous positive airway pressure, and oxygen therapy (National Heart, Lung, and Blood Institute [NHLBI], 2019b).

Hayes (2018; 2019) published a directory report to evaluate the use of inhaled nitric oxide (INO) therapy to reduce mortality and prevent early lung injury in ventilated preterm newborns (less than 35 weeks gestational age) with hypoxic respiratory failure. The evidence included one systematic review/meta-analysis (SR/MA) 17 randomized controlled trials (30 publications included in SR/MA with two subsequent publications) and one retrospective, propensity score matched cohort study. Findings include

- For early rescue treatment with INO compared with placebo in combination with conventional management or conventional management-alone: Did not improve mortality or BPD (one SR/MA and one propensity-matched cohort study).
- For later treatment (after three days of life) with INO compared with placebo in combination with conventional management or conventional management alone in infants at increased risk of BPD: Did not improve mortality or BPD (1 SRMA).
- For routine use of INO compared with placebo in combination with conventional management or conventional management-alone in infants with respiratory failure and receiving respiratory support: Did not improve mortality or BPD (1 SRMA).

The report concluded that a high-quality, consistent body of evidence indicates that early rescue use INO within the first three days of life does not increase survival, decrease pulmonary morbidity, or improve neurodevelopmental outcomes in preterm infants <35 weeks gestation who require respiratory support. Similarly, two moderate-quality, consistent bodies of evidence assessing later treatment (after three days of life) in preterm infants at increased risk of BPD and routine treatment in preterm infants requiring respiratory support suggest no benefit of INO regimens for survival, pulmonary morbidity, or improved neurodevelopmental outcomes.

Chandrasekharan et al. (2020) conducted a study to evaluate the survival and neurodevelopmental impairment (NDI) in extremely low birth weight (ELBW) infants at 18 to 26 months with early hypoxemic respiratory failure (HRF) and to assess whether African American infants with early HRF had improved outcomes after exposure to inhaled nitric oxide (iNO). The study included retrospective analysis, and also included prospectively collected individual patient data from an established neonatal research network of academic institutions. The study included ELBW infants ≤1000 g and gestational age ≤26 weeks with maximal oxygen ≥60% on either day one or day three that were labeled as "early HRF" and born between 2007 and 2015 in the Neonatal Research Network.

Using a propensity score regression model, outcomes and effects of exposure to iNO overall and separately by race were analyzed. Among 7,639 ELBW infants born ≤26 weeks, 22.7% had early HRF. Early HRF was associated with a mortality of 51.3%. The incidence of moderate-severe NDI among survivors was 41.2% at 18 to 26 months. Mortality among infants treated with iNO was 59.4%. Female sex (adjusted odds ratio [aOR]: 2.4, 95% confidence interval [CI]: 1.8-3.3), birth weight ≥720 g (aOR: 2.3, 95% CI: 1.7-3.1) and complete course of antenatal steroids (aOR: 1.6, 95% CI: 1.1-2.2) were associated with intact survival. African American infants had a similar incidence of early HRF (21.7% vs 23.3%) but lower exposure to iNO (16.4% vs 21.6%). Among infants with HRF exposed to iNO, intact survival (no death or NDI) was not significantly different between African American and other races (aOR: 1.5, 95% CI: 0.6-3.6). The authors concluded that early HRF in infants ≤26 weeks' gestation is associated with high mortality and NDI at 18 to 26 months and that use of iNO did not decrease mortality or NDI.

Barrington et al. (2017b) conducted a Cochrane review of randomized and quasi-randomized controlled trials to evaluate the effects of INO on death, bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH), other serious brain injury events and on adverse long-term neurodevelopmental outcomes in preterm newborn infants (less than 35 weeks' gestation) with hypoxic respiratory failure . Seventeen randomized controlled trials met inclusion criteria. Due to the substantial variation in study eligibility criteria which decreases the utility of an overall analysis, the trials were grouped into the following three categories: 1) treatment during the first three days of life for impaired oxygenation; 2) routine use in preterm babies along with respiratory support; and 3) later treatment for infants at increased risk for BPD. No overall analyses were performed. Eight trials (n=958) providing early rescue treatment for infants on the basis of oxygenation criteria demonstrated no significant effect of INO on mortality or BPD. Four studies (n=1924) evaluating routine use of INO in infants with pulmonary disease reported no significant reduction in death or BPD. The three trials (n=1075) evaluating later treatment with INO based on the risk of BPD revealed no significant benefit. No clear effect of INO was found on the frequency of all grades of IVH or severe IVH. Early rescue treatment was associated with a non-significant 20% increase in severe IVH. No effect was found on the incidence of neurodevelopmental impairment. Based on the data INO does not appear to be an effective rescue therapy for the very ill preterm infant. Early routine use of INO in preterm infants with respiratory disease did not prevent serious brain injury or improve survival without BPD. Additional studies are required to determine if late use of INO is effective in preventing BPD.

Tal et al. (2018) conducted a pilot, double-blinded, randomized controlled study (phase IIa) study to determine safety, tolerability (primary outcome) and efficacy (secondary outcome) of high-dose inhaled nitric oxide for the treatment of infants with moderately severe bronchiolitis. Intermittent inhalations of nitric oxide 160 ppm for 30min or oxygen/air (control) were given five times/day to hospitalized infants (2–11 months) (n=43; 21 NO group and 22 control) with acute bronchiolitis. Oxygen saturation, methemoglobin, and nitric dioxide (NO2) levels and vital signs were monitored. Mean clinical score, comprised of four components: respiratory rate, use of accessory muscles, wheezes and crackles, and % room-air oxygen saturation, was 7.86 (±1.1) and 8.09 (±1.2) in the NO and control groups, respectively, consistent with moderate severity. The overall frequency of adverse events was similar between the groups. Repeated nitric oxide inhalations did not result in increased inhaled NO2 levels or cumulative effect on methemoglobin levels. Secondary outcomes of efficacy were measured by length of hospitalization (LOS) in hours: LOS did not differ between groups. However, in a post-hoc analysis of a subgroup of infants hospitalized for >24 h (n = 24), the median LOS was shorter in the nitric oxide (41.9 h) than in the control group (62.5 h) (P = 0.014). the authors concluded that safety and tolerability of intermittent inhalation NO treatment were comparable to those in the standard supportive treatment and larger scale trials are needed to corroborate the safety and the beneficial effect of inhaled NO in bronchiolitis.

Ellsworth et al. (2018) reported on a cohort study to determine whether treatment with inhaled nitric oxide during the first week of life was associated with improved in-hospital survival in a cohort of extremely preterm neonates with pulmonary hypoplasia. The study used a 1-to-1 propensity score matching to reduce the imbalance of measured covariates between two treatment groups. The initial, unmatched cohort included singleton neonates who were born between 22 and 29 weeks' gestation, with birth weight of 400 g or more, with pulmonary hypoplasia as a cause of their respiratory distress, remained free of major anomalies. Exposure was defined as the initiation of inhaled nitric oxide on day t in days 0 to 7 of the life of a neonate. Each exposed neonate was matched 1-to-1 to a neonate who had not initiated inhaled nitric oxide on a given day. The primary outcome was mortality defined as death prior to transfer or discharge home. Secondary outcomes were any-stage necrotizing enterocolitis, retinopathy of prematurity requiring treatment, chronic lung disease, and periventricular

leukomalacia. Among 92,635 neonates in the study sample, 767 (0.8%) were identified with pulmonary hypoplasia who met all study inclusion criteria, of whom 185 (0.2%) were exposed to inhaled nitric oxide. Among 151 matched pairs of exposed and unexposed neonates, there was not a significant association between inhaled nitric oxide use and mortality (hazard ratio [HR], 0.79; 95% CI, 0.57-1.11) identified. Subgroup analyses of neonates with and without persistent pulmonary hypertension (PPHN) likewise revealed no significant association between inhaled nitric oxide use and mortality (pulmonary hypoplasia with PPHN: HR, 0.67; 95% CI, 0.45-1.01; pulmonary hypoplasia without PPHN: HR, 1.11; 95% CI, 0.61-2.02), but the authors noted that these findings may have been influenced by ascertainment bias. The authors concluded that early treatment with inhaled nitric oxide is not associated with improved survival among extremely preterm neonates with pulmonary hypoplasia and clinical trials are warranted to clarify the matter.

Carey et al. (2018) reported on a cohort study that examined inhaled nitric oxide (INO) in extremely premature neonates with respiratory distress syndrome (RDS). The study included singletons who required mechanical ventilation for treatment of RDS and excluded those with anomalies. The primary outcome was death before discharge. Through a sequential risk set approach, each patient who received INO during the first 7 days of life (case patient) was matched by using propensity scores to a patient who had not received INO at a chronological age before the case patient's INO initiation age (defined as the index age for the matched pair). The association between INO status and in-hospital mortality was evaluated in a Cox proportional hazards regression model by using age as the time scale with patients entering the risk set at their respective index age. The study sample included 37,909 neonates, of which 993 (2.6%) received INO. The two matched cohorts each contained 971 patients. The authors did not observe a significant association between INO exposure and mortality (hazard ratio, 1.08; 95% confidence interval, 0.94-1.25; P = .29). The authors concluded that off-label prescription of INO is not associated with reduced in-hospital mortality among extremely premature neonates with RDS.

