8.01.37	Inhaled Nitric Oxide		
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Policy Statement

I. Inhaled nitric oxide (INO) may be considered **medically necessary** as a component of treatment of:
   A. Hypoxic respiratory failure in neonates born at more than 34 weeks of gestation

II. Other indications for inhaled nitric oxide are considered **investigational**, including, but not limited to:
   A. Treatment of premature neonates born at less than or equal to 34 weeks of gestation with hypoxic respiratory failure
   B. Treatment of adults and children with acute hypoxemic respiratory failure
   C. Postoperative use in adults and children with congenital heart disease
   D. In lung transplantation, during and/or after graft reperfusion

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

Inhaled nitric oxide (INO) appears to be of greatest benefit to neonates born at more than 34 weeks for whom primary or secondary pulmonary hypertension is a component of hypoxic respiratory failure.

The benefit of INO appears limited in term or near-term infants whose hypoxic respiratory failure is due to diaphragmatic hernia, unless there is associated pulmonary hypertension.

The following criterion for hypoxic respiratory failure has been reported:

- An oxygenation index (OI) of at least 25 on 2 measurements made at least 15 minutes apart.

(The OI is calculated as the mean airway pressure times the fraction of inspired oxygen divided by the partial pressure of arterial oxygen times 100. An OI of 25 is associated with a 50% risk of requiring extracorporeal membrane oxygenation [ECMO] or dying. An OI of 40 or more is often used as a criterion to initiate ECMO therapy.)

If ECMO is initiated in near-term neonates, INO should be discontinued because there is no benefit to combined treatment.

Coding

See the Codes table for details.

Description

Inhaled nitric oxide (INO) is a natural vasodilator and has been studied for a variety of types of respiratory failure. Most commonly, it is used as an initial treatment for neonates with hypoxic respiratory failure to improve oxygenation and reduce the need for invasive extracorporeal

membrane oxygenation (ECMO). It is also proposed as a treatment for premature infants, critically ill children, and adults with respiratory failure, as well as in the postoperative management of children undergoing repair of congenital heart disease and individuals after lung transplantation to prevent or reduce reperfusion injury.

Summary of Evidence

For individuals who are neonates, are term or late preterm at birth, and have hypoxic respiratory failure who receive inhaled nitric oxide (INO), the evidence includes randomized controlled trials (RCTs) and a systematic review. Relevant outcomes are overall survival (OS), hospitalizations, resource utilization, and treatment-related morbidity. Evidence from RCTs and a meta-analysis have supported the use of INO in term or late preterm infants. Pooled analyses of RCT data have found that use of INO significantly reduced the need for extracorporeal membrane oxygenation (ECMO) and the combined outcome of ECMO or death. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are neonates, are premature at birth, and have hypoxic respiratory failure who receive INO, the evidence includes RCTs and systematic reviews. Relevant outcomes are OS, hospitalizations, resource utilization, and treatment-related morbidity. A large number of RCTs have evaluated INO for premature neonates, and most trials have reported no significant difference for primary endpoints such as mortality and bronchopulmonary dysplasia (BPD). Meta-analyses of these RCTs have not found better survival rates in patients who received INO compared with a control intervention. Most meta-analyses also did not report improvements in other outcomes with INO (e.g., BPD, intracranial hemorrhage). The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are adults or children in acute hypoxemic respiratory failure who receive INO, the evidence includes RCTs and systematic reviews. Relevant outcomes are OS, hospitalizations, resource utilization, and treatment-related morbidity. A large number of RCTs have evaluated INO for treatment of acute hypoxemic respiratory failure. Meta-analyses of these RCTs have not found that INO significantly reduced mortality or shortened the duration of mechanical ventilation. Some evidence from a meta-analysis of 4 RCTs, a cohort study, and a separate meta-analysis has suggested that INO may be associated with an increased risk of renal impairment in patients with acute respiratory distress syndrome (ARDS). The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are adults or children with congenital heart disease who have had heart surgery who receive INO, the evidence includes RCTs and systematic reviews. Relevant outcomes are OS, hospitalizations, resource utilization, and treatment-related morbidity. Evidence from a number of small RCTs and systematic reviews of these trials did not find a significant benefit for INO on mortality and other health outcomes in the postoperative management of children with congenital heart disease. There is less evidence on INO for adults with congenital heart disease. One RCT found that treatment with INO did not improve the postoperative outcomes of adults with congestive heart failure. A systematic review found no difference in length of hospitalization or mortality with INO treatment. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have a lung transplant who receive INO, the evidence includes RCTs and a systematic review. Relevant outcomes are OS, hospitalizations, resource utilization, and treatment-related morbidity. Several small RCTs have evaluated INO after lung transplantation; none found statistically significant improvements in health outcomes with INO. A systematic review of RCTs and observational studies concluded that available evidence did not support the routine use of INO after lung transplant. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Additional Information

2021 Input

Clinical input was sought to help determine whether the use of INO for individuals with various conditions would provide a clinically meaningful improvement in net health outcome and whether the use is consistent with generally accepted medical practice. In response to requests, clinical input on the use of INO was received from 4 respondents, including: 3 physician-level responses with academic affiliations identified through 1 specialty society and 1 physician-level response identified through BCBSA.

For individuals who are neonates, premature at birth, and have hypoxic respiratory failure, a limited quantity of clinical input indicated high confidence that the use of INO provides a clinically meaningful improvement in the net health outcome and is consistent with generally accepted medical practice. Cited evidence notes that the majority of RCTs, and meta-analyses of these RCTs, have reported no significant difference with INO therapy for primary endpoints such as survival and BPD. Guidelines from the American Heart Association/American Thoracic Society and an expert workshop consensus statement state that INO can be beneficial for a subset of preterm infants with severe hypoxemia that is primarily due to persistent pulmonary hypertension of the newborn physiology rather than parenchymal disease; however, this recommendation is based on case series. Limited quantity of clinical input and insufficient published evidence showing improved health outcomes provide insufficient support regarding the effect on net health outcome.

For individuals who are adults or children in acute hypoxemic respiratory failure, clinical input responses were mixed as to whether use of INO provides a clinically meaningful improvement in net health outcome. Clinical input indicates this use of INO is consistent with generally accepted medical practice, and some respondents suggested that INO is often used as a rescue therapy and bridge to ECMO. Cited evidence notes improved physiologic outcomes such as transient improvement of oxygenation in the first 24 hours; however, the evidence does not demonstrate significant improvements in health outcomes such as overall mortality.

For individuals who are adults or children with congenital heart disease who have had heart surgery, clinical input responses indicate moderate confidence that the use of INO provides a clinically meaningful improvement in net health outcome and moderate to high confidence that this use is consistent with generally accepted medical practice. This appears to be based on cited evidence suggesting that INO can improve perioperative pulmonary hypertension; however, it is unclear that health outcomes are improved as no significant mortality benefit was observed in these patients. Further, some evidence suggests that use of INO may be associated with an increase in mortality for those without pulmonary hypertension.

For individuals with lung transplant, a limited quantity of clinical input respondents provided moderate to high confidence that use of INO during the perioperative period to manage pulmonary vascular resistance and pulmonary hypertension provides a clinically meaningful improvement in net health outcome and is consistent with generally accepted medical practice. Cited evidence includes small RCTs that found no statistically significant improvement in health outcomes with INO and case series or non-randomized trials of a limited number of patients with inconsistent endpoints, suggesting that INO may decrease the incidence of graft rejection and dysfunction and potentially prevent reperfusion injury. Limited quantity of clinical input and insufficient published evidence showing improved health outcomes provide insufficient support regarding the effect on net health outcome.

