



Kaiser Foundation Health Plan of Washington

Clinical Review Criteria Inhaled Nitric Oxide (iNO) Therapy

NOTICE: Kaiser Foundation Health Plan of Washington and Kaiser Foundation Health Plan of Washington Options, Inc., provide these Clinical Review Criteria for internal use by their members and health care providers. The Clinical Review Criteria only apply to Kaiser Foundation Health Plan of Washington and Kaiser Foundation Health Plan of Washington Options, Inc. Use of the Clinical Review Criteria or any Kaiser Permanente entity name, logo, trade name, trademark, or service mark for marketing or publicity purposes, including on any website, or in any press release or promotional material, is strictly prohibited.

Kaiser Permanente Clinical Review Criteria are developed to assist in administering plan benefits. These criteria neither offer medical advice nor guarantee coverage. Kaiser Permanente reserves the exclusive right to modify, revoke, suspend or change any or all of these Review Criteria, at Kaiser Permanente's sole discretion, at any time, with or without notice. **Member contracts differ in their benefits. Always consult the patient's Medical Coverage Agreement or call Kaiser Permanente Customer Service to determine coverage for a specific medical service.**

Criteria

For Non-Medicare Members

- A. Treatment of pulmonary hypertension (PHN) to reduce risk of chronic lung disease, and respiratory failure in infants born or at near term (>34 weeks)
 1. Neonate does not have congenital diaphragmatic hernia, and
 2. Conventional therapies such as administration of high concentrations of oxygen, hyperventilation, high-frequency ventilation, the induction of alkalosis, neuromuscular blockade, and sedation have failed or are expected to fail.
 3. Treatment of Congenital Diaphragmatic Hernia (CDH)
 - a. iNO is required to stabilize a patient during transition to ECMO (Usually required for a few hours before)
 - b. iNO is required during transition off of ECMO when pulmonary arterial pressures are high (this can be a period of time ranging from hours to several days)
- B. Treatment of pulmonary hypertension in pre-term newborns (\leq 34 weeks)

There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies and/or provides better long-term outcomes than current standard services/therapies.
- C. Treatment of acute respiratory distress syndrome (ARDS) in adults and children

There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies and/or provides better long-term outcomes than current standard services/therapies.
- D. Treatment of Cyanotic Congenital Heart Disease with pulmonary hypertensive crisis (all pediatric patients)
 1. The patient is being managed for acute pulmonary hypertension crisis and acute right heart failure with a predisposition to unrestricted over-circulation. OR
 2. The patient requires a surgical intervention with increased risk of pulmonary hypertension crisis and is receiving pulmonary vascular therapy AND
 - a. Typical course of treatment 3 days (this may be longer on a case by case basis) to transition to oral medications and wean-off iNO OR
 - b. The patient needs transplant for right heart failure and requires iNO for 1 week to several months.

The following information was used in the development of this document and is provided as background only. It is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Treatment of persistent pulmonary hypertension (PPHN) and respiratory failure in infants born or at near term.

Persistent pulmonary hypertension of the newborn (PPHN) is an important cause of cardiorespiratory failure in the near-term neonate (>34 weeks). It occurs when normal cardiopulmonary transition fails to take place after birth; the newborn's arteries to the lungs remain constricted limiting the amount of blood flow to the lungs and therefore

the amount of oxygen into the blood stream. PPHN can occur either as a primary condition of neonatal maladaptation or secondary to other conditions such as pneumonia, sepsis, hyaline membrane disease, meconium aspiration, congenital diaphragmatic hernia, or pulmonary hyperplasia. Causes of PPHN may be variable, but all lead to same physiologic changes; a persistently raised pulmonary vascular resistance that leads to severe hypoxemia due to extra pulmonary shunting. Even with appropriate therapy, the mortality for PPHN remains between 5 and 10% (Gonzales 2009, Finer 2009, Steinhorn 2010).

The goal of therapy of PPHN is to maximize the amount of oxygen transported to the lungs and in turn to the systemic circulation. Conventional therapies include supplemental oxygen with often requires intubation and mechanical ventilation, induction of alkalosis, paralysis, sedation, as well as maintenance of temperature, electrolytes, glucose, and intravascular volume. Infants who fail conventional therapies may require treatment with extracorporeal membrane oxygenation (ECMO). During ECMO, the jugular vein and/or carotid artery is surgically bisected and connected to a heart-lung machine with a cannula to oxygenate the infant's blood. ECMO therapy can be life-saving, but is highly invasive, labor intensive, and has potential side-effects such as intracranial hemorrhage and ligation of the right common carotid artery (Steinhorn 2010).