Durrmeyer et al. (2013) conducted a follow-up of the European Union Nitric Oxide (EUNO) randomized controlled trial (Mercier, et al., 2010) to evaluate neurodevelopmental outcomes at age two years (n=514). A total of 244 out of 363 INO treated infants and 270 of 374 placebo-treated infants were alive for assessment. The study groups included preterm infants born at 14–28 weeks' gestation with moderate respiratory failure who receive 5 ppms of INO or placebo for 7 to 21 days. There was no significant difference in the mean (SD) cognitive composite scores (Bayley Scales of Infant and Toddler Development, third edition) between the two groups (p=0.11). There were no significant differences in the frequency of cerebral palsy (p=0.89), seizure disorders (p=0.47), hearing impairment (p=0.45), vision deficits (p=0.09), hospitalizations in past year (p=1.0), home oxygen therapy (p=0.10), or growth (weight, length, head circumference; p=0.61, .086, 0.16, respectively) between the groups. At the two year-follow-up, INO started 24 hours after birth for a median of 20 days did not affect neurodevelopmental or other health outcomes for this preterm infant population.

Askie et al. (2011) conducted an individual-patient data (IPD) meta-analysis which involved the central collection and reanalysis of line-by-line raw data from each randomly assigned preterm infant (< 34 weeks' gestational age) (n=3298) from 11 randomized controlled trials (96% of published world-wide data). The objective of the study was to determine if INO in preterm infants who received ventilatory support improved survival without morbidity, specifically without chronic lung disease (CLD) or major neurological injury and if the effects of INO differed according to patient or intervention-related factors (e.g., gestation age at birth, birth weight, oxygen index, pulmonary hypertension). The preterm infants were randomly assigned to INO or a control group. Overall, death or CLD occurred in 59% INO-treated infants compared to 61% control infants (p=0.11). Severe neurologic events occurred in 25% of infants in the INO group compared to 23% of infants in the control group (p=0.09). There were no statistically significant differences between INO- and control-treated infants for any secondary outcomes, or for the primary end points according to patient or intervention-related factors (p>0.5, each). The relative risk of treatment effect on death or CLD in the lower-starting-dose group was significantly different than in the higher-starting-dose group (>5 ppm) (p=0.02), suggesting more benefit with the higher dose. The duration of treatment had no significant impact on the effect of treatment. The trials differed in many ways including variation in the inclusion criteria which impacted the number of high-risk infants in a group, lack of blinding to treatment after allocation, and treatment regimens. However, the authors noted that due to the variations in the treatment regimens it was difficult to draw firm conclusion regarding this data. The authors concluded that the results revealed no benefit for the routine early use of INO in preterm infants receiving respiratory support (either mechanical ventilation or continuous positive airway pressure). Within some individual subgroups there were suggestions of significant benefits but the result was likely due to selection of particular trials with the relevant

information. On the basis of treatment-by-subgroup interaction tests for differences between subgroups, there was no clear evidence that INO was more or less effective for any particular subgroup of preterm patients. The results of this meta-analysis indicated that routine use of INO for treatment of respiratory failure in preterm infants could not be recommended.

Barrington and Finer (2010) conducted a systematic review to evaluate the efficacy and toxicities of INO in infants less than 35 weeks gestation with respiratory disease to determine if INO reduced the rates of death, bronchopulmonary dysplasia (BPD), intracranial hemorrhage, or neurodevelopmental disability. Fourteen randomized controlled trials were included. The infants had received treatment with surfactant prior to inclusion in the studies. Due to the differences in the inclusion criteria, pooling of the results was considered "not appropriate" and the 11 trials were subdivided for analysis. The first group of studies (n=9), considered "early rescue treatment," included acutely ill infants, undergoing ventilation who were enrolled within the first three days of life. The second group included infants three days of age who were at risk for developing BPD (n=3 studies). The third group was comprised of two studies in which infants were less than age three days and were intubated but had no criteria regarding severity of illness. In these two studies INO was considered "early routine use." INO did not appear to improve the chances of the babies having improved outcomes and may have caused excessive bleeding.

Huddy et al. (2008) reported 4–5 year outcomes of 108 infants, age less than 34 weeks gestation, who had severe respiratory failure, required ventilatory support, and were age less than 28 days when INO was administered. Infants were randomized to ventilation with INO (n=55) or ventilation without INO (n=53). "A satisfactory response was defined as an increase in post-ductal arterial oxygen tension (PaO2) of more than 3 kPa [kilopascal] (22.5 millimeters of mercury) after the first 15 minutes of giving INO." Dosage began at 5 ppm, was doubled to 10 ppm and maximized at 40 ppm if no satisfactory response was achieved. No evidence of dose-response relationship was reported. Overall assessments included the following outcomes:

- eight children were classified as normal across all domains at the age of 4–5 years (five INO vs. three no INO);
- five children (three INO vs. two no INO) had impairment only;
- ten children were classified as having mild disability (six INO vs. four no INO);
- nine children had moderate disability (five INO vs. four no INO);
- six children were severely disabled (three in each group); and
- 34 of 55 INO (62%) died or were severely disabled at the last follow-up compared to 37 of 53 (70%) of the no INO group.

Of the four children unable to participate in cognitive assessment due to the severity of disability, three were in the INO group. Of the 19 INO and 15 no INO children able to participate in cognitive assessment, there were no significant differences between the two groups in mean general conceptual ability score, verbal ability scores, pictorial reasoning, spatial abilities, or non-verbal composite. There were no significant differences in neuromotor, sensory, communication, and behavior outcomes. Based on the results of this study, there were no benefits or harms to the use of INO in preterm infants.

Di Fiore et al. (2007) conducted a study to determine if INO improved airway resistance and compliance in ventilated infants (n=71) with evolving BPD. The infants, gestational age 24.3–26.7 weeks, weight 574–930 grams (g), ages 11.5–19.6, days, were randomized to either INO (n=34) or placebo gas (n=37). Pulmonary function was assessed prior to initiation of the study, one hour and 24 hours following the initiation of therapy, and weekly thereafter until the infant was extubated or switched to high-frequency ventilation. Pulmonary function measurements included expiratory resistance (Rexp) and compliance normalized by weight (Ckg). There were no significant differences in the two groups in the one hour Rexp and Ckg values (p=0.66, p=0.40, respectively) nor at the end of week one (p=0.63, p=0.29, respectively). During week one, eight placebo-treated infants were switched to high frequency ventilation and one infant expired compared to seven INO-treated infants who were switched to high frequency ventilation. At the end of two weeks, 16 placebo-treated infants and ten INO-treated infants were available for assessment. Values at the end of week two were constant from week one. Limitations of the study include the small patient population and the number of infants lost to follow-up.

Hintz et al. (2007) conducted a multicenter randomized controlled trial to evaluate the effects of INO on neurodevelopmental impairment (NDI) and mortality in infants (n=418), gestational age less than 34 weeks, weight 401–1500 g, with severe respiratory failure. NDI was defined as moderate to severe cerebral palsy (CP), bilateral blindness, or deafness, and a score less than 70 on Bayley Scales of Infant Development [BSID] II, Mental Developmental Index [MDI] or Psychomotor Developmental Index [PDI]. Follow-up occurred at 18 to 22 months of age corrected for prematurity. The infants were randomized to receive either INO (n=210) or placebo (n=208) based upon birth weight (i.e., 401–750 g; 751–1000 g; 1001–1500 g). Of the available infants at follow-up, 91 of 101 (90%) INO-treated infants and 102 of 112 (91%) placebo-treated infants survived. There were no significant differences in the death rate or NDI of the INO group compared to the placebo group (78% vs. 73%, respectively). Compared to the placebo group, a slightly increased risk of moderate to severe CP or death was reported in INO-treated infants with a birth weight less than 1000 g (p=0.01). Limitations of the study include the number of infants lost to follow-up and the short-term follow-up.

Van Meurs et al. (2007) conducted a randomized controlled trial to determine if INO would reduce the incidence of death and bronchopulmonary dysplasia (BPD). Infants requiring mechanical ventilation for severe respiratory failure, less than 34 weeks gestation, weight greater than 1500 g, were randomized to either INO (n=14) or placebo (n=15). Five INO-treated infants and four control group infants died before discharge. There were no significant differences between the two groups in death, BPD, death and/or BPD or NDI outcomes. The trial was terminated due to the high incidence of grade 3 or 4 intraventricular hemorrhage or periventricular leukomalacia in the INO-treated infants. Author noted limitations of the study included the small patient population and the short duration of INO administration (i.e., maximum 14 days).

A Kinsella 2006 systematic review of INO therapy in premature newborns with hypoxemic respiratory failure and PPHN summarized the results of nine randomized controlled studies. The author reported that the studies reported conflicting results and the role of INO in this population remained controversial.

Ballard et al. (2006) conducted a randomized controlled trial including 582 infants from 21 centers (Nitric Oxide for Chronic Lung Disease [No CLD] trial). The infants, gestational age 26 weeks, had a birth weight of 1250 g or less, were on mechanical ventilators, at high risk for BPD and between ages seven and 21 days. Infants were randomly assigned to INO (n=294) and non-INO (n=288) and stratified according to weight (i.e., 500–799 g and 800–1250 g). INO was initially administered at 20 ppm, and the dosage was decreased at weekly intervals until a minimal of 24 days of treatment had been administered. The goal was survival without BPD. In the study group, 43.9% survived without BPD compared to 36.8% in the control group. INO infants received supplemental oxygen for a shorter period of time and were discharged sooner. Survival without BPD was similar in both birth-weight strata. Infants treated with INO required less supplemental oxygen and were discharged sooner. INO administered between 7 and 21 days of age improved pulmonary outcomes in preterm infants at risk for BPD. The authors pointed out that this trial differed in design from other studies in that INO was not started until the seventh day, and INO was administered for a longer period of time (i.e., 24 days versus 76 hours to 14 days). They also stated that definitive recommendations for the use of INO in this population were contingent upon long-term neurodevelopmental outcomes.