Further details from clinical input are included in the Appendix.

Related Policies

- N/A

Benefit Application

Benefit determinations should be based in all cases on the applicable member health services contract language. To the extent there are conflicts between this Medical Policy and the member health services contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal law may prohibit health plans from denying FDA-approved Healthcare Services as investigational or experimental. In these instances, Blue Shield of California may be obligated to determine if these FDA-approved Healthcare Services are Medically Necessary.

Regulatory Status

In 1999, INOmax™ (Ikaria) was cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process for the following indication: "INOmax, in conjunction with ventilatory support and other appropriate agents, is indicated for the treatment of term and near-term (>34 weeks) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension." In 2015, Mallinckrodt acquired Ikaria.

In 2014, Advanced Inhalation Therapies received orphan drug designation for its proprietary formulation of nitric oxide as an adjunctive treatment of cystic fibrosis.

In 2019, Genosyl® (nitric oxide for inhalation; Vero Biotech, LLC) received FDA approval to "improve oxygenation and reduce the need for extracorporeal membrane oxygenation in term and near-term (>34 weeks gestation) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension." In April 2021, the GENOSYL DS Nitric Oxide Delivery System was recalled due to a software issue that leads to errors in the delivery of nitric oxide. For impacted devices, the issue was corrected with the release of Software 2.2.4.[1,]

In 2020, FDA granted emergency expanded access for INOpulse (Bellerophon Therapeutics) inhaled nitric oxide delivery system for treating COVID-19.

Rationale

Background
Hypoxic Respiratory Failure
Hypoxic respiratory failure may result from respiratory distress syndrome, persistent pulmonary hypertension, meconium aspiration, pneumonia, or sepsis.

Treatment
Treatment typically includes oxygen support, mechanical ventilation, induction of alkalosis, neuromuscular blockade, or sedation.

Extracorporeal membrane oxygenation (ECMO) is an invasive technique that may be considered in neonates when other therapies fail. Inhaled nitric oxide (INO) is both a vasodilator and a mediator in many physiologic and pathologic processes. Inhaled nitric oxide has also been proposed for use in preterm infants less than 34 weeks of gestation and in adults.

Also, there are several potential uses in surgery. One is the proposed use of INO to manage pulmonary hypertension after cardiac surgery in infants and children with congenital heart disease. In congenital heart disease patients, increased pulmonary blood flow can cause pulmonary hypertension. Cardiac surgery can restore the pulmonary vasculature to normal, but there is the potential for complications, including postoperative pulmonary hypertension, which can prevent weaning from ventilation and is associated with substantial morbidity and mortality. Another potential surgical application is the use of INO in lung transplantation to prevent or reduce reperfusion injury.

Literature Review

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function, including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Hypoxic Respiratory Failure in Term or Late Preterm Neonates

Clinical Context and Therapy Purpose

The purpose of inhaled nitric oxide (INO) is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals who are neonates, are term or late preterm at birth, and have hypoxic respiratory failure.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals who are neonates, are term or late preterm at birth, and have hypoxic respiratory failure.

Interventions

The therapy being considered is INO. Inhaled nitric oxide is a natural vasodilator and has been studied for a variety of types of respiratory failure. Most commonly, it is used as an initial treatment for neonates with hypoxic respiratory failure to improve oxygenation and reduce the need for invasive extracorporeal membrane oxygenation (ECMO). In late preterm neonates, INO primarily functions as a vasodilator to treat pulmonary hypertension, often due to meconium aspiration or bacterial pneumonia. However, in earlier preterm neonates with respiratory failure, pulmonary hypertension with shunting is less of a risk. Therefore, these 2 groups of neonates represent distinct clinical issues, and the results of INO in late preterm neonates cannot be extrapolated to preterm neonates. Also, the risk of intraventricular hemorrhage associated with INO is higher in premature infants.

Comparators
The following practice is currently being used to treat hypoxic respiratory failure in term or late preterm neonates: standard neonatal specialty care without INO.

Outcomes
The general outcomes of interest are overall survival (OS), hospitalizations, resource utilization, and treatment-related morbidity (Table 1).

Table 1. Outcomes of Interest

Outcomes	Details	Timing
Resource utilization	Evaluated through outcomes such as requirement for ECMO before hospital discharge	1 week to 6 months
Treatment-related morbidity	Evaluated through outcomes such as rates of adverse events including BPD and severe intracranial hemorrhage	1 week to 6 months

BPD: bronchopulmonary dysplasia; ECMO: extracorporeal membrane oxygenation.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence
Systematic Reviews
A number of RCTs and a Cochrane review of RCT data on INO in infants with hypoxia born at or late preterm (>34 weeks of gestation) have been published. The Cochrane review, last updated by Barrington et al (2017), identified 17 trials.[2,] Ten trials compared INO with a control (placebo or standard neonatal intensive care without INO) in infants who had moderately severe illness scores. One trial permitted backup treatment with INO and 2 enrolled only infants with a diaphragmatic hernia. Another 6 trials included infants with moderately severe disease and compared immediate INO with INO only when infants' conditions deteriorated to a more severe illness. The remaining trial compared INO with high-frequency ventilation. In all trials, hypoxemic respiratory failure was required for study entry, and most also required echocardiographic evidence of persistent pulmonary hypertension. The main findings of the meta-analysis are provided in Table 2. Only findings of trials that did not allow backup INO or were not limited to patients with a diaphragmatic hernia are presented; there were too few studies on other subgroups to permit meaningful meta-analysis.

Table 2. Main Cochrane Findings on INO in Term or Near-Term Infants

No. of Trials	N	Outcomes	Relative Risk	95% CI	p	I^2	QOE[a]
8	860	Death before hospital discharge	0.89	0.60 to 1.31	.55	0%	High
7	815	ECMO before hospital discharge	0.60	0.50 to 0.71	<.001	0%	High
8	859	Death or requirement of ECMO	0.66	0.57 to 0.77	<.001	0%	High

Adapted from Barrington et al (2017).[2,]
CI: confidence interval; ECMO: extracorporeal membrane oxygenation: INO: inhaled nitric oxide; QOE: quality of evidence.
[a] QOE assessed using the GRADE tool.

Reviewers found that INO in hypoxic infants significantly reduced the incidence of the combined endpoint of death or the need for ECMO compared with controls, in studies that did not allow INO backup in controls. Inhaled nitric oxide did not have a statistically significant effect on mortality when analyzed as the sole outcome measure; however, there was a significant effect of INO on the need for ECMO only. The analysis of mortality alone may have been underpowered.

Section Summary: Hypoxic Respiratory Failure in Term or Late Preterm Neonates

Evidence from RCTs and a meta-analysis of RCTs has supported the use of INO in term or late preterm infants to improve the net health outcome. Pooled analyses of RCT data have found that INO leads to a significant reduction in the combined outcome of ECMO or death and a significant reduction of ECMO use before hospital discharge.

Hypoxic Respiratory Failure in Premature Neonates

Clinical Context and Therapy Purpose

The purpose of INO is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals who are neonates, are premature at birth, and have hypoxic respiratory failure.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals who are neonates, are premature at birth, and have hypoxic respiratory failure.