Inhaled nitric oxide (iNO) has been investigated for the treatment of PPHN to improve oxidation, reduce the need for ECMO, and decrease mortality. Nitric oxide is a colorless, almost odorless gas that is naturally produced by various human tissues and is involved in several physiologic functions. It is a rapid and potent vasodilator, and because of its small gas molecule, it can be delivered as inhalation therapy to airspaces in close proximity to the pulmonary vascular bed. Once in the blood stream NO binds to hemoglobin and is rapidly inactivated with an estimated half-life of 3-5 seconds. The effect of iNO is limited to the lungs making it a selective pulmonary vasodilator without adverse systemic hemodynamic effect (DiBlasi 2010, Steinhorn 2010).

iNO therapy is not without harmful side effects. When oxygen and nitric oxide mix together, they chemically react to form nitrogen dioxide (NO₂), which is toxic to the lungs. Nitrogen dioxide concentrations greater than 10 parts per million (ppm) have been known to induce pulmonary edema, alveolar hemorrhage, changes in the surface tension properties of surfactant, and death. NO₂ is dose- dependent and its concentrations should be maintained below 3 ppm by decreasing the iNO concentration if its level increases. Methemoglobinemia (MetHb), which impairs the ability of the hemoglobin molecule to bind with oxygen, is another harmful side effect of iNO therapy. MetHb is dose-dependent and its levels must be carefully monitored. Significant methemoglobinemia has been reported after accidental overdose of iNO, and a level >10% may cause cyanosis, headaches, muscle weakness, and tissue hypoxia. Laboratory and clinical studies have suggested that high doses of inhaled nitric oxide may increase the risk of bleeding, which is a serious concern because of the predisposition of premature newborns to intracranial hemorrhage (Kinsella 2006, Finer 2009, Henry 2012).

The recommended initial dose of iNO is 20 ppm, and the duration of its use is normally less than 5 days but may be maintained for up to 14 days, or until the underlying oxygen desaturation has been resolved. Abrupt discontinuation of the therapy can lead to worsening of PaO₂ and increasing pulmonary artery pressure. The use of iNO was approved by the Food and Drug Administration (FDA) in 1999 for the treatment of term and near-term neonates (>34 weeks) with hypoxic respiratory failure with clinical or echocardiographic evidence of pulmonary hypertension. Using iNO for other medical conditions is considered "off label" usage.

iNO therapy is provided through a delivery system used in conjunction with a ventilator or other breathing gas administration system. Nitric oxide delivery system consists of a nitric oxide administration apparatus, a nitric oxide gas analyzer, and a nitrogen dioxide gas analyzer. INOmax® (INO Therapeutics Inc., Clinton NJ) is a commercially available brand of iNO that received initial Food and Drug Administration approval in 1999 to be used as a vasodilator in conjunction with ventilatory support and other appropriate agents. In 2009, the FDA updated the INOmax safety labeling indicating that in patients with pre-existing left ventricular dysfunction, iNO may increase pulmonary capillary wedge pressure leading to pulmonary edema, even when used for a short time (FDA webpage accessed July 20, 2012).

Treatment of pulmonary hypertension in pre-term newborns

Approximately 8-13% of all babies are born preterm (<37 weeks of gestation) across developed countries. Although survival rates have improved markedly in recent decades, preterm delivery still accounts for more than 75% of all perinatal complications and death. It is estimated that three fourths of preterm infants with birth weight <1000g develop respiratory distress syndrome (RDS), and 30- 40% are still oxygen dependent at a postmenstrual age (gestational age plus chronological age) of 36 weeks. Breathing failure in premature newborns may be complicated by raised pressure within the vessels that carry blood to the lungs (pulmonary hypertension). Those who require assisted ventilation are at high risk of developing long-term medical and neurocognitive impairment including bronchopulmonary dysplasia (BPD), which is characterized by arrested lung growth, reduced

alveolarisation, and dysmorphic vasculature (i.e. the infants' lungs are not fully formed or are not able to make enough surfactant, which is a liquid that coats the inside of the lungs and helps keep them open so an infant can breathe in air once he or she is born). Without surfactant, the lungs collapse and the infant may not be able to breathe in enough oxygen to support the body's organs. This may lead to neurodevelopmental impairment and damage to other organs (Barrington 2006, Askie 2010, 2011).