Several follow-up studies have been conducted on the Ballard et al. (2006) study discussed above. Because of the known role of INO in oxidative damage and the concern that INO could potentially increase formation of reactive oxygen and nitrogen species, Ballard et al. (2008) prospectively collected blood samples from a subset of 100 infants to determine the effect of INO on plasma biomarkers of oxidative stress for premature infants. Birth weights ranged from 502–1105 g and gestational age ranged from 22.7–30.0 weeks. Infants were entered into the study between days 7 and 21. At each of the three time points (1–10 days) during exposure to study gas, there were no significant differences between control and treated infants for concentrations of plasma protein, 3-nitrotyrosine, and carbonylation. The authors noted that the blood samples were collected over a period of four years and stored for prolonged periods. Hibbs et al. (2008) reported one-year outcomes to determine if INO decreased indicators of long-term pulmonary morbidities in this study group. There were 230 INO-treated infants and 225 control group infants available for follow-up. Following discharge from neonatal intensive care, the INO infants received significantly less bronchodilators, inhaled steroids, systemic steroids, diuretics, and supplemental oxygen. There were no significant differences in wheezing, whistling or rehospitalizations. Walsh et al. (2010) prospectively reported the two-year neurodevelopmental and growth outcomes of this study group.

There were 243 surviving INO study patients and 234 non-INO patients available for evaluation. There were no significant differences in the growth variable or the neurodevelopment impairments (i.e., moderate or severe cerebral palsy, bilateral blindness, bilateral hearing loss, or score <70 on the Bayley Scales II) in the INO group compared to the placebo group (p=0.39). Kilbride et al. (2019) reported on follow-up of 34 children at 7-9 years of age that included pulmonary function testing (PFT), exercise testing, and measurement of altered exhaled nitric oxide (FeNO) levels. It was noted that there were no differences in PFTs or exercise capacity between INO treated and controls. FeNO levels showed large interpatient variability but tended to be lower in the INO treated group.

Kinsella et al. (2006) conducted a multicenter randomized controlled trial (n=793) to evaluate the effectiveness of INO in the treatment of newborns, 34 weeks or less gestational age, requiring mechanical ventilation. Infants were randomized to the INO group (n=398) or to the control-placebo group (n=395). The groups were further stratified by weight (i.e., 500–749 g, 750–999 g, 1000–1250 g). The study group received 5 ppm INO, within 48 hours of birth, for a median of 14 days (range 0–24). Primary outcome was death or bronchopulmonary dysplasia (BPD), at 36 weeks of postmenstrual age. Overall, there were no significant differences in the outcomes between the INO group (71.6% experienced death or BPD) and the control group (75.3% experienced death or BPD). In the 1000–1250 g birth-weight group, INO reduced BPD compared to the control group, 29.8% and 59.6%, respectively. For all the subjects, the occurrence of intracranial hemorrhage, periventricular leukomalacia, ventriculomegaly, and periventricular leukomalacia alone was reduced. INO infants had a lower incidence of periventricular leukomalacia than the control group infants. The largest reduction of periventricular leukomalacia or intracranial hemorrhage was seen in the INO 750–999 g subgroup and, overall, the INO group experienced fewer incidences of ventriculomegaly (5.2% compared to 8.9%). In the overall population, INO reduced the risk of brain injury, but it did not reduce the risk of BPD in 500–1250 g infants.

A meta-analysis by Hoehn et al. (2006) of INO in the treatment of severe hypoxemic respiratory failure in preterm infants was conducted. The analysis incorporated five randomized controlled trials, which included 808 infants age less than 34 weeks gestation. As a result of their study, the authors concluded that there was no significant difference in the rate of major intracranial hemorrhage and mortality rate in infants treated with INO. It was also noted that INO significantly reduced the incidence of chronic lung disease (CLD) and mortality of infants with CLD. However, the authors stated that the data from these studies were preliminary and should be regarded cautiously.

Van Meurs (2005) reviewed the results of five randomized clinical trials of preterm infants with respiratory distress syndrome who were treated with INO. One trial demonstrated improvement with the use of INO, but the other studies showed no improvement. Other authors have noted discrepancies among outcomes and stated that they may be attributed to variations in the severity of illness, underlying conditions, composition of the study population, and single-center versus multicenter (Martin and Walsh, 2005).

Van Meurs et al. (2005) conducted a randomized clinical trial on the use of INO in premature infants with severe respiratory distress. The study included 42 neonates < 34 weeks gestation with respiratory distress who had received one dose of surfactant at least four hours prior to meeting inclusion criteria. Subjects were randomly assigned to the simulated gas flow control group (n=21) or to the INO group (n=21). The authors reported that there was no difference in the outcomes between the two groups. INO did not reduce the incidence of death or of bronchopulmonary dysplasia. Another randomized study was conducted by Hamon et al. (2005) “to assess the oxidative balance in premature infants who were exposed to low dose INO and the relationship with their clinical outcome on day 28 of life.” The study included 274 infants, < 32 weeks gestation, randomly assigned to receive 5 ppm INO. The results of the study group were compared to a nonhypoxemic infant group as a reference. They reported that INO seemed to be clinically beneficial for up to 28 days of life.

In a technology assessment, the Agency for Healthcare Research and Quality (AHRQ) (2010) conducted a systematic review and meta-analysis of the evidence on INO for the treatment of preterm infants born at or before 34 weeks gestation age who received respiratory support. The review included 14 randomized controlled trials and eight observational studies. There were no significant differences in the mortality rate, incidence of cerebral palsy, neurodevelopment impairment, cognitive impairment or bronchopulmonary dysplasia (BPD) at 36 weeks. Meta-analysis showed no difference in the risk of brain injury. There was a seven percent reduction in the risk of the composite outcome of death or BPD at 36 weeks postmenstrual age, but no reduction in death or BPD

alone. AHRQ concluded that there was no evidence to support the use of INO in preterm infants with respiratory failure outside the context of randomized clinical trials.

Acute Respiratory Distress Syndrome (ARDS): ARDS, or respiratory distress syndrome (RDS), is the acute onset of pulmonary edema in the absence of volume overload or depressed left ventricular function. ARDS, found in children and adults, occurs as a result of an insult or injury involving damage to the alveolar epithelium and vascular endothelium. The injury results in an accumulation of fluid, disrupts the production and function of pulmonary surfactant, and results in poor gas exchange. Treatment includes 100% oxygen administration, high levels of positive end-expiratory pressure (PEEP), high inspiratory flow rates and pharmacological therapy. It has been proposed that INO may be a treatment modality for ARDS for its pulmonary vasodilation effect in cases unresponsive to conventional therapy. ARDS is often accompanied by multisystem organ failure and patients typically, do not die of primary lung injury. Outcomes of clinical trials have not demonstrated that INO has a significant effect on mortality, and it is speculated that the administration of INO may increase the risk of mortality.

INO has been proposed as a treatment for ARDS associated with COVID-19. It is theorized that INO may improve oxygenation, and also that it may have antiviral properties. While there are several clinical trials underway that are examining the use of INO for ARDS with COVID-19. The treatment of this condition with INO is currently unproven.

Gebistorf et al. (2016) conducted a Cochrane systematic review of 14 randomized controlled trials (n=1275) to evaluate the effect of INO on mortality in adults and children with ARDS. Secondary outcomes included pulmonary bleeding events, duration of mechanical ventilation and length of stay. No statistically significant effects were found on longest follow-up (one year) mortality in the INO group (250/654 deaths) (38.2%) compared to the control group (221/589 deaths) (37.5%) (moderate quality of evidence). No statistically significant effects were found on mortality at 28 days in the INO group (202/587 deaths) (34.4%) vs the control group (166/518 deaths) (32.0%). In children, there were no statistically significant effects of INO on mortality with 25/89 deaths (28.1%) in the INO group vs 34/96 deaths (35.4%) in the control group. At 24 hours following the administration of INO, a transient significant improvement was seen in arterial blood (PaO2)/fraction of inspired oxygen (FiO2) (moderate quality evidence), and oxygenation index (moderate quality evidence). There was no significant difference in ventilator-free days (high quality evidence). There was a statistically significant increase in renal failure in the INO groups (high quality evidence). There is insufficient evidence to support INO in any category of critically ill patients with ARDS. Inhaled nitric oxide resulted in a transient improvement in oxygenation but did not reduce mortality and may be harmful, as it seemed to increase renal impairment.

Dzierba et al. (2014) conducted a systematic review of the literature to evaluate the safety and efficacy of inhaled vasodilators focusing on INO and aerosolized epoprostenol for the treatment of ARDS or acute lung injury (ALI) in adults age 18 years or older. Nine randomized controlled trials describing the effects of INO on indexes of oxygenation and clinical outcomes met inclusion criteria. Seven studies evaluated INO for the treatment of ARDS and two studies used INO for the treatment of ALI. Conventional therapy/usual care were the most common comparator with three studies using nitrogen gas as the placebo comparator. No improvements in mortality were observed. Limitations of the studies included lack of sufficient power to detect differences in long-term outcomes. Pooled data did not show a difference in mortality and ventilation-free days with INO. The authors noted that the optimal dose of INO to maximize oxygenation is unknown but doses of INO greater than 40 ppm did not further improve clinical outcomes and may have increased the risk of toxicity. The initial improvements seen with INO were transient with no significant differences in mortality, ventilator-free days or reduction in disease severity. Limitations of the studies included small patient populations; lack of appropriate control subjects; heterogeneity of dosage, timing of therapy, delivery mode of INO and heterogeneity of the definitions of ALI and ARDS in the studies. The incident of toxic effects was minimal. There is insufficient evidence to support the routine use of INO for the treatment of ARDS or ALI.