Interventions

The therapy being considered is INO. Inhaled nitric oxide is a natural vasodilator and has been studied for a variety of types of respiratory failure. Most commonly, it is used as an initial treatment for neonates with hypoxic respiratory failure to improve oxygenation and reduce the need for invasive ECMO.

Comparators

The following practice is currently being used to treat hypoxic respiratory failure in premature neonates: standard neonatal intensive care without INO.

Outcomes

The general outcomes of interest are OS, hospitalizations, resource utilization, and treatment-related morbidity (Table 3).

Table 3. Outcomes of Interest

Outcomes	Details	Timing
Resource utilization	Evaluated through outcomes such as utilization of ECMO before hospital discharge	1 week to 6 months
Treatment-related morbidity	Evaluated through outcomes such as rates of adverse events including BPD and severe intracranial hemorrhage	1 week to 6 months

BPD: bronchopulmonary dysplasia; ECMO: extracorporeal membrane oxygenation.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.

- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Systematic Reviews

Numerous systematic reviews and RCTs on INO for treating hypoxic respiratory failure in preterm neonates have been published. A Cochrane review by Barrington et al (2017) identified 17 RCTs on the efficacy of INO for treating premature infants (i.e., <35 weeks of gestation) with respiratory disease.[3] The main findings of the meta-analysis are provided in Table 4. Results are reported separately for studies with entry before 3 days based on oxygenation, studies with entry after 3 days based on oxygenation and bronchopulmonary dysplasia (BPD) risk, and studies of routine use of INO in premature infants on respiratory support. Pooled analyses of 3 or more studies are shown.

Table 4. Main Cochrane Findings on INO in Preterm Infants

No. of Trials	N	Outcomes	Relative Risk	95% CI	p	I^2	QOE[a]
Death before hospital discharge							
10	1066	Studies with entry before 3 days	1.02	0.89 to 1.18	.75	3%	High
3	1075	Studies with entry after 3 days	1.18	0.81 to 1.71	.39	0%	High
4	1924	Studies of routine use	0.90	0.74 to 1.10	.32	50%	Moderate
BPD at 36 weeks of gestation							
8	681	Studies with entry before 3 days	0.89	0.76 to 1.04	.13	29%	NR
3	990	Studies with entry after 3 days	0.91	0.83 to 1.01	.068	11%	NR
4	1782	Studies of routine use	0.95	0.85 to 1.05	.32	10%	NR
BPD or death at 36 weeks of gestation							
8	957	Studies with entry before 3 days	0.94	0.87 to 1.01	.084	26%	High
3	1075	Studies with entry after 3 days	0.92	0.85 to 1.01	.079	51%	High
4	1924	Studies of routine use	0.94	0.87 to 1.02	.12	11%	High

Adapted from Barrington et al (2017).[3]
BPD: bronchopulmonary dysplasia; CI: confidence interval; INO: inhaled nitric oxide; NR: not reported; QOE: quality of evidence.
[a] QOE assessed using the GRADE tool.

Reviewers found that use of INO in premature infants with respiratory failure did not significantly improve individual outcomes (e.g., death before hospital discharge, BPD at 36 weeks of postmenstrual age) or the combined outcome (BPD or death at 36 weeks of postmenstrual age). Findings were not statistically significant in subgroups of studies that enrolled patients before 3 days old, enrolled patients after 3 days, and that used INO routinely. A fourth primary outcome (intraventricular hemorrhage) was only pooled in studies with entry before 3 days, and again did not find a significant benefit of INO versus control (relative risk [RR], 0.94; 95% confidence interval [CI], 0.69 to 1.28).

A meta-analysis by Yang et al (2016) identified 22 trials comparing INO with a control intervention in preterm infants.[4] Reviewers did not define "preterm" as used to identify studies, beyond use of the keyword in literature searches. A pooled analysis of all 22 studies did not find a significant difference between groups in mortality (RR, 1.00; 95% CI, 0.92 to 1.09). There was also no significant difference between INO and control in the rate of severe intracranial hemorrhage in a pooled analysis of 17 studies (RR, 0.99; 95% CI, 0.83 to 1.16). However, a pooled analysis of 20 studies did find a significantly lower rate of BPD in the INO groups than in the control groups (RR, 0.88; 95% CI, 0.82 to 0.95).

Reviewers noted that their findings on BPD differed from those in other meta-analyses and suggested that the difference might have been due to their inclusion of Chinese-language studies.

Previously, an Agency for Healthcare Research and Quality-sponsored systematic review by Donohue et al (2011) of randomized trials on INO for premature infants (<35 weeks gestation) was published.[5] Thirty-one articles were initially selected; the authors included 14 unique RCTs. Regardless of how mortality was reported or defined (e.g., death ≤7 days or ≤28 days, or death in the neonatal intensive care unit), there were no statistically significant differences between the INO group and the control group in any of the 14 RCTs or pooled analyses of these RCTs. For example, in a pooled analysis of 11 trials that reported death by 36 weeks of postmenstrual age or in the neonatal intensive care unit, the RR was 0.97 (95% CI, 0.82 to 1.15). Twelve trials reported data on BPD at 36 weeks of postmenstrual age, and despite variations in reporting of BPD, there was no significant benefit of INO treatment in any trial. A pooled analysis of data from 8 trials reporting BPD at 36 weeks of postmenstrual age among survivors found a RR of 0.93 (95% CI, 0.86 to 1.00).

Randomized Controlled Trials

The largest trial to date was published by Mercier et al (2010).[6] This multicenter industry-sponsored study, known as the European Union Nitric Oxide (EUNO) trial, evaluated low-dose INO therapy. Of 800 patients, 792 (99%) received their assigned treatment, and all 800 were included in the intention-to-treat analysis. Primary outcomes were survival without BPD at 36 weeks of postmenstrual age, OS at 36 weeks of postmenstrual age, and BPD at 36 weeks of postmenstrual age. The number of patients with BPD at 36 weeks of postmenstrual age was 81 (24%) in the INO group and 96 (27%) in the control group (RR, 0.83; 95% CI, 0.58 to 1.17; p=.29). The secondary endpoint (survival without brain injury at gestational age 36 weeks) also did not differ significantly between groups (RR, 0.78; 95% CI, 0.53 to 1.17; p=.23). This endpoint was attained by 181 (69%) patients in the INO group and 188 (76%) patients in the placebo group. The most common adverse event was intracranial hemorrhage, which affected 114 (29%) patients in the INO group and 91 (23%) patients in the control group (p value not reported).

Durrmeyer et al (2013) published 2-year outcomes of the EUNO trial.[7] Of the original 800 patients, 737 (92%) were evaluable at this time point. There were also no statistically significant differences between groups in other outcomes (e.g., hospitalization rates, use of respiratory medications, growth). At 7 years of follow-up, 305 patients were available for evaluation, with no deaths reported from the end of the 2-year follow-up to the 7-year follow-up and no significant differences in any questionnaire-documented health outcomes between groups.[8] Tables 5 and 6 summarize the key characteristics and results of the EUNO trial and its 2- and 7-year follow-ups.