Conventional therapy of respiratory failure complicated by pulmonary hypertension in preterm newborn involves respiratory support, which includes assisted ventilation and continued distending pressure, the administration of surfactant, and sedation or muscle relaxation if needed.

iNO has been investigated as a treatment to prevent lung injury in preterm infants based on the findings from experimental studies performed on a variety of fetal animals and/ or premature animal models with hyaline membrane disease and elevated pulmonary artery pressure. These experiments showed that iNO therapy may enhance pulmonary angiogenesis and lung alveolarisation, reduce the pulmonary vascular resistance and improve oxygenation. Studies in full-term infants also showed that iNO may cause selective pulmonary vasodilatation reduce pulmonary artery pressure and improve ventilation /perfusion mismatch. However, the results of studies conducted among term or near-term infants cannot be extrapolated to the preterm babies because of the difference in pathophysiology of respiratory failure, and the difference in the potential risks of iNO in preterm infants. If iNO therapy leads to a decrease in required ventilation support, it may also lead to a reduction in lung injury and bronchopulmonary dysplasia. However, it is still uncertain which subpopulation of premature infants may profit most from iNO. There is also opposing data on whether exogenous NO is protective or destructive in the presence of hyperoxia. Inhaled nitric oxide has pro-oxidation and antioxidants activities and can potentially worsen lung injury. Preterm infants are also at higher risk of developing intracranial hemorrhage, and there is a concern about the effect of iNO in increasing the bleeding time (Barrington 2006, Love 2012).

Inhaled nitric oxide is provided through a delivery system used in conjunction with a ventilator or other breathing gas administration system. iNO delivery system consists of a nitric oxide administration apparatus, a nitric oxide gas analyzer, and a nitrogen dioxide gas analyzer. INOmax® (INO Therapeutics Inc., Clinton NJ) is a commercially available brand of iNO that received initial Food and Drug Administration approval in 1999 to be used as a vasodilator in conjunction with ventilatory support and other appropriate agents for the treatment of term and near-term (>34 weeks gestation) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension. The use of iNO for other neonatal medical conditions is considered "off label" use.

Treatment of acute respiratory distress syndrome (ARDS) in adults and children

Acute respiratory distress syndrome (ARDS) is a major source of morbidity and mortality, with a case fatality rate exceeding 30%. ARDS is defined by acute non-cardiogenic pulmonary edema, acute severe hypoxemia irrespective of positive end expiratory pressure, bilateral infiltrates on chest radiography, and a pulmonary artery occlusion pressure ≤ 18 in any adult or child more than one month old. Acute lung injury (ALI) is a milder form of the syndrome and both conditions are often referred to as acute hypoxemic respiratory failure (AHRF). They are characterized by an inflammatory process of the alveolar-capillary membrane that may result from a primary lung disease or is secondary to a number of systemic diseases. AHRF results in intrapulmonary shunting with hypoxemia and pulmonary hypertension. Hypoxemia in ARDS is mainly caused by ventilation perfusion mismatch leading to increased pulmonary shunting due to pulmonary vasodilatation in non-ventilated lung regions and vasoconstriction in ventilated areas (Milberg 1995, Afshari 2011, 2012).

Treatment of ARDS/ALI is mainly supportive and aims at improving gas exchange, control of infection, and preventing complications. The optimal therapy involves judicious fluid management, protective mechanical lung ventilation with low tidal volumes and moderate positive end expiratory pressure, multi-organ support, and treatment of the underlying cause, when possible. Pharmacotherapies have a very limited role in the management of ARDS, and to-date there is no effective medical treatment that improves survival for adult patients with the syndrome, although exogenous surfactant is beneficial in the pediatric population (Dushianthan 2011).

In 1991, inhaled nitric oxide (iNO) was shown to be a selective pulmonary vasodilator in patients with pulmonary hypertension, as well as in animals with pulmonary hypertension induced by drugs or hypoxia. Two years later, inhaled nitric oxide was introduced as a potential therapy for ARDS. Nitric oxide is a colorless, odorless gas that rapidly diffuses from alveoli through epithelial cells to gain direct access to the vasculature. Once in the blood stream it binds to hemoglobin and is rapidly inactivated with an estimated half-life of 3-5 seconds. The effect of iNO is limited to the lungs making it a selective pulmonary vasodilator without adverse systemic hemodynamic effects. iNO causes vasodilatation of ventilated lung units and redistribution of pulmonary blood flow away from non-ventilated lung areas. It decreases pulmonary vascular resistance, improves the ventilation perfusion

mismatch, and subsequently reduces the elevated vascular resistance and pulmonary hypertension. It is also believed that iNO may also regulate both the immune and inflammatory responses (oxygenation by redistributing pulmonary blood flow toward ventilated lung units in patients with this condition (Griffiths 2005, DiBlasi 2010, Dushianthan 2011, Pierrakos 2011).