Adhikari et al. (2014) conducted a systematic review and meta-analysis of randomized controlled trials to determine if INO reduced hospital mortality in adults and children (excluding neonates) with severe acute respiratory distress syndrome (Pao2/Fio2 ≤ 100 mm Hg) but not in patients with mild-moderate acute respiratory distress syndrome (100 mm HG < Pao2/Fio2 ≤ 300 mm Hg). Nine trials (n=1142 patients) met inclusion criteria. The primary outcome was hospital mortality. Subgroup analysis compared outcomes using other Pao2/Fio2

thresholds. INO did not reduce mortality in patients with severe acute (p=0.93) or mild-moderate acute respiratory distress syndrome (p=0.33). The effect of INO did not differ based on the level of hypoxemia (p=0.24).

Afshari et al. (2010) conducted a systematic review of randomized controlled trials (n=14 studies; 1303 patients) that compared INO with no intervention or placebo for the treatment of ARDS in adults and children. A transient statistically significant improvement in oxygenation in the first 24 hours, expressed as the ratio of partial pressure of oxygen to fraction of inspired oxygen and the oxygenation index, was seen. However, there was no statistically significant difference in overall mortality in the INO groups compared to the control groups (40.2% vs. 38.6%). Available data indicated a statistically insignificant effect of INO on duration of ventilation, ventilator free days, and length of stay in the intensive care unit and hospital. INO appeared to increase the risk of renal impairment among adults but not the risk of bleeding or the formation of methaemoglobin or nitrogen dioxide. Based on their analysis, the authors concluded that INO could not be recommended for the treatment of ARDS because its use did not reduce mortality and it may be harmful.

Adhikari et al. (2007) conducted a systematic review and meta-analysis of 12 randomized trials including 1237 subjects, adults and children, in which patients were treated with INO for acute lung injury and ARDS compared to infants treated with placebo or usual treatment. Outcomes included mortality, duration of ventilation, oxygenation, pulmonary arterial pressure and adverse events. Although INO increased the ratio of partial pressure of oxygen to a fraction of inspired oxygen and decreased the oxygen index on day one, and in some cases, up to day four, there was no effect on mean pulmonary arterial pressure. There was no significant effect on the outcomes, and some patients exhibited an increased risk of developing renal dysfunction.

Angus et al. (2006) conducted a randomized controlled trial (n=378) to evaluate the effects of INO on survival and quality of life in adults with ARDS. The study also included a cost-effective analysis. Patients with an onset of ARDS within the preceding 72 hours were eligible for the study. Subjects were randomly assigned to the study group, treated with 5 ppm of INO (n=184) or to the placebo group, treated with nitrogen (n=184). Treatment was administered until oxygenation was adequate, or for up to 28 days, or death. Because the study included subjects from multiple centers across the country, survival and quality of life data were collected via telephone interviews at six months and one year following treatment. Interview tools included the Quality of Well-Being scale and interview questions. There was no significant difference in survival between the two groups at 28 days. Activities of daily living (ADL) decreased during the first 28 days (i.e., 40% below baseline), improved by the end of year one, but did not return to baseline levels. There were no significant differences in the ADLs between the study group and the control group. The Quality of Well-Being scores between the two groups were not statistically significant. The one-year survival rate for the study group was 67.3% compared to 68.3% for the control group (p=0.71). Limitations of the study as recognized by the authors included: possible selection bias, self-reported telephone interviews; and one-year follow-up.

Taylor et al. (2004) conducted a randomized controlled trial (n=385) to evaluate the effectiveness of INO at 5 ppm for the treatment of patients with acute lung injury not due to sepsis and without evidence of nonpulmonary organ system dysfunction. This study included patients from 46 hospitals. The patients, age ≥ 18 years old, had sustained a moderately severe, acute lung injury from multiple causes, and met the criteria for definition of ARDS. Patients were randomly assigned to the INO group (n=192) or to the nitrogen oxide placebo group (n=193). INO was administered for up to 28 days, or until the assisted device was discontinued, or the patient died. Utilizing intent-to-treat analyses, INO did not improve the number of days alive and off assisted ventilation (p=0.97). There were no significant differences in mortality (p=0.54), days alive following a 2-hour unassisted ventilation trial (p=0.54), days alive without assisted breathing by day 28 (p=0.40), or days alive and meeting extubation criteria (p=0.89). A statistically significant increase in PaO_2 occurred during the initial 24 hours, but was resolved by 48 hours. There were no significant differences in the complications.

Sokol et al. (2003) conducted a Cochrane meta-analysis of five randomized controlled trials including 535 patients with acute hypoxemic respiratory failure (AHRF). Participants were adults and children, older than age one month, who were treated in an intensive care setting. The analysis revealed that INO had some immediate benefit on oxygenation (i.e., within the first four days), but did not demonstrate any statistically significant effect on mortality. Methemoglobinemia occurred with the administration of 40 ppm or more of INO, otherwise there

were no reports of significant side effects. The authors stated that data were lacking, clinical indicators for effectiveness were inconsistent, and future trials were indicated.

Cardiac Surgery: INO has been proposed for use during cardiac surgery to reduce pulmonary hypertension. However, data from large randomized controlled trials have not shown that INO improves health outcomes.

Sardo et al. (2018) conducted a meta-analysis of randomized controlled trials (RCTs) to investigate the efficacy and safety of perioperative administration of nitric oxide in cardiac surgery. The study included 18 RCTs comprising 958 patients. The primary outcome was intensive care unit (ICU) stay, and secondary outcomes were mortality, duration of mechanical ventilation, and reduction of mean pulmonary artery pressure. The authors calculated the pooled odds ratio (OR) and the mean difference (MD) with random-effects model. Quantitative synthesis of data demonstrated a clinically negligible reduction in the length of ICU stay (MD -0.38 days, confidence interval CI [-0.65 to -0.11]; p = 0.005) and mechanical ventilation duration (MD -4.81 hours, CI [-7.79 to -1.83]; p = 0.002) compared with all control interventions with no benefit on mortality. The authors concluded that perioperative delivery of inhaled nitric oxide resulted to be of no or minimal benefit in patients with pulmonary hypertension undergoing cardiac surgery and that large, randomized trials are needed to further assess the effect on major clinical outcomes and cost-effectiveness.

Fernandes et al. (2011) conducted a randomized controlled trial (n=29) to assess if INO would improve the hemodynamic effects and clinical outcomes in patients with mitral stenosis and severe pulmonary hypertension following cardiac surgery. Immediately before being weaned off cardiopulmonary bypass, patients were randomized to receive either INO (n=14) or oxygen (control group) (n=15) and outcomes were measured for 48 hours. Compared to the control group, there was a significant increase in cardiac index ($p<0.001$) at 24 and 48 hours following INO and a significant reduction in pulmonary vascular resistance ($p=0.005$) at 48 hours. INO patients also had a shorter intensive care length of stay ($p=0.02$), but total hospital days were not significantly different between the groups. One patient withdrew prior to initiation of the study and one patient died. There were no significant differences between the two groups in complications. Limitations noted by the authors were the use of vasoactive drugs during the first 48 hours of treatment and the use of right ventricular parameters as outcomes of the study which may have enhanced the results. Another limitation of the study is the small patient population.

In a randomized controlled trial, Winterhalter et al. (2008) compared the efficacy of inhaled iloprost (n=23) to inhaled nitric oxide (n=23) in reducing pulmonary hypertension immediately following weaning from cardiopulmonary bypass during cardiac surgery. Although both drugs resulted in a significant increase in cardiac output within 30 minutes of administration ($p<0.0001$), iloprost resulted in a significantly greater reduction in pulmonary vascular resistance ($p<0.013$) and mean pulmonary artery pressure ($p=0.0006$). Iloprost also caused a significantly greater increase in cardiac output ($p=0.002$) compared to INO. A limitation of the study is the small patient population.

A randomized controlled trial by Fattouch et al. (2006) assessed the effectiveness of INO and inhaled prostacyclin (iPGI2) compared to intravenous vasodilators in patients with pulmonary hypertension undergoing cardiac surgery (n=58) for mitral valve replacement. INO and iPGI2 reduced and maintained the mean pulmonary artery pressure and PVR compared to baseline. These findings were not demonstrated by the control group. Although INO was effective, the authors stated that iPGI2 has a “number of advantages over INO” including the fact that neither iPGI2 nor its metabolites have any toxic effects.

Chronic Lung Disease (CLD): CLD or bronchopulmonary dysplasia (BPD) is defined as the “continuing need in preterm infants for supplemental inspired oxygen at 36 weeks postconceptional age” (Clark, et al., 2000). Causes of CLD include low birth weight, inflammation, mechanical distortion of the lung, and oxidative injury. INO is proposed as a treatment option due to its anti-inflammatory effect and its ability to reduce neutrophil accumulation, improve ventilation-perfusion matching, and reduce pulmonary hypertension. There is insufficient evidence to support INO for the treatment of CLD or BPD (Ichinose, et al., 2009; Marks and Schreiber; 2008; Truog, 2005; Clark, et al., 2000).

Kinsella et al. (2014) conducted a multicenter, randomized controlled trial (n=124) to assess the safety and efficacy of INO (10 ppm) vs. placebo gas for the treatment of BPD in premature infants who required noninvasive

supplemental oxygen within the first 72 hours after birth. The authors wanted to determine if the use of early, noninvasive INO (nasal CPAP or nasal cannula) would reduce the need for intubation, mechanical ventilation and the risk for BPD. Prior to randomization, the newborns were stratified into three different birth weight groups (500-749 g, 750-999 g, 1000-1250 g) until 30 weeks postmenstrual age. There were no differences between the INO vs. placebo in any group re the incidence of death (p=1.0), BPD (p=0.86), death/BPD (n=0.85), the need for mechanical ventilation (p=0.89), duration of ventilation (p=0.27) or safety outcomes including severe intracranial hemorrhage) (p=0.68), necrotizing enterocolitis (p=0.23), and retinopathy of prematurity requiring treatment (p=1.00). The clinical course was not altered with the use of INO in any group nor between groups.