Table 5. Summary of Key RCT Characteristics

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Mercier (2010); EUNO[6]	EU	35	2005-2008	Preterm infants (between 24 and 28 weeks gestational age) weighing ≥500 g and requiring surfactant within 24 hours of birth	INO 5 ppm (n=399)	Placebo-equivalent nitrogen gas (n=401)
Durrmeyer (2013); EUNO[7]	EU	35	2005-2008	Infants born at <29 weeks gestational age with moderate respiratory failure	INO 5 ppm (n=306)	Placebo-equivalent nitrogen gas (n=324)
Greenough (2021); EUNO[8]	EU	24	2005-2008	Preterm infants (between 24 and 28 weeks gestational age) weighing ≥500 g and requiring surfactant within 24 hours of birth	INO 5 ppm (n=152)	Placebo-equivalent nitrogen gas (n=153)

EU: European Union; EUNO: European Union Nitric Oxide trial; INO: inhaled nitric oxide; RCT: randomized controlled trial.

Table 6. Summary of Key RCT Results

Study	Survival Outcomes	Adverse Events
Mercier (2010); EUNO[6,]	OS at 36 weeks postmenstrual age	Serious adverse events[a]
INO	343 (86%)	158 (40%)
Placebo	359 (90%)	164 (41%)
RR; 95% CI; p-value	0.74; 0.48 to 1.15;.21	NR; NR;.72
	Survival without BPD at 36 weeks postmenstrual age	
INO	258 (65%)	
Placebo	262 (66%)	
RR; 95% CI; p-value	1.05; 0.78 to 1.43;.73	
Durrmeyer (2013); EUNO[7,]	OS between 36 weeks postmenstrual age and 2 years	
INO	391 (99%)	
Placebo	390 (98.2%)	
RR; 95% CI; p-value	NR; NR; NR	
	Survival without severe or moderate disability at 2 years	
INO	244 (79.7%)	
Placebo	270 (83.3%)	
RR; 95% CI; p-value	NR; NR;.29	
Greenough (2021); EUNO[8,]	Hospitalization rates - end of 2 years to the 7-year follow-up	
INO	44 (28.9%)	
Placebo	53 (34.6%)	
p-value	.29	
	Proportion of patients using respiratory medications at 7 years	
INO	10 (6.6%)	
Placebo	14 (9.2%)	
p-value	.40	

AEs: adverse events; BPD: bronchopulmonary dysplasia; CI: confidence interval; EUNO: European Union Nitric Oxide trial; INO: inhaled nitric oxide; NR: not reported; OS: overall survival; RCT: randomized controlled trial; RR: risk ratio.

[a] Serious AEs included intraventricular hemorrhage, periventricular leukomalacia, patent ductus arteriosus, pneumothorax, pulmonary hemorrhage, necrotizing enterocolitis, and sepsis.

The purpose of the study design and conduct limitation table (Table 7) is to display notable limitations identified in each study. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of evidence supporting the position statement. No relevance limitations were noted from these trials.

Table 7. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Mercier (2010); EUNO[6,]	3. Allocation concealment unclear					
Durrmeyer (2013); EUNO[7,]	3. Allocation concealment unclear					3. Confidence intervals not reported for all outcomes

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Greenough (2021); EUNO[8,]	3. Allocation concealment unclear					3. Confidence intervals not reported

EUNO: European Union Nitric Oxide trial.
The evidence limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4.Comparative treatment effects not calculated.

Section Summary: Hypoxic Respiratory Failure in Premature Neonates

A large number of RCTs have evaluated INO for premature neonates, and most trials have reported no significant differences in primary endpoints such as mortality and BPD. Meta-analyses of these RCTs have not found better survival rates in patients who receive INO compared with a control intervention. Most meta-analyses also did not find other outcomes (e.g., BPD, intracranial hemorrhage) were improved by INO.

Acute Hypoxemic Respiratory Failure in Adults and Children

Clinical Context and Therapy Purpose

The purpose of INO is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals who are adults or children in acute hypoxemic respiratory failure.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals who are adults or children in acute hypoxemic respiratory failure.

Interventions

The therapy being considered is INO. Inhaled nitric oxide is a natural vasodilator and has been studied for a variety of types of respiratory failure.

Comparators

The following practice is currently being used to treat acute hypoxemic respiratory failure in adults and children: standard medical intensive care without INO.

Outcomes

The general outcomes of interest are OS, hospitalizations, resource utilization, and treatment-related morbidity (Table 8).

Table 8. Outcomes of Interest

Outcomes	Details	Timing
Treatment-related morbidity	Evaluated through outcomes such as rates of adverse events including renal dysfunction	1 week to 6 months

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Systematic Reviews

Several meta-analyses and RCTs have evaluated the efficacy of INO for treating acute respiratory distress syndrome (ARDS) and acute lung injury (together known as acute hypoxemic respiratory failure). A Cochrane review by Gebistorf et al (2016) identified 14 RCTs comparing INO with control interventions in adults and children with ARDS.[9] The primary objective of the review was to evaluate the effects of INO on mortality, which was measured in several ways. The main findings of the meta-analysis are provided in Table 9.

Table 9. Main Cochrane Findings on INO in Patients With ARDS

No. of Trials	N	Outcomes	Relative Risk	95% CI	p	I^2	QOE[a]
11	1243	Overall mortality	1.04	0.90 to 1.19	.63	0%	Moderate
9	1105	Mortality at 28-30 days	1.08	0.92 to 1.27	.36	0%	Moderate
		Overall mortality stratified by age group					
3	185	Pediatric	0.78	0.51 to 1.18	.24	22%	Moderate
10	1085	Adult	1.09	0.93 to 1.25	.32	0%	NR

Adapted from Gebistorf et al (2016).[9]
ARDS: acute respiratory distress syndrome; CI: confidence interval; INO: inhaled nitric oxide; NR: not reported; QOE: quality of evidence.
[a] QOE assessed using the GRADE tool.

Inhaled nitric oxide was not found to significantly improve mortality when used to treat ARDS. Other outcomes (e.g., mean number of ventilator days, duration of mechanical ventilation) also did not differ significantly between groups. Regarding potential harms associated with INO use in this population, a pooled analysis of 4 trials found a significantly higher rate of renal impairment in groups treated with INO than with a control intervention (RR, 1.59; 95% CI, 1.17 to 2.16).

Other systematic reviews and meta-analyses have reported similar findings on mortality.[10,11] For example, a systematic review by Adhikari et al (2014) identified 9 RCTs conducted with adults or children (other than neonates) in which at least 80% of patients, or a separately reported subgroup, had ARDS.[10] The trials selected compared INO with placebo or no gas, used INO as a treatment of ARDS (i.e., not a preventive measure), and had less than 50% crossover between groups. Findings were not stratified by adult and pediatric populations. A pooled analysis of data from the 9 trials (N=1142 patients) found no statistically significant benefit of INO on mortality (RR, 1.10; 95% CI, 0.94 to 1.29; p=.24). In a preplanned subgroup analysis, INO did not reduce mortality in patients with severe ARDS (baseline partial pressure of oxygen, arterial [Pao_2]/fraction of expired oxygen [Fio_2] ≤100 mm Hg) or patients with mild-to-moderate ARDS (baseline Pao_2/Fio_2 >100 mg Hg).

A systematic review by Prakash et al (2021) reviewed the impact of INO compared to standard of care in the treatment of severe ARDS in the context of the 2019 Coronavirus disease (COVID-19).[12] The review included 14 retrospective or prospective studies including 423 patients (range, 5 to 169). Racial and ethnic demographics of patients included in these studies were not described. Across these studies, INO demonstrated a slight increase in oxygenation, but appeared to have no impact on mortality.