iNO therapy is also associated with harmful side effects. Nitric oxide is unstable in air and when inhaled with high concentrations of oxygen, the gaseous NO slowly forms nitrogen dioxide which is potentially cytotoxic. A NO₂ concentrations higher than 10 parts per million (ppm) has been known to induce pulmonary edema, alveolar hemorrhage, changes in the surface tension properties of surfactant, and death. NO₂ is dose-dependent and its concentration should be maintained at a level below 3 ppm by decreasing the iNO concentration if it goes any higher. Methemoglobinemia (MetHb), which impairs the ability of the hemoglobin molecule to bind with oxygen, is another harmful side effect of iNO therapy. MetHb is dose-dependent and must be carefully monitored as significant methemoglobinemia has been reported after accidental overdose of iNO. A MetHb level >10% may cause cyanosis, headaches, muscle weakness, and tissue. Renal failure has also been reported with iNO use (Kinsella 2006, Finer 2009, Dushianthan 2011, Henry 2012).

Inhaled nitric oxide is provided through a delivery system used in conjunction with a ventilator or other breathing gas administration system. The delivery system consists of a nitric oxide administration apparatus, a nitric oxide gas analyzer, and a nitrogen dioxide gas analyzer. INOmax® (INO Therapeutics Inc., Clinton NJ) is a commercially available brand of iNO that received initial Food and Drug Administration approval in 1999. It was approved for use as a vasodilator, in conjunction with ventilatory support and other appropriate agents for the treatment of term and near-term (>34 weeks gestation) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension. The use of iNO for other neonatal medical conditions and for treatment in the adult patient population is considered "off label" usage.

Medical Technology Assessment Committee (MTAC)

iNO for Treatment of Persistent Pulmonary Hypertension

08/20/2012: MTAC REVIEW

Evidence Conclusion: Treatment of persistent pulmonary hypertension (PPHN) and respiratory failure in infants born or at near term: There is fair evidence that inhaled nitric oxide therapy may improve oxygenation, and reduce the need for extracorporeal membrane oxygenation (ECMO), but does not significantly improve survival among term or near-term neonates with hypoxic respiratory failure and without congenital diaphragmatic hernia or other congenital heart disease. A Cochrane review conducted by Barrington and Finer (2006, updated 2009) pooled the results of 14 published trials on iNO for respiratory failure in term or near-term infants >34 weeks gestation. The studies included in the analysis had generally similar eligibility criteria, but with some variations in quality and size, as well as in the use of other therapies with some allowing high frequency ventilation with the jet or oscillator and surfactant treatment. The pooled results of the trials show that iNO given at an initial concentration of 20 ppm for term or near-term infants with hypoxic respiratory failure and who do not have a diaphragmatic hernia or congenital heart disease, is effective in reducing the need for ECMO therapy with NNT of 5. iNO did not have a survival benefit, and the two studies that reported long-term neurological and developmental outcomes showed that the therapy did not significantly increase or reduce neurodevelopmental disability or cerebral palsy among survivors. The limited evidence on the use of use of iNO in infants with diaphragmatic hernia, suggest that the outcomes were slightly worsened rather than improved with iNO therapy. A more recent RCT (Gonzalez 2010), not included in the Cochrane review, evaluated the efficacy of early vs. delayed use of iNO therapy in preventing newborns with moderate respiratory failure from developing severe hypoxemic respiratory failure. The study included infants born at ≥35 weeks of gestation, were less than 48 hours old, had moderate respiratory failure with an oxygenation index (OI) between 10 and 30, and with evidence of pulmonary hypertension. The study participants were randomized to receive early iNO with conventional mechanical ventilation at an initial concentration of 20 ppm, or to a control group that received conventional mechanical ventilation. The controls received iNO therapy and high frequency oscillatory ventilation (HFOV) if they reached an OI>40 (treatment failure). The trial was a RCT with valid analysis, but was not blinded and as the authors indicated it took over 5 years to be completed due to difficulty in early recruitment and interrupted supply of iNO. The availability of HFOV was also limited during the study and was thus only used for infants with treatment failure. In addition, ECMO was not available in Chile at the study period. The overall results of the trial show that early use of iNO given at a 20 ppm concentration to newborns who are ≥35 weeks gestation, <48 hours old, with birth weights >2000 g, and with moderate hypoxemic failure (OI between 10 and 30), increases oxygenation and decreases the risk of developing severe hypoxemic respiratory failure. Early iNO therapy was also found to significantly reduce oxygen therapy days, but not the mechanical ventilation. The difference in survival between the two treatment groups was statistically insignificant, but the study was not powered to detect a difference in survival. No adverse effects of iNO were reported. Treatment of pulmonary hypertension in pre-term newborns:

Several RCTs were conducted among preterm infants to determine whether iNO reduces the rates of death and/or chronic lung disease. The studies had differences in their inclusion criteria, design, indications and protocols or iNO therapy, and outcomes. The majority enrolled the preterm infants in the first 48 hours after birth; two trials enrolled them after 3 days of preterm birth, and one after 7 days. Two studies used iNO in all intubated preterm infants with relatively low oxygen requirement and severity of illness, while two other studies enrolled only preterm infants with severe hypoxic respiratory failure. The results of the studies varied and were contradictory at times. The majority showed no effect, few showed a reduction in lung injury, and in one there was a reduction in cerebral injury. Barrington and Finer, 2010 conducted a meta-analysis of 14 published trials on iNO for respiratory failure in preterm infants. The authors did not perform an overall analysis of all trials, but grouped them into three categories depending on inclusion criteria: 1. Entry in the first 3 days of life based on oxygenation criteria (N=9 trials), 2. Later enrollment based on increased risk bronchopulmonary dysplasia (BPD) (N=two trials), and 3. Routine use in preterm babies with pulmonary disease (N=3 trials). The results of the analysis showed that inhaled nitric oxide had no effect on death or BPD at 36 weeks whether it was used routinely, in the first 3 days based on oxygenation criteria, or after 3 days based on BPD risk. Askie and colleagues (2011), performed an individual patient data meta-analysis of 12 trials (all included in the Barrington's meta-analysis except for 2 small trials whose authors could not be contacted or were unable to provide individual patient data. The results of the meta-analysis showed no statistically significant effect of iNO on death, chronic lung disease, or severe neurologic events among preterm infants. Post-hoc analysis did not show any significant difference in outcomes between iNO given to infants in different birth weight /illness severity categories, or between infants who were started on the gas earlier vs. later (using 3-or 7-day cut off). A subanalysis on the starting dose of iNO of >5 vs. < 5 ppm showed a statistically significant improvement in the primary outcome (p=.02). However, this was driven by one study which also differed according to duration, timing and indication of treatment). Based on these results, the authors of the meta-analysis concluded that the routine use of iNO in preterm infants cannot be recommended for the treatment of respiratory failure in preterm infants. Donahue and colleagues' 2011 meta-analysis of the same 14 trials included in Barrington's meta-analysis also showed no survival benefit of using iNO in preterm infants. There was no difference between preterm infants treated with iNO vs. controls in the incidence of cerebral palsy, neurodevelopmental or cognitive impairment. The NIH Consensus Development Conference Statement (Cole 2011) on inhaled nitric oxide therapy for premature infants also concluded that the available evidence does not support use of iNO in early routine, early rescue, or later-rescue regimens in the care of premature infants of <34 weeks gestation who require respiratory support. The statement also concluded, "On the basis of the currently available data, hospitals, clinicians, and the pharmaceutical industry should avoid marketing iNO for the premature infants of <34 weeks' gestation". Conclusion: There is fair evidence that the use of iNO for preterm infants does not improve their survival, reduce chronic pulmonary disease, cerebral injury and/or other neurodevelopmental impairments. Treatment of acute respiratory distress syndrome (ARDS) in adults and children:

Afshari and colleagues (2010, 2011) conducted a meta-analysis of 14 RCTs (N=1,303 patients) on inhaled nitric oxide therapy for acute respiratory distress syndrome (ARDS) and acute lung injury (ALI) in children and adults (three pediatric studies, one combined pediatric and adults, and the rest included only adults). The meta-analysis had generally valid methodology and analysis. However, only four of the included trials had low risk of bias. There were also some variations between the studies in patient population, type, dose and duration of iNO therapy, as well as length of follow-up. The results of the meta-analysis suggest that iNO may only transiently improve oxygenation. It was not found to have a survival benefit, increase ventilation-free days, or improve other clinical outcomes in adults with ALI or ARDS. There was a significantly higher risk of renal impairment in the adult patients treated with iNO. Adhikari and colleagues meta-analysis (2007) of 12 RCTs also showed no survival benefit of iNO therapy, but an increased risk of renal dysfunction patients with ALI/ARDS. Conclusion: There is fair evidence that inhaled nitric oxide therapy for adult patients with acute respiratory distress syndrome or acute lung injury does not improve survival or other clinical outcomes, and may increase the risk of renal impairment. There are insufficient published pediatric trials to determine any benefit or harm of iNO therapy in children with ARDS or ALI.

Articles: Treatment of persistent pulmonary hypertension (PPHN) and respiratory failure in infants born or at near term: The literature search revealed a number of randomized controlled studies and a Cochrane review with a meta-analysis that pooled the results of 12 RCTs. The Cochrane review and the RCT published after the meta-analyses were selected for critical appraisal. Finer N and Barrington KJ. Nitric Oxide for respiratory failure in infants born at or near term. *Cochrane Database Syst Rev.* 2006 (updated 2009) Issue 4. Art No. CD000399. [See Evidence Table](#). Gonzalez A, Fabres J, D'Apremont I, et al. Randomized controlled trails of early compared with delayed use of inhaled nitric oxide in newborns with a moderate respiratory failure and pulmonary hypertension. *J Perinatol* 2010;30:420-424. [See Evidence Table](#). Treatment of pulmonary hypertension in pre-term newborns. The literature search revealed a number of randomized controlled studies published between the late 1990s and 2010 and four meta-analyses that pooled the results of all, or some of these trials including a Cochrane review (Burrington and Finer) first published in 2006 and last updated in 2010, an earlier meta-analysis (Hoehn 2000 updated in 2006) and two more recent meta-analysis (Askie 2011, and Donahue 2011). The Cochrane review and Askie and colleagues' meta-analysis of individual patient data from the same trials included in the Cochrane review were selected for critical appraisal. Askie LM, Ballard RA, Cutter GR, Dani C, et al for the Meta-analysis of

Preterm Patients on Inhaled Nitric Oxide (MAPPiNO) Collaboration. Inhaled nitric oxide in preterm infants: An individual -patient data meta-analysis of randomized trials. *Pediatrics*. 2011;128:729-739. [See Evidence Table](#) . Barrington KJ, Finer N. Inhaled nitric oxide for respiratory failure in preterm infants. *Cochrane Database Syst Rev*. 2010 Dec 8;(12):CD000509. [See Evidence Table](#) . Treatment of acute respiratory distress syndrome (ARDS) in adults and children The literature search revealed a number of randomized controlled studies and two meta-analyses of RCTs (Adhikari 2007, and Afshari (described in 2 publications 2010 and 2011). No trials published after the last meta-analysis were identified by the search. The more recent meta-analysis was selected for critical appraisal. Afshari A, Brok J, Moller AM et al. Inhaled nitric oxide for acute respiratory distress syndrome (ARDS) and acute lung injury in children and adults. *Cochrane Database of Systematic Reviews* 2010, Issue 7. Art. No.:CD002787.pub2. [See Evidence Table](#) . Afshari A, Brok J, Moller AM et al. Inhaled nitric oxide for acute respiratory distress syndrome (ARDS) and acute lung injury in children and adults. A systematic review with meta-analysis and trial sequential analysis. *Anesth Analg* 2011;112:1411-1421. [See Evidence Table](#).

The use of iNO for Treatment of persistent pulmonary hypertension (PPHN) and respiratory failure in infants born or at near term does meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

The use of iNO for treatment of pulmonary hypertension pre- term newborns does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

The use of iNO for treatment of ARDS in adults and children does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

Date Created	Review Dates	Date Last Revised
09/04/2012	09/04/2012 ^{MDCRPC} , 10/02/2012 ^{MDCRPC} , 08/06/2013 ^{MPC} , 11/05/2013 ^{MPC} , 09/02/2014 ^{MPC} , 07/07/2015 ^{MPC} , 05/03/2016 ^{MPC} , 03/07/2017 ^{MPC}	08/06/2013

^{MDCRPC} Medical Director Clinical Review and Policy Committee
^{MPC} Medical Policy Committee

Revision History	Description

Codes

No specific codes