Mercier et al. (2010) conducted the European Union Nitric Oxide (EUNO) multicenter (n=36) randomized controlled trial to investigate the potential of INO (n=399) compared to placebo (n=401) in reducing the incidence of bronchopulmonary dysplasia (BPD) in preterm infants. Inclusion criteria included: gestation age at birth of 24–28 weeks plus six days (inclusive), a weight of at least 500 grams and required surfactant or continuous positive airway pressure within 24 hours of birth. The primary endpoint was survival without BPD at 36 weeks postmenstrual age. Secondary endpoints included survival without substantial brain injury (i.e., grade 3 or 4 intraventricular hemorrhage; periventricular hemorrhage or periventricular leukomalacia as seen on ultrasound of the head). Mean duration of therapy was 16.3 ± 3.5 days in the INO group and 16.4 ± 6.5 days in the placebo group. There were no statistically significant differences between the two groups in the primary or secondary outcomes at days seven, 14 and 21. There were no significant differences in adverse events. INO as a preventative strategy in this patient population was unsuccessful.

Durrmeyer et al. (2013) conducted a follow-up of the above European Union Nitric Oxide (EUNO) randomized controlled trial (Mercier, et al., 2010) to evaluate neurodevelopmental outcomes at age two years (n=514). A total of 244 out of 363 INO treated infants and 270 of 374 placebo-treated infants were alive for assessment. The study groups included preterm infants born at 14–28 weeks' gestation with moderate respiratory failure who receive 5 ppms of INO or placebo for 7 to 21 days. There was no significant difference in the mean (SD) cognitive composite scores (Bayley Scales of Infant and Toddler Development, third edition) between the two groups (p=0.11). There were no significant differences in the frequency of cerebral palsy (p=0.89), seizure disorders (p=0.47), hearing impairment (p=0.45), vision deficits (p=0.09), hospitalizations in past year (p=1.0), home oxygen therapy (p=0.10), or growth (weight, length, head circumference; p=0.61, .086, 0.16, respectively) between the groups. At the two year-follow-up, INO started 24 hours after birth for a median of 20 days did not affect neurodevelopmental or other health outcomes for this preterm infant population.

Greenough et al. (2020) conducted a seven year follow-up of the above European Union Nitric Oxide (EUNO) randomized controlled trial (Mercier, et al., 2010) with the aim to determine the long-term effects of iNO. A seven-year follow-up was undertaken of infants entered into the multicenter, double-blind, randomized, placebo-controlled trial of iNO for prevention of BPD in premature infants born between 24 and 28 weeks plus six days of gestation. At seven years, survival and hospital admissions since the two-year follow-up, home oxygen therapy in the past year, therapies used in the previous month and growth assessments were determined. Questionnaires were used to compare general health, well-being, and quality of life. A total of 305 children were assessed. No deaths were reported. Rates of hospitalization for respiratory problems (6.6 vs. 10.5%, iNO and placebo group, respectively) and use of respiratory medications (6.6 vs. 9.2%) were similar. Two patients who received iNO and one who received placebo had received home oxygen therapy. There were no significant differences in any questionnaire-documented health outcomes. The authors concluded that iNO for prevention of BPD in very premature infants with respiratory distress did not result in long-term benefits or adverse long-term sequelae and that in the light of current evidence, routine use of iNO cannot be recommended for prevention of BPD in preterm infants.

Schreiber et al. (2003) conducted a randomized controlled trial (n=207) to determine if INO would decrease the incidence of CLD and death in infants less than 34 weeks gestation with respiratory distress syndrome who were treated with mechanical ventilation. Gestational age in the INO group was 27.4 ± 2.5 weeks with a birth weight of 1017 ± 369 g and 27.0 ± 2.8 weeks in the control group with a birth weight of 949 ± 387. Infants in the INO group were treated with 10 ppm on day 1, followed by 5 ppm for six days. In addition, infants in each group were randomized to receive intermittent mandatory or high-frequency oscillatory ventilation. In the INO group, 51 infants had CLD or died (48.6%) compared to 65 infants (63.7%) in the placebo group. There were no significant differences between the groups in the overall incidence of intraventricular hemorrhage and periventricular

leukomalacia, but the incidence was less severe in the INO group. Analysis of the data according to the mode of ventilation showed a significant decrease in the risk of chronic lung disease and death in the INO group and intermittent mandatory ventilation. However, the authors noted that because the study did not have sufficient power to detect a significant interaction, conclusions could not be drawn regarding the question of whether the benefit of inhaled nitric oxide is restricted to infants receiving intermittent mandatory ventilation. The beneficial effect of INO on CLD or death and long-term neurologic outcomes may have been amplified by the high rate of CLD in the control group (63.7%) and more mature neonates in the INO group.

Heart and Lung Transplantation (Adults): INO has been proposed for use in heart and lung transplantations in adult patients but there is insufficient evidence to support its efficacy. In a randomized controlled trial (n=20), Botha et al. (2007) evaluated the ability of INO to reduce neutrophil infiltration and primary graft dysfunction when administered from the onset of ventilation following lung transplantation. The outcomes demonstrated no significant effect following INO therapy. Perrin et al. (2006) conducted a randomized controlled trial to determine if INO would be effective in the treatment of pulmonary edema following lung transplantation (n=30) and concluded that INO had no effect on this population.

In addition to conducting a cost analysis, George et al. (2006) conducted a prospective review of 376 adult patients with pulmonary and right ventricular failure who were undergoing orthotopic heart transplantation (OHT) (n=67), orthotopic lung transplantation (OLT) (n=45), cardiac surgery (105), ventricular assist device (VAD) placement (n=66), and patients who experienced hypoxemia in other surgeries (n=34) and some medical patients (n=59) who received INO. The overall mortality was highest among medical patients and lowest after OHT and OLT. Although mortality in the VAD group was not significantly different than the cardiac surgery group, only five of the 66 cardiac patients required VAD. INO may have allowed avoidance of VAD. However, additional studies are needed to validate the outcomes of this study.

Liver Transplantation (Adults): Lang et al. (2014) conducted a two-center randomized controlled trial to assess the effectiveness of INO vs. placebo for enhancing allograft function in the immediate post-operative period and reducing longer term complications in 40 liver transplant patients. Subjects were excluded if age was less than 19 years, diagnosed with hepatopulmonary syndrome and/or allograft was being used for split liver transplantation. Patients were randomly assigned to receive 80 ppm of INO or placebo (nitrogen) which was administered until one hour post-reperfusion. Favorable changes in aminotransferase (AST) were significantly different in the INO vs. placebo group, with no treatment effect being noted for alanine transaminase (ALT), aspartate alkaline phosphatase (AP) or bilirubin. Significantly reduced complications were reported in the INO group at nine months (p=0.0062). INO also increased the concentrations of nitrate (p=0.001), nitrite (p=0.001) and nitrosylhemoglobin (p=0.001). Significant increases in liver injury occurred post-reperfusion in both groups. There were no significant differences between the groups in intensive care and hospital length of stay, or post-operative hepatobiliary complications within the first nine months post-transplantation. There were no reported adverse events due to INO administration. Limitations of the study included the small patient population and reported significant differences in patient and surgery demographics between the two centers. The authors noted that definitive conclusions regarding the use of INO as a preemptive strategy to reduce ischemia-reperfusion injury (IRI) in liver transplantation were not possible based on this study.

Left Ventricular Assist Device (LVAD): INO has been proposed to be of benefit in the intraoperative management of patients in the setting of right ventricular dysfunction after LVAD insertion. However, data supporting favorable clinical outcomes are lacking. Potapov et al. (2011) conducted a multicenter (n=8) randomized controlled trial (n=150) to study the safety and efficacy of INO on post-operative outcomes following placement of a left ventricular assist device (LVAD). Patients received either 40 ppm INO (n=73) or nitrogen placebo (n=77) initiated at least five minutes prior to the first weaning attempt from cardiopulmonary bypass (CPB), and therapy was continued until the patient was extubated, reached a study end point, or was treated for 48 hours. For ethical reasons, patients had the option to cross over to open-label INO immediately if they failed to wean at least once from CPB due to hemodynamic failure, still required pulmonary vasodilator support at 48 hours, or met predefined right ventricular dysfunction (RVD) criteria. Four INO patients and nine placebo patients did not undergo treatment and 15 INO patients and 20 placebo patients crossed over to open-label INO. Eighteen patients crossed over before RVD criteria were met. Although there was a trend for better outcomes in the INO group, there were no significant differences in the INO- and placebo-treated patients who met RVD criteria (p=0.330), spent time on mechanical ventilation (p=0.077), or required a right ventricular assist device

(RVAD) (p=0.468). There were also no significant differences in the intensive care unit length of stay, hospital length of stay, 28-day mortality rates and adverse events. INO did not improve outcomes in this patient population.

Kukucka et al. (2011) conducted a randomized controlled trial to evaluate the acute effect of LVAD on right ventricular geometry and function and pulmonary circulation, as well as the effects of INO (n=24) compared to placebo (n=23). The study included elective patients without acute decompensation for chronic heart failure but with preoperative increased pulmonary vascular resistance. Following LVAD implantation, a significant decrease was seen in pulmonary capillary wedge pressure ($p<0.01$) and mean pulmonary artery pressure ($p<0.01$) in both groups with no significant difference between the INO and placebo groups. Significant improvements were also seen on transesophageal echocardiography of right ventricular geometry and function in both groups, but with no significant difference between the groups. Three INO patients and one placebo patient developed right ventricular failure due to different clinical problems. INO added no measurable effect on right ventricular geometry and function.