Randomized Controlled Trials

Di Fenza et al (2023) published results of an RCT investigating INO on hypoxemia with COVID-19.[13] Adults with COVID-19 pneumonia who were mechanically ventilated (N=193) were included and randomized to receive either INO at 80 ppm for 48 hours or usual care without INO. The primary outcome was the change in oxygenation (Pao_2/Fio_2) at 48 hours. Secondary outcomes included mortality at 28 and 90 days. The mean change in Pao_2/Fio_2 at 48 hours was 28.3 mmHg in the INO group and 21.4 mmHg in the usual care group (mean difference, 39.1 mmHg; 95% credible interval [CrI], 18.1 to 60.3). However, secondary outcomes, including mortality at 28 and 90 days, did not differ between groups.

Adverse Events

A cohort study by Ruan et al (2016) evaluated the risk of renal dysfunction in patients with ARDS treated using INO.[14] Using electronic medical record data from a teaching hospital, 547 patients with ARDS were identified. Among these patients, 216 had been treated with and 331 without INO. The 30-day incidence of renal replacement therapy was 34% in the INO group and 23% in the non-INO group. In the final propensity-matched analysis, there was a significantly higher risk of need for renal replacement therapy in the INO group than in the non-INO group (hazard ratio, 1.59; 95% CI, 1.08 to 2.34; p=.02). Similarly, in a meta-analysis of 15 RCTs involving 1853 patients, INO therapy was associated with a significant increase in the risk of acute kidney injury in patients with ARDS (RR, 1.55; 95% CI, 1.15 to 2.10; p=.004).[15]

Section Summary: Acute Hypoxemic Respiratory Failure in Adults and Children

A large number of RCTs have evaluated INO for treatment of acute hypoxemic respiratory failure in adults and children. Meta-analyses of these RCTs have not found that INO significantly reduced mortality or shortened the duration of mechanical ventilation. Moreover, subgroup analysis by age group in a 2016 Cochrane review did not find a significant benefit of INO on mortality in either pediatric or adult studies. There is evidence from a meta-analysis of 4 RCTs included in the Cochrane review and from a cohort study and separate meta-analysis that INO increases the risk of renal impairment in patients with ARDS.

Adults and Children With Congenital Heart Disease Who Have had Heart Surgery

Clinical Context and Therapy Purpose

The purpose of INO is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals who are adults or children with congenital heart disease who have had heart surgery.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals who are adults or children with congenital heart disease who have had heart surgery.

Interventions

The therapy being considered is INO. Inhaled nitric oxide is a natural vasodilator and has been studied for a variety of types of respiratory failure.

Comparators
The following practice is currently being used to treat adults and children with congenital heart disease who have had heart surgery: standard medical care without INO.

Outcomes
The general outcomes of interest are OS, hospitalizations, resource utilization, and treatment-related morbidity (Table 10).

Table 10. Outcomes of Interest

Outcomes	Details	Timing
Treatment-related morbidity	Evaluated through outcomes such as RVD, pulmonary arterial hypertension, mean arterial pressure, and neurodevelopmental disability	1 week to 6 months
Resource utilization	Evaluated through outcomes such as mean number of days on mechanical ventilation, length of stay in intensive care unit or hospital	1 to 6 weeks

RVD: right ventricular dysfunction.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence
Systematic Reviews
Yan et al (2024) published a systematic review investigating the impact of INO on postoperative outcomes after cardiac surgery.[16] Twenty-seven trials with adults or children were included and results were pooled. Investigators found a significant difference between the INO group and control group in 16 studies that reported the duration of mechanical ventilation (mean difference, 0.17; 95%CI, 0.24 to 0.09; I^2 = 17%). Subgroup analyses demonstrated that mechanical ventilation duration was significantly shortened in both children and adults using INO, and with various concentrations of INO (10, 20, and 40 ppm). However, there were no significant differences with INO use versus control on the length of stay in the critical care units, length of hospitalization, or mortality. Additionally, results were limited by variety of sample sizes, dosages, and timing of INO.

Adults
A trial by Potapov et al (2011) evaluated the prophylactic use of INO in adults undergoing left ventricular assist device implantation for congestive heart failure.[17] This double-blind trial was conducted at 8 centers in the US and Germany. Patients were randomized to INO 40 ppm (n=73) or placebo (n=77) beginning at least 5 minutes before the first weaning attempt from mechanical ventilation. The primary trial outcome was right ventricular dysfunction (RVD). Patients continued use of INO or placebo until they were extubated, reached the study criteria for RVD, or were treated for 48 hours, whichever came first. Patients were permitted to crossover to open-label INO if they failed to wean from mechanical ventilation, still required pulmonary vasodilator support at 48 hours, or met criteria for RVD. Thirteen (9%) of 150 randomized patients did not receive the trial treatment. Also, crossover to open-label INO occurred in 15 (21%) of 73 patients in the INO group and 20 (26%) of 77 in the placebo group. In an intention-to-treat analysis, RVD criteria were met by 7 (9.6%) of 73 patients in the INO group and 12 (15.6%) of 77 patients in the placebo group; this difference between groups was not statistically significant (p=.33). Other outcomes also did not differ significantly between

groups; e.g., mean number of days on mechanical ventilation (5.4 days for INO vs. 11.1 days for placebo; p=.77) and mean number of days in the hospital (41 in each group).

Children

Systematic Reviews

A Cochrane review by Bizzarro et al (2014) identified 4 RCTs (N=210 patients) comparing postoperative INO with placebo or usual care in the management of children who had congenital heart disease.[18] All trials included participants identified as having pulmonary hypertension in the preoperative or postoperative period. Three trials were parallel group, and 1 trial was a crossover. Mortality was the primary outcome of the meta-analysis. Two trials (n=162 patients) reported mortality before discharge. A pooled analysis of findings from these 2 trials did not find a significant difference in mortality between the INO group and the control group (odds ratio, 1.67; 95% CI, 0.38 to 7.30). Among secondary outcomes, a pooled analysis of 2 studies did not find a significant between-group difference in mean pulmonary arterial hypertension (pooled treatment effect, -2.94 mm Hg; 95% CI, -9.28 to 3.40 mm Hg), and likewise a pooled analysis of 3 studies did not find a significant difference between groups in mean arterial pressure (pooled treatment effect, -3.55 mm Hg; 95% CI, -11.86 to 4.76 mm Hg). Insufficient data were available for pooling other outcomes. Reviewers noted a lack of data on long-term mortality, length of stay in an intensive care unit or hospital, and neurodevelopmental disability, and concerns about the methodologic quality of studies, sample sizes, and heterogeneity between studies. These results did not support a benefit for INO treatment for this patient group. Wide CIs around the pooled treatment effects reflect the relative paucity of available data for each outcome.