Acute Pulmonary Embolism (PE): Acute PE is typically a complication secondary to migration of a deep venous clot or thrombi to the lungs and is associated with considerable morbidity and mortality. Because treatment options are limited, INO has been proposed as a therapeutic option for these patients (Bhat, et al., 2015).

Kline et al. (2019) conducted a randomized, placebo-controlled, double blind trial test the hypothesis that adjunctive inhaled NO would improve right ventricular (RV) function and viability in acute PE. Eligible patients had acute PE without systemic arterial hypotension but had RV dysfunction and a treatment plan of standard anticoagulation. Subjects received either oxygen plus 50 parts per million nitrogen (placebo) or oxygen plus 50 ppm NO for 24 h. The primary composite endpoint required a normal RV on echocardiography and a plasma troponin T concentration <14 pg/mL. The secondary endpoint required a blood brain natriuretic peptide concentration <90 pg/mL and a Borg dyspnea score ≤ 2. The sample size of N = 76 tested if 30% more patients treated with NO would achieve the primary endpoint with 80% power and alpha = 5%. Seventy-eight patients were randomized and after two withdrawals, 38 were treated per protocol in each group. At 24 h, 5/38 (13%) of patients treated with placebo and 9/38 (24%) of patients treated with NO reached the primary endpoint (P = 0.375). The secondary endpoint was reached in 34% with placebo and 13% of the NO (P = 0.11). In a pre-planned post-hoc analysis, it was noted how many patients with RV hypokinesis or dilation at enrollment resolved these abnormalities; 29% more patients treated with NO resolved both abnormalities at 24 h (P = 0.010, Cochrane's Q test). the authors concluded that compared with placebo, 24 hours of nasally inhaled NO did not increase the proportion of patients with intermediate-high risk PE who normalized their RV function, circulating troponin T or BNP concentrations after 24 hours of treatment and the secondary analysis suggests that inhaled NO may increase likelihood of resolving echocardiographically-observed RV hypokinesis and dilation.

Bhat et al. (2015) conducted a systematic review of the literature and reported that no large randomized controlled trials comparing INO to placebo for the treatment of PE have been reported. Studies are primarily in the form of case reports and case series with small patient populations (n=8). There is insufficient evidence to support INO for the treatment of PE.

Sickle Cell Disease: INO has been proposed for the treatment of acute chest syndrome and pain associated with vaso-occlusive crisis in patients with sickle cell disease. However, favorable clinical outcomes have not been reported in the peer-reviewed scientific literature.

Abboursheid et al. (2019) conducted a Cochrane review to capture the available body of evidence evaluating the efficacy and safety of the use of inhaled nitric oxide in treating pain crises in people with sickle cell disease. The selection criteria included randomized and quasi-randomized trials comparing inhaled nitric oxide with placebo, or standardized way of treatment of pain crises in people with sickle cell disease. The review included studies (188 participants) that compared inhaled nitric oxygen (80 ppm) to placebo (room air) for four hours; one trial continued administering nitric oxide (40 ppm) for a further four hours. This extended trial had an overall low risk of bias; however, in the remaining two trials we had concerns about the risk of bias from the small sample size and additionally a high risk of bias due to financial conflicts of interest in one of these smaller trials. The time to pain resolution was only reported in one trial (150 participants), showing there may be little or no difference

between the two groups: with inhaled nitric oxide median 73.0 hours (95% confidence interval (CI) 46.0 to 91.0) and with placebo median 65.5 hours (95% CI 48.1 to 84.0) (low-quality evidence). No trial reported on the duration of the initial pain crisis. Only one large trial reported on the frequency of pain crises in the follow-up period and found there may be little or no difference between the inhaled nitric oxide and placebo groups for a return to the ED, risk ratio 0.73 (95% CI 0.31 to 1.71) or for re-hospitalization, risk ratio 0.53 (95% CI 0.25 to 1.11) (150 participants; low-quality evidence).There may be little or no difference between treatment and placebo in terms of reduction in pain score at any time point up to eight hours (150 participants). The two smaller trials reported a beneficial effect of inhaled nitric oxide in reducing the visual analogue pain score after four hours of the intervention, but these trials were small and limited compared to the first trial. The authors concluded that the currently available trials do not provide sufficient evidence to determine the effects of using inhaled nitric oxide to treat pain (vaso-occlusive) crises in people with sickle cell disease and that large-scale, long-term trials are needed to provide more robust data in this area.

Gladwin et al. (2011) conducted a prospective, multicenter (n=11), double-blind, randomized controlled trial to compare the outcomes of INO (n=75) to inhaled nitrogen placebo (n=75) for the treatment of vaso-occlusive crisis (VOC) due to sickle cell disease. Time to VOC resolution, the primary outcome, was not significantly different (p=0.87) in the study group compared to the placebo group. There were also no statistically significant differences in median length of hospital stay (p=0.30), mean visual analog scale (VAS) pain scores at 24 hours (p=0.90), decrease in mean VAS scores over 2-hour intervals during the first eight hours of treatment (p=0.90), median total opioid use (p=0.73), or acute chest syndrome requiring transfusion (p=0.79). Although not statistically significant, the number of rehospitalizations within thirty days was higher in the placebo group. INO recipients had significantly higher nitrate levels in plasma (p=0.03) and levels of methemoglobin in the venous blood compared to placebo (p=0.001), but the levels were not toxic. INO did not improve time to crisis resolution.

Professional Societies/Organizations
American Academy of Pediatrics (AAP): In the 2014 clinical report on the use of inhaled nitric oxide in preterm infants, AAP stated that based on randomized controlled trials, traditional meta-analyses, and an individualized patient data meta-analysis study, neither rescue nor routine use of INO improves survival in preterm infants with respiratory failure. The AAP also stated that the evidence does not support INO for the purpose of preventing or improving bronchopulmonary dysplasia (BPD), severe intraventricular hemorrhage, or other neonatal morbidities. The results of the one study that suggested that 20 ppm of INO beginning in the second postnatal week may provide a small reduction in the rate of BPD needs to be confirmed by other trials. AAP concluded that the data is limited and inconsistent regarding the effects of INO on pulmonary outcomes in preterm infants in early childhood.

The AAP Committee on Fetus and Newborn (2000; reaffirmed 2010) recommendations for INO for the treatment of neonates born at or near term with hypoxic respiratory failure included the following:

- Infants with progressive hypoxic respiratory failure should be cared for in centers with the expertise and experience to provide multiple modes of ventilatory support and rescue therapies or be transferred in a timely manner to such an institution.
- INO therapy should be given using the indications, dosing, administration, and monitoring guidelines outlined on the product label. An echocardiogram to rule out congenital heart disease is recommended. Center-specific criteria for treatment failure should be developed to facilitate timely consideration of alternative therapies.
- INO therapy should be directed by physicians qualified by education and experience in its use and offered only at centers that are qualified to provide multisystem support, generally including on-site ECMO capability.
- Generally, INO should be initiated in centers with ECMO capability. If INO is offered by a center without ECMO capability, for geographic or other compelling reasons, mutually acceptable treatment failure criteria and mechanisms for timely transfer of infants to a collaborating ECMO center should be established prospectively. Transfer must be accomplished without interruption of INO therapy.
- Centers that provide INO therapy should provide comprehensive long-term medical and neurodevelopmental follow-up.
- Centers that provide INO therapy should establish prospective data collection for treatment time course, toxic effects, treatment failure, use of alternative therapies, and outcomes.

- Administration of INO for indications other than those approved by the FDA or in other neonatal populations, including compassionate use, remains experimental. As such, INO should be administered according to a formal protocol that has been approved by the FDA and the institutional review board and with informed parental consent.

American Association for Respiratory Care (AACR): Based on a systematic review of the literature, the AACR (2010) published evidence-based clinical practice guidelines for INO for neonates with acute hypoxic respiratory failure. The recommendations included:

1. "A trial of INO is recommended in newborns (≥ 34 wk gestation, < 14 d [days] of age) with P_{aO2} < 100 mm Hg [millimeters of mercury] on F_{IO2} 1.0 and/or an oxygenation index (OI) > 25.
2. It is recommended that INO therapy be instituted early in the disease course, which potentially reduces the length of mechanical ventilation, oxygen requirement, and stay within the intensive care unit.
3. It is recommended that INO should not be used routinely in newborns with congenital diaphragmatic hernia.
4. It is suggested that INO therapy should not be used routinely in newborns with cardiac anomalies dependent on right-to-left shunts, congestive heart failure, and those with lethal congenital anomalies.
5. It is suggested that there are insufficient data to support the routine use of INO therapy in postoperative management of hypoxic term or near-term infants with congenital heart disease.
6. The recommended starting dose for INO is 20 ppm [parts per million].
7. It is recommended that response to a short trial (30–60 min) of INO should be judged by an improvement in P_{aO2} or oxygenation index (OI); if there is no response, INO should be discontinued.
8. For the newborn with parenchymal lung disease, it is recommended that optimal alveolar recruitment be established prior to initiation of INO therapy.
9. For newborns with a response to INO therapy, it is recommended that the dose should be weaned to the lowest dose that maintains that response.
10. It is recommended that INO should not be discontinued until there is an appreciable clinical improvement; that the INO dose should be weaned to 1 ppm before an attempt is made to discontinue; and that the F_{IO2} should be increased prior to discontinuation of INO therapy.
11. It is recommended that FDA-approved INO delivery systems should be used to assure consistent and safe gas delivery during therapy.
12. During conventional mechanical ventilation, it is suggested that the INO gas injector module should be placed on the dry side of the humidifier.
13. During conventional ventilation, it is suggested that the sampling port be placed in the inspiratory limb of the ventilator, downstream from the site of injection, no greater than 15 cm [centimeters] proximal the patient connection/interface.
14. It is suggested that the F_{IO2} be measured downstream from the injection of INO into the circuit.
15. It is suggested that the patient/ventilator system be continuously monitored for changes in ventilation parameters, with adjustments to maintain desired settings during INO therapy (Grade 2C).
16. It is suggested that the lowest effective doses of INO and O2 be used, to avoid excessive exposure to NO, NO2, and methemoglobinemia.
17. It is suggested that the INO delivery system be properly purged before use to minimize inadvertent exposure to NO2.
18. It is suggested that the high NO2 alarm be set at 2 ppm on the delivery system to prevent toxic gas exposure to the lungs.
19. It is suggested that methemoglobin be monitored approximately 8 hours and 24 hours after therapy initiation and daily thereafter.
20. It is suggested that the INO dose be weaned or discontinued if methemoglobin rises above 5%.
21. It is suggested that continuous pulse oximetry and hemodynamic monitoring be used to assess patient response to INO therapy.
22. It is suggested that scavenging of exhaled and unused gases during INO therapy is not necessary".