Randomized Controlled Trials

The RCT assessing the largest sample was published by Miller et al (2000).[19] This trial out of Australia included 124 infants (median age, 3 months) who were candidates for corrective heart surgery. Eligibility requirements included the presence of congenital heart lesions, high pulmonary flow pressure, or both, and objective evidence of pulmonary hypertension in the immediate preoperative period. Participants were randomized to INO gas 10 ppm (n=63) or placebo nitrogen gas (n=61) after surgery until just before extubation. Randomization was stratified by the presence (45/124 [36%]) or absence (79/124 [64%]) of Down syndrome. The primary outcome was a reduction of pulmonary hypertensive crisis episodes, defined as a pulmonary/systemic artery pressure ratio greater than 0.75. Episodes were classified as major if there was a fall in systemic artery pressure of at least 20% and/or a fall in transcutaneous oxygen saturation to less than 90%. Episodes were classified as minor if the systemic artery pressure and transcutaneous oxygen saturation remained stable. The trial found that infants who received INO after surgery had significantly fewer pulmonary hypertensive crisis episodes (median, 4) than those who received placebo (median, 7; unadjusted RR, 0.66; 95% CI, 0.59 to 0.74; p<.001). Among secondary outcomes, the median time to eligibility for extubation was significantly shorter in the INO group (80 hours) than in the placebo group (112 hours; p=.019). There were 5 deaths in the INO group and 3 deaths in the placebo group; this difference was not statistically significant (p=.49). Similarly, there was no significant between-group difference in median time to discharge from intensive care (138 hours for INO vs. 162 hours for placebo; p>.05). Although this trial reported a reduction in pulmonary hypertensive crisis episodes, changes in this physiologic outcome did not result in improvements in survival or other clinical outcomes. The trial was likely underpowered to detect differences in these more clinically relevant secondary outcomes.

Section Summary: Adults and Children With Congenital Heart Disease Who Have Had Heart Surgery

Evidence from a number of small RCTs and systematic reviews of these trials did not find a significant benefit for INO on mortality and other health outcomes in the postoperative management of children with congenital heart disease. There is less evidence on the use of INO for adults with congenital heart disease. One RCT did not find a significant effect of INO treatment on the improvement of postoperative outcomes in adults with congestive heart failure who had left

ventricular assist device surgery. A systematic review found no difference in length of hospitalization or mortality with INO treatment.

Lung Transplantation

Clinical Context and Therapy Purpose

The purpose of INO is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with lung transplant.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with a lung transplant.

Interventions

The therapy being considered is INO. Inhaled nitric oxide is a natural vasodilator and has been studied for a variety of types of respiratory failure.

Comparators

The following practice is currently being used to treat patients with a lung transplant: standard post-transplant care without INO.

Outcomes

The general outcomes of interest are OS, hospitalizations, resource utilization, and treatment-related morbidity (Table 11).

Table 11. Outcomes of Interest

Outcomes	Details	Timing
Resource utilization	Evaluated through outcomes such as length of hospital or intensive care unit stay	1 to 6 weeks
Treatment-related morbidity	Evaluated through outcomes such as time to extubation, duration of ventilation, fluid balance during 24 hours after intensive care unit admission, development of grade II to III primary graft dysfunction or gas exchange	1 week to 6 months

Study Selection Criteria

Methodologically credible studies were selected using the following principles

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Systematic Reviews

Tavare and Tsakok (2011) reviewed the literature to assess whether the use of prophylactic INO in patients undergoing a lung transplant reduces morbidity and mortality.[20] They identified 6 studies, 2 RCTs (Meade et al [2003],[21] Perrin et al [2006][22]) and 4 uncontrolled cohort studies. They also identified a third RCT (Botha et al [2007][23]), which they excluded from their review based on the utility of that trial's clinical outcomes. Reviewers noted the paucity of controlled studies and the small sample sizes of all available studies. Moreover, they found that none of the RCTs showed that INO reduced mortality or morbidity (e.g., time to extubation, length of hospital stay). Thus they concluded

that "it is difficult to currently recommend the routine use of prophylactic inhaled NO [nitric oxide] in lung transplant surgery." Published RCTs are summarized in Table 12.

Table 12. Summary of RCTs Evaluating INO After Lung Transplantation

Study	N	Interventions	Primary Endpoints	Results
Meade et al (2003)[21],	84	INO 20 ppm 10 min after reperfusion vs. placebo gas mixture	Duration of mechanical ventilation from admission to intensive care unit to first successful extubation	No statistically significant difference in time to successful extubation (mean, 25.7 hours in INO group vs. 27.3 hours in control group; p=.76) No statistically significant differences in secondary outcomes (e.g., severe reperfusion injury, time to hospital discharge, hospital mortality, 30-day mortality)
Perrin et al (2006)[22],	30	INO 20 ppm at reperfusion for 12 hours vs. no intervention	Not specified	No statistically significant differences between groups in outcomes (e.g., intensive care unit length of stay, duration of ventilation, fluid balance during 24 hours after intensive care unit admission)
Botha et al (2007)[23],	20	Prophylactic INO 20 ppm vs. standard gas mixture for 30 min of reperfusion	Not specified	No statistically significant differences between groups in development of grade II to III primary graft dysfunction or gas exchange

INO: Inhaled nitric oxide; RCT: randomized controlled trial.

Section Summary: Lung Transplantation

Three small RCTs have evaluated INO after lung transplantation, and none found statistically significant improvements in health outcomes. A systematic review of RCTs and observational studies concluded that available evidence did not support the routine use of INO after lung transplant.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Clinical Input From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2021 Input

Clinical input was sought to help determine whether the use of inhaled nitric oxide (INO) for individuals with various conditions would provide a clinically meaningful improvement in net health outcome and whether the use is consistent with generally accepted medical practice. In response to requests, clinical input on the use of INO was received from 4 respondents, including: 3 physician-level responses with academic affiliations identified through 1 specialty society and 1 physician-level response identified through BCBSA.

For individuals who are neonates, premature at birth, and have hypoxic respiratory failure, a limited quantity of clinical input indicated high confidence that the use of INO provides a clinically meaningful improvement in the net health outcome and is consistent with generally accepted medical practice. Cited evidence notes that the majority of randomized controlled trials (RCTs), and meta-analyses of these RCTs, have reported no significant difference with INO therapy for primary endpoints such as survival and bronchopulmonary dysplasia (BPD). Guidelines from the American Heart Association/American Thoracic Society and an expert workshop consensus statement state

that INO can be beneficial for a subset of preterm infants with severe hypoxemia that is primarily due to persistent pulmonary hypertension of the newborn physiology rather than parenchymal disease; however, this recommendation is based on case series. Limited quantity of clinical input and insufficient published evidence showing improved health outcomes provide insufficient support regarding the effect on net health outcome.

For individuals who are adults or children in acute hypoxemic respiratory failure, clinical input responses were mixed as to whether use of INO provides a clinically meaningful improvement in net health outcome. Clinical input indicates this use of INO is consistent with generally accepted medical practice, and some respondents suggested that INO is often used as a rescue therapy and bridge to extracorporeal membrane oxygenation (ECMO). Cited evidence notes improved physiologic outcomes such as transient improvement of oxygenation in the first 24 hours; however, the evidence does not demonstrate significant improvements in health outcomes such as overall mortality. For individuals who are adults or children with congenital heart disease who have had heart surgery, clinical input responses indicate moderate confidence that the use of INO provides a clinically meaningful improvement in net health outcome and moderate to high confidence that this use is consistent with generally accepted medical practice. This appears to be based on cited evidence suggesting that INO can improve perioperative pulmonary hypertension; however, it is unclear that health outcomes are improved as no significant mortality benefit was observed in these patients. Further, some evidence suggests that use of INO may be associated with an increase in mortality for those without pulmonary hypertension.

For individuals with lung transplant, a limited quantity of clinical input respondents provided moderate to high confidence that use of INO during the perioperative period to manage pulmonary vascular resistance and pulmonary hypertension provides a clinically meaningful improvement in net health outcome and is consistent with generally accepted medical practice. Cited evidence includes small RCTs that found no statistically significant improvement in health outcomes with INO and case series or non-randomized trials of a limited number of patients with inconsistent endpoints, suggesting that INO may decrease the incidence of graft rejection and dysfunction and potentially prevent reperfusion injury. Limited quantity of clinical input and insufficient published evidence showing improved health outcomes provide insufficient support regarding the effect on net health outcome.

2012 Input

Input was received from 2 physician specialty societies and 9 academic medical centers while this policy was under review in 2012. There was a consensus that INO may be considered medically necessary as a component of treatment of hypoxic respiratory failure in neonates born at more than 34 weeks of gestation. There was general agreement with the criterion in the Policy Guidelines section for hypoxic respiratory failure: an oxygenation index of at least 25 on 2 measurements made at least 15 minutes apart. Also, input was mixed on whether other indications for INO should be considered investigational. Several reviewers stated that INO is clinically useful for the postoperative treatment of select patients with congenital heart disease.

Also, clinician reviewers generally agreed that INO should be discontinued when ECMO is initiated. There was near-consensus agreement that prolonged use of INO (e.g., >1 to 2 weeks in near-term neonates) does not improve outcomes (i.e., beyond a transient improvement in oxygenation). However, there was a wide range of responses to the question on how long INO should be continued once initiated; most reviewers who responded cited an upper limit of not more than 2 weeks.

2010 Input

Input was received from 4 physician specialty societies and 5 academic medical centers while this policy was under review in 2010. Input was consistent in its agreement with the policy statements on the treatment of hypoxic respiratory failure in neonates born at 34 or more weeks of gestation and adults with acute respiratory distress syndrome (ARDS); it was mixed for the statement on premature

neonates born at less than 34 weeks of gestation. There was no consensus among reviewers on potential additional medically necessary indications for INO therapy.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Academy of Pediatrics

In 2014, the American Academy of Pediatrics provided the following recommendations on the use of INO in premature infants (Table 13).[24,]

Table 13. Guidelines on Use of INO for Premature Infants

Recommendation	QOE	GOR
"Neither rescue nor routine use of iNO improves survival in preterm infants with respiratory failure."	A	Strong
"The preponderance of evidence does not support treating preterm infants who have respiratory failure with INO for the purpose of preventing/ameliorating BPD, severe intraventricular hemorrhage, or other neonatal morbidities."	A	Strong
"The incidence of cerebral palsy, neurodevelopmental impairment, or cognitive impairment in preterm infants treated within INO is similar to that of control infants."	A	NR

BPD: bronchopulmonary dysplasia; GOR: grade of recommendation; INO: inhaled nitric oxide; NR: not reported; QOE: quality of evidence.

American Heart Association/American Thoracic Society

The American Heart Association and American Thoracic Society (2015) published guidelines on the management of pediatric pulmonary hypertension.[25,] Relevant recommendations related to INO included:

- "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 of the newborn (PPHN) 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)."

National Institute for Health and Care Excellence

In April 2019, NICE issued a guidance on specialist neonatal respiratory care for preterm infants.[26,] The guidance recommends against the routine use of INO for preterm infants who need respiratory support for respiratory distress syndrome, unless there are other indications such as pulmonary hypoplasia or pulmonary hypertension.

National Institutes of Health

The National Institutes of Health (2011) published a consensus development conference statement on INO for premature infants,[27,], which was based on the Agency for Healthcare Research and Quality–sponsored systematic review of the literature, previously described.[5,] Conclusions included:
"Taken as a whole, the available evidence does not support use of INO (inhaled NO) in early-routine, early-rescue, or later-rescue regimens in the care of premature infants of <34 weeks' gestation who require respiratory support."

"There are rare clinical situations, including pulmonary hypertension or hypoplasia, that have been inadequately studied in which INO may have benefit in infants of <34 weeks' gestation. In such

situations, clinicians should communicate with families regarding the current evidence on its risks and benefits as well as remaining uncertainties."

Pediatric Academic Society

In April 2019, the Pediatric Academic Society convened a workshop regarding the role of INO in infants born preterm.[28,] The controversy surrounding its use in this patient population was reviewed by established experts in the field. The experts at the workshop concluded that the "rate of INO use in the infant born preterm is not declining, despite the publication of RCTs and related consensus statements that discourage its routine use due to lack of evidence for bronchopulmonary dysplasia prevention." These experts stated that "none of these studies or recommendations are based on its role in the management of persistent primary hypertension of the newborn in infants born preterm." In this setting, "extensive case series, guidelines, and others recommend the selective use of INO in infants born preterm with documented persistent primary hypertension of the newborn physiology as a contributing cause of hypoxemia, as best confirmed by echocardiography."

Pediatric Pulmonary Hypertension Network

In 2016, the Pediatric Pulmonary Hypertension Network (a network of clinicians, researchers, and centers) published recommendations on the use of INO in premature infants with severe pulmonary hypertension.[29,] Key recommendations included:
(1) "iNO therapy should not be used in premature infants for the prevention of BPD, as multicenter studies data have failed to consistently demonstrate efficacy for this purpose.
(2) iNO therapy can be beneficial for preterm infants with severe hypoxemia that is primarily due to PPHN physiology rather than parenchymal lung disease, particularly if associated with prolonged rupture of membranes and oligohydramnios.
(3) iNO is preferred over other pulmonary vasodilators in preterm infants based on a strong safety signal from short- and long-term follow-up of large numbers of patients from multicenter randomized clinical trials for BPD prevention..."

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 14.

Table 14. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT05757557	Perioperative Nitric oxiDE-conditioning, Produced by Plasma-chemical Synthesis Technology, For prevEnt Acute kidNey Injury During carDiac surgEry in Patients With chRonic Kidney Disease (DEFENDER-trial)	136	Jan 2025
NCT02836899	Prevention of Acute Kidney Injury by Nitric Oxide in Prolonged Cardiopulmonary Bypass. A Double Blind Controlled Randomized Trial in Cardiac Surgical Patients With Endothelial Dysfunction (MGHK23)	250	Nov 2023
NCT04305457	Nitric Oxide Gas Inhalation Therapy in Spontaneous Breathing Patients With Mild/Moderate COVID-19: a Randomized Clinical Trial (NoCovid)	70	Apr 2025
Unpublished			
NCT03661385	A Randomised Controlled Trial of Nitric Oxide Administration During Cardiopulmonary Bypass in Infants Undergoing Arterial	300	Apr 2023

NCT No.	Trial Name	Planned Enrollment	Completion Date
	Switch Operation for Repair of Transposition of the Great Arteries (NASO)		

NCT: national clinical trial.

Appendix 1

2021 Clinical Input

Clinical Input Objective

Clinical input was sought to help determine whether the use of inhaled nitric oxide for various populations would provide a clinically meaningful improvement in net health outcome and whether the use is consistent with generally accepted medical practice.