American College of Chest Physicians (ACCP): In their evidence-based practice guidelines for the treatment of pulmonary arterial hypertension, ACCP (2007) stated that patients with idiopathic pulmonary hypertension should undergo acute vasoreactivity testing using a short-acting agent such as IV epoprostenol, adenosine or inhaled nitric oxide. In the assessment of symptomatic pulmonary arterial hypertension, AACP noted that a

positive acute vasodilator response is defined as a fall in mean PAP ≥ 10 mm Hg to ≤ 40 mm Hg, with an unchanged or increased cardiac output when challenged with inhaled nitric oxide, IV epoprostenol, or IV adenosine.

American College of Critical Care Medicine (ACCCM): In the 2017 update of ACCCM Clinical Practice Parameters for Hemodynamic Support of Pediatric and Neonatal Septic Shock (Davis, et al., 2017) discussed the treatment of PPHN in the newborn. ACCCM stated, "Hyperoxygenate initially with 100% oxygen and institute metabolic alkalinization (up to pH 7.50) with NaHCO3 or tromethamine unless and until inhaled NO is available. Mild hyperventilation to produce a respiratory alkalosis can also be instituted until 100% oxygen saturation and less than 5% difference in preductal and postductal saturations are obtained. Inhaled nitric oxide should be administered as the first treatment when available."

American Heart Association (AHA) and American Thoracic Society (ATS): AHA and ATS (Abman, et al., 2015) established a working group of clinicians and clinician-scientists in an effort to define a comprehensive set of clinical care guidelines, based on a systematic review of the literature and expert opinion, for the treatment of pulmonary hypertension (PH) in children. PH in children is defined as a resting mean pulmonary artery pressure (mPAP) >25 mm Hg beyond the first few months of life. The Society noted that there is a lack of extensive clinical research in children and a significant paucity of multicenter, randomized controlled trials. The recommendations in the guidelines are scored based on the American College of Cardiology Foundation/AHA Clinical Practice Guideline Methodology Summit Report. The ratings include four classes and four levels of evidence. The Class of Recommendation is an estimate of the magnitude of the treatment effect, with consideration given to risks versus benefits, and the evidence and agreement that a given treatment or procedure is or is not useful or effective. The Level of Evidence is an estimate of the certainty or precision of the treatment effect.

Classes of the recommendations include:

- Class I: Benefit >>> risk; procedure/treatment should be performed/administered
- Class IIa: Benefit >> risk; additional studies with focused objectives needed. It is reasonable to perform procedure/administer treatment.
- Class IIb: Benefit ≥ risk; additional studies with broad objectives needed; additional registry data would be helpful. Procedure/treatment may be considered
- Class III: No benefit: procedure/test, not helpful; treatment of no proven benefit OR
- Class III: Harm: procedure/test, excess cost, without benefit or harmful; treatment harmful to patients

The weight of evidence supporting each recommendation is classified as follows:

- Level A: Multiple populations evaluated. Data derived from multiple randomized clinical trials or meta-analyses
- Level B: Limited populations evaluated. Data derived from a single randomized trial or nonrandomized studies
- Level C: Very limited populations evaluated. Only consensus opinion of experts, case studies, or standard of care

The authors noted that that many more conditions are associated with PH in children than in adults, casting some doubt about the direct applicability of the adult classification system and treatment guidelines to children. Therapeutic strategies for adult pulmonary artery hypertension (PAH) have not been sufficiently studied in children to allow definition of potential toxicities or optimal dosing. Moreover, clinical research in pediatric PH suffers from a lack of age appropriate clinical end points.

The guidelines include the following recommendations regarding the use of INO:

- Persistent pulmonary hypertension (PH) in infants
  - Inhaled nitric oxide (iNO) is indicated to reduce the need for extracorporeal membrane oxygenation (ECMO) support in term and near-term infants with persistent pulmonary hypertension (PPHN) of the newborn or hypoxemic respiratory failure who have an oxygenation index that exceeds 25 (Class I; Level of Evidence A)

- iNO can be beneficial for preterm infants with severe hypoxemia that is due primarily to PPHN physiology rather than parenchymal lung disease, particularly if associated with prolonged rupture of membranes and oligohydramnios (Class IIa; Level of Evidence B).
- Congenital diaphragmatic hernia (CDH) in infants
  - iNO therapy can be used to improve oxygenation in infants with CDH and severe PH but should be used cautiously in subjects with suspected LV dysfunction (Class IIa; Level of Evidence B). In the discussion of this recommendation, it was noted that iNO may plan an important role in stabilizing patients before ECMO is initiated improving the chances that ECMO cannulation may proceed safely. However, the Societies stated that overall, there was consensus that iNO should not be used routinely in CDH. Its use should be limited to patients with suprasystemic pulmonary vascular resistance (PVR) with right-to-left shunting across the oval foramen causing critical preductal hypoxemia and after optimal lung inflation and adequate left ventricular (LV) performance are established.
- Bronchopulmonary dysplasia (BPD) in infants
  - Treatment with iNO can be effective for infants with established and symptomatic pulmonary hypertension (PH) (Class IIa; Level of Evidence C). AHA/ATS noted that current therapies used for PH therapy in infants with BPD generally include INO, sildenafil, endothelin receptor antagonist (ERAs), and calcium channel blockers (CCBs). INO causes selective pulmonary vasodilation and improves oxygenation in infants with established BPD. Although, long-term iNO therapy has been used in infants with BPD, efficacy data are not available. INO is not recommended for the prevention of BPD.
- PH crises/acute right ventricular (RV) failure in children
  - In addition to conventional postoperative care, iNO and/or inhaled PGI_2 [inhaled prostacyclin] should be used as the initial therapy for pulmonary hypertensive crisis (PHCs) and failure of the right side of the heart (Class I; Level of Evidence B). According to AHA/ATS, INO has become an accepted standard for the treatment of postoperative PH at low doses to improve ventilation-perfusion matching, decrease intrapulmonary shunt fraction and in some cases, improvement in systemic arterial oxygenation. iNO is commonly used to treat postoperative PH in CHD patients. A retrospective review suggested that iNO may reduce mortality following repair of atrioventricular septal defects.

Global Initiative for Chronic Obstructive Lung Disease (GOLD): The 2020 Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease report includes a discussion regarding the administration of INO in patients with COPD in whom hypoxemia is caused primarily by ventilation-perfusion mismatching rather than by increased intrapulmonary shunt (as in noncardiogenic pulmonary edema). GOLD stated that INO can worsen the gas exchange because of altered hypoxic regulation of ventilation-perfusion balance and is, therefore, contraindicated in stable COPD (GOLD, 2020).

National Institutes of Health (NIH) COVID-19 Treatment Guidelines Panel: this organization published Coronavirus Disease 2019 (COVID-19) Treatment Guidelines (updated 2021). The guidelines include the following recommendations:

For mechanically ventilated adults with COVID-19 and acute respiratory distress syndrome (ARDS):

- The Panel recommends using low tidal volume (VT) ventilation (VT 4–8 mL/kg of predicted body weight) over higher VT ventilation (VT >8 mL/kg) (AI).
- The Panel recommends targeting plateau pressures of <30 cm H_2O (AIIa).
- The Panel recommends using a conservative fluid strategy over a liberal fluid strategy (BIIa).
- The Panel recommends against the routine use of inhaled nitric oxide (AIIa).

The review notes that, “Although there are no published studies of inhaled nitric oxide in patients with COVID-19, a Cochrane review of 13 trials of inhaled nitric oxide [Gebistorf, et al., 2016] use in patients with ARDS found no mortality benefit. Because the review showed a transient benefit in oxygenation, it is reasonable to attempt inhaled nitric oxide as a rescue therapy in COVID patients with severe ARDS after other options have failed. However, if there is no benefit in oxygenation with inhaled nitric oxide, it should be tapered quickly to avoid rebound pulmonary vasoconstriction that may occur with discontinuation after prolonged use.”

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

Use Outside of the United States

European Paediatric Pulmonary Vascular Disease (PVD) Network: The European Paediatric Pulmonary Vascular Disease Network published three consensus statements regarding INO for the treatment of preterm and term neonates, infants and children. These consensus statements were endorsed by the International Society of Heart and Lung Transplantation (ISHLT) and the German Society of Paediatric Cardiology (DGPK). The recommendations were graded according to the European Society of Cardiology and the American Heart Association and included the following levels of evidence and classifications (Hansmann, et al., 2016):

Classes of recommendations (COR):

- Class I: Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective (is recommended/is indicated)
- Class II: Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure
- Class IIa: Weight of evidence/opinion is in favor of usefulness/efficacy (should be considered)
- Class IIb: Usefulness/efficacy is less well established by evidence/opinion (may be considered)
- Class III: Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful (is not recommended)

:

Levels of Evidence (LOE)

- LOE A: Data derived from multiple randomized clinical trials or meta-analyses
- LOE B: Data derived from a single randomized clinical trial or large non-randomized studies
- LOE C: Consensus of opinion of the experts and/or small studies, retrospective studies, registries

The consensus statement on the diagnosis and treatment of pediatric pulmonary hypertension in the intensive care unit stated that INO may be considered for the treatment of postoperative pulmonary hypertension in mechanically ventilated patients to improve oxygenation and reduce the risk of pulmonary hypertension (PHN) crisis (COR IIb; LOE B). The Network stated that INO has less impact on systemic vascular resistance (SVR) and should be considered early, especially if the systemic blood pressure is low. After cardiopulmonary bypass, INO reduces pulmonary vascular resistance (PVR) and may lower the risk of PH crisis and shorten the postoperative course (Kaestner, et al., 2016).

Regarding persistent pulmonary hypertension (PPHN) associated with acute or chronic lung disease in the preterm and term neonate and in the infant, the Network recommended INO for treatment of PPHN in mechanically ventilated newborns to improve oxygenation and to reduce the need for ECMO (a) if PaO2 is less than 100 mm Hg (while receiving 100% oxygen), or (b) if the oxygenation index exceeds 25 (COE Ia; LOE A). The guideline stated that INO is the mainstay of PPHN therapy in most cases. INO reduces the incidence of the combined endpoint death or need for extracorporeal membrane oxygenation (ECMO). Oxygenation improves in approximately 50% of infants receiving INO. A second recommendation stated that the preterm infant with respiratory failure should not receive INO for the prevention of bronchopulmonary dysplasia (BPD) and associated PH if not enrolled in a rigorously conducted randomized clinical trial (COR III; LOE A) (Hilgendorff, et al., 2016).

The third consensus statement (Apitz, et al., 2016) addressed hemodynamic assessment and acute pulmonary vasoreactivity testing in the evaluation of children with pulmonary vascular disease. The recommendations included: 1) vasoreactivity testing should be performed using nitric oxide as the vasodilator (COR I; LOE C) and 2) vasoreactivity testing with the initial combination of nitric oxide and oxygen is reasonable and shortens the acute vasoreactivity testing (COR II a; LOE C). The ideal vasodilatory agent for acute vasoreactivity testing should be (1) selective for the pulmonary circulation (with little effects on ventricular performance and systemic vascular resistance) and 2) short-acting (short biological half-life). INO (20–80 ppm) acts in seconds. However,

careful monitoring is recommended during the weaning of INO, since paradox or rebound pulmonary hypertension has been reported in a few cases.

European Society of Intensive Care Medicine (ESICM): The European expert recommendations from the ESICM and the European Association of Cardiothoracic Anaesthesiologists (Germann, et al., 2005) identified conditions in which it is reasonable to use INO as a rescue treatment in patients with severe acute pulmonary arterial hypertension and/or severe refractory arterial hypoxemia. INO is useful for testing for pulmonary vasoreactivity in patients undergoing heart transplantation or in patients with pulmonary arterial hypertension. According to the recommendations, benefits of INO therapy include the following: 1) in relation to heart failure, "response to iNO treatment may identify patients still suitable for heart or heart/lung transplantation or to help to identify patients with congenital heart disease" and "iNO testing is useful to demonstrate the remaining reactivity of the precapillary component or postcapillary pulmonary hypertension;" 2) in pulmonary arterial hypertension, INO may be useful in revealing the extent of reversibility in selected patients, but there is insufficient data to recommend long-term INO therapy; 3) for perioperative pulmonary hypertension in adult cardiac surgery, "clinical experience suggests that in patients with confirmed acute right ventricular dysfunction and elevated PVR use of iNO may result in hemodynamic improvement when used during or after cardiac surgery;" 4) for left ventricular assist devices (VAD), the panel recommended that INO therapy "is effective in providing favorable pulmonary hemodynamics leading to improved right ventricular and left-sided VAD assisted cardiac output in patients with pulmonary hypertension and inadequate left-sided VAD flow refractory to conventional maneuvers. On the basis of these improved critical physiological variables the expert panel recommended that it is reasonable to consider the use of iNO in this clinical situation among other vasodilator therapies;" 5) regarding ARDS, INO improves oxygenation and hemodynamics acutely, but no benefit is seen beyond 24–72 hours, but it is reasonable to use INO as a "rescue treatment in patients with severe refractory hypoxaemia."

The European recommendations stated that there is insufficient evidence to support the routine use of INO in the management of thromboembolic disease, pulmonary arterial hypertension, sickle cell disease, COPD, one-lung ventilation, and ischemia-reperfusion injury.

European Society of Pediatric and Neonatal Intensive Care (ESPNIC): The consensus guidelines for the use of INO in neonates and children from ESPNIC (Macrae, et al., 2004) stated that INO appeared to improve outcomes in hypoxemic term and near-term infants with the exception of infants with congenital heart disease, and stated that sufficient data is lacking to recommend the routine use of INO in preterm infants. ESPNIC also noted that INO may be justified as rescue therapy in life threatening hypoxemia after lung recruitment has been optimized. As it relates to cardiac disease, the guidelines concluded that there is insufficient evidence to recommend the routine use of prophylactic postoperative INO in congenital heart patients at risk of pulmonary hypertension. There is sufficient evidence "to support a trial of 20 ppm INO for 10 minutes, increasing to 40 ppm if no response to the lower dose, in patients with clinically significant pulmonary hypertension complicating their perioperative course. In this setting it is recommended that iNO should only be continued if there is documented evidence of important hemodynamic improvement. After a 30-minute trial of iNO at 20 ppm, increasing to 40 ppm, consideration should be given to the discontinuing the drug if no clinically significant response has occurred."

European Society of Cardiology (ESC)/European Respiratory Society (ERS): In the 2015 updated guidelines on the diagnosis and management of pulmonary hypertension, the ESC stated that INO is the standard of care for vasoreactivity testing for identification of patients who may be candidates for high-dose calcium channel blocker treatment. According to the guidelines intravenous (IV) epoprostenol, IV adenosine or inhaled iloprost can be used as alternatives to INO. These guidelines are endorsed by the Association for European Pediatric and Congenital Cardiology (AEPC), and the International Society for Heart and Lung Transplantation (ISHLT).

Faculty of Intensive Care Medicine and Intensive Care Society Guideline Development Group (British Thoracic Society supports the recommendations in this guideline): These organizations published guidelines for the management of adult patients with acute respiratory distress syndrome (ARDS). the guidelines note a grade recommendation statement: "We do not suggest using iNO in patients with ARDS". (GRADE recommendation: weakly against) (Griffiths et al., 2019).

Scandinavian Society of Anaesthesiology and Intensive Care Medicine (SSAI): In the 2016 guideline on fluid and drug therapy in adults with ARDS, SSAI made a strong recommendation that INO not be used routinely in the treatment of this condition. This did not preclude the use of INO in adults with an underlying condition or co-existing disease in which INO is indicated, such as severe pulmonary hypertension. The evidence reported that INO had no effect on the risk of death and did have an increased risk of kidney injury, a severe complication in ARDS. Noted as a "weak" recommendation, SSAI "suggested" that INO "may be attempted" as a rescue measure in immediately life-threatening hypoxemia situations that are unresponsive to conventional therapy. The intent would be to temporarily increase oxygenation in patients with catastrophic hypoxemia and imminent risk of death (Claesson, et al., 2016).

Société de Réanimation de Langue Française (SRLF): Guidelines from SRLF for management of acute respiratory distress syndrome (Papazian, et a., 2019) include the recommendation, ".The experts suggest that inhaled nitric oxide can be used in cases of ARDS with deep hypoxemia, despite the implementation of a protective ventilation strategy and prone positioning and before envisaging use of venovenous ECMO." The recommendation is based on expert opinion.

Medicare Coverage Determinations

	Contractor	Policy Name/Number	Revision Effective Date
NCD		No National Coverage Determination found	
LCD		No Local Coverage Determination found	

Note: Please review the current Medicare Policy for the most up-to-date information.

Coding/Billing Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered medically necessary when used in association with the administration of inhaled nitric oxide when criteria in the applicable policy statements listed above are met:

CPT®* Codes	Description
93463	Pharmacologic agent administration (eg, inhaled nitric oxide, intravenous infusion of nitroprusside, dobutamine, milrinone, or other agent) including assessing hemodynamic measurements before, during, after and repeat pharmacologic agent administration, when performed (List separately in addition to code for primary procedure)
94002	Ventilation assist and management, initiation of pressure or volume preset ventilators for assisted or controlled breathing; hospital inpatient/observation, initial day
94003	Ventilation assist and management, initiation of pressure or volume preset ventilators for assisted or controlled breathing; hospital inpatient/observation, each subsequent day

Considered medically necessary when criteria in the applicable policy statements listed above are met:

ICD-10-CM Procedure Codes	Description
3E0F3SD	Introduction of Nitric Oxide Gas into Respiratory Tract, Percutaneous Approach
3E0F7SD	Introduction of Nitric Oxide Gas into Respiratory Tract, Via Natural or Artificial Opening
3E0F8SD	Introduction of Nitric Oxide Gas into Respiratory Tract, Via Natural or Artificial Opening Endoscopic

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