Respondents

Clinical input was provided by the following specialty societies and physician members identified by a specialty society or clinical health system:

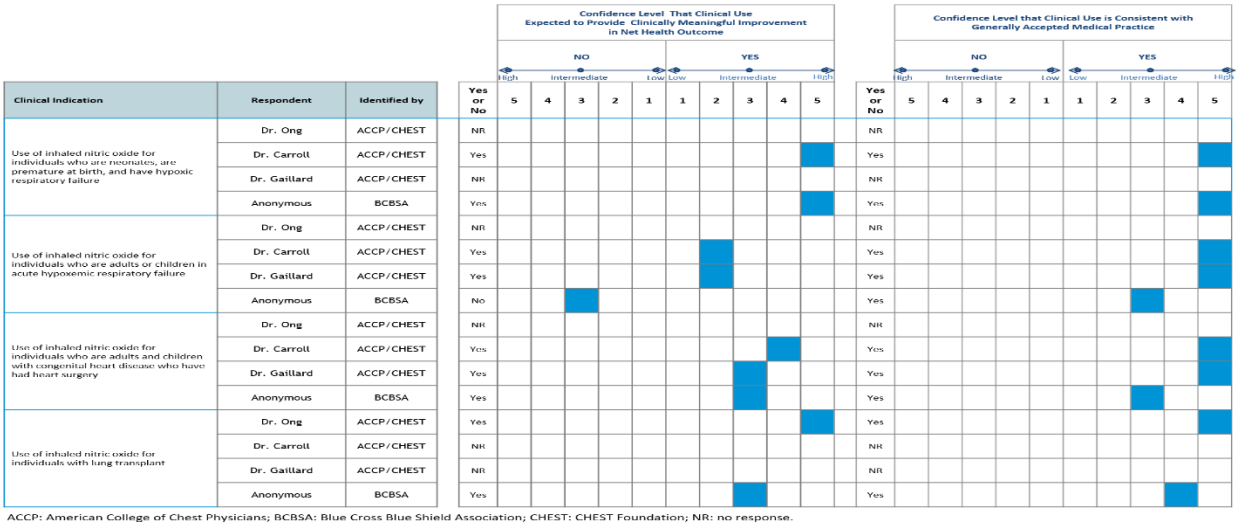
- Philip Ong, MD; Pulmonology/Lung Transplantation/Interventional Pulmonology, Assistant Professor, University of Texas Health San Antonio, identified by American College of Chest Physicians (ACCP/CHEST)
- Christopher L. Carroll, MD; Pediatric Critical Care; Professor of Pediatrics, University of Connecticut and Connecticut Children's, identified by ACCP/CHEST
- John P. Gaillard, MD; Critical Care, Emergency Medicine; Associate Professor of Anesthesia; Pulmonary, Critical Care, Allergy, and Immunologic Diseases; Emergency Medicine, Wake Forest Baptist Health, identified by ACCP/CHEST
- Anonymous, MD; Neonatology; Physician at an integrated healthcare organization, identified by BCBSA

* Indicates that no response was provided regarding conflicts of interest related to the topic where clinical input is being sought.

** Indicates that conflicts of interest related to the topic where clinical input is being sought were identified by this respondent (see Appendix).

Clinical input provided by the specialty society at an aggregate level is attributed to the specialty society. Clinical input provided by a physician member designated by a specialty society or health system is attributed to the individual physician and is not a statement from the specialty society or health system. Specialty society and physician respondents participating in the Evidence Street® clinical input process provide review, input, and feedback on topics being evaluated by Evidence Street. However, participation in the clinical input process by a specialty society and/or physician member designated by a specialty society or health system does not imply an endorsement or explicit agreement with the Evidence Opinion published by BCBSA or any Blue Plan.

Ratings



Clinical Indication	Respondent	Identified by	Yes or No	Confidence Level That Clinical Use Expected to Provide Clinically Meaningful Improvement in Net Health Outcome: NO (High 5, 4, Intermediate 3, 2, Low 1)	Confidence Level That Clinical Use Expected to Provide Clinically Meaningful Improvement in Net Health Outcome: YES (Low 1, Intermediate 2, 3, 4, High 5)	Yes or No	Confidence Level that Clinical Use is Consistent with Generally Accepted Medical Practice: NO (High 5, 4, Intermediate 3, 2, Low 1)	Confidence Level that Clinical Use is Consistent with Generally Accepted Medical Practice: YES (Low 1, 2, Intermediate 3, 4, High 5)
Use of inhaled nitric oxide for individuals who are neonates, are premature at birth, and have hypoxic respiratory failure	Dr. Ong	ACCP/CHEST	NR			NR		
	Dr. Carroll	ACCP/CHEST	Yes		5	Yes		5
	Dr. Gaillard	ACCP/CHEST	NR			NR		
	Anonymous	BCBSA	Yes		5	Yes		5
Use of inhaled nitric oxide for individuals who are adults or children in acute hypoxemic respiratory failure	Dr. Ong	ACCP/CHEST	NR			NR		
	Dr. Carroll	ACCP/CHEST	Yes		2	Yes		5
	Dr. Gaillard	ACCP/CHEST	Yes		2	Yes		5
	Anonymous	BCBSA	No	3		Yes	3	
Use of inhaled nitric oxide for individuals who are adults and children with congenital heart disease who have had heart surgery	Dr. Ong	ACCP/CHEST	NR			NR		
	Dr. Carroll	ACCP/CHEST	Yes		4	Yes		5
	Dr. Gaillard	ACCP/CHEST	Yes		3	Yes		5
	Anonymous	BCBSA	Yes		3	Yes	3	
Use of inhaled nitric oxide for individuals with lung transplant	Dr. Ong	ACCP/CHEST	Yes		5	Yes		5
	Dr. Carroll	ACCP/CHEST	NR			NR		
	Dr. Gaillard	ACCP/CHEST	NR			NR		
	Anonymous	BCBSA	Yes		3	Yes		4

ACCP: American College of Chest Physicians; BCBSA: Blue Cross Blue Shield Association; CHEST: CHEST Foundation; NR: no response.

* Indicates that no response was provided regarding conflicts of interest related to the topic where clinical input is being sought.

** Indicates that conflicts of interest related to the topic where clinical input is being sought were identified by this respondent (see Appendix).

Respondent Profile

	Physician				
#	Name	Degree	Institutional Affiliation	Clinical Specialty	Board Certification and Fellowship Training
Identified by American College of Chest Physicians (ACCP) / CHEST					
1	Philip Ong	MD	Assistant Professor, Pulmonary Diseases & Critical Care Medicine, University of Texas Health San Antonio	Pulmonology, Lung Transplantation, Interventional Pulmonology	Pulmonology, Critical Care, Lung Transplantation, Interventional Pulmonology
2	Christopher L. Carroll	MD	Professor of Pediatrics, University of Connecticut School of Medicine; Connecticut Children's Medical Center, Medical Director, Surgical Critical Care; Research Director, Pediatric Critical Care	Pediatric Critical Care	Pediatrics, Pediatric Clinical Care
3	John P. Gaillard	MD	Associate Professor, Anesthesia; Pulmonary, Critical Care, Allergy, and Immunologic Diseases; Emergency Medicine, Wake	Critical Care, Emergency Medicine	Critical Care, Emergency Medicine, Critical Care

	Physician				
			Forest Baptist Health		
Identified by Blue Cross Blue Shield Association (BCBSA)					
4	Anonymous	MD	Integrated healthcare organization	Neonatology	Neonatal-Perinatal Medicine

Respondent Conflict of Interest Disclosure

#	1) Research support related to the topic where clinical input is being sought		2) Positions, paid or unpaid, related to the topic where clinical input is being sought		3) Reportable, more than $1,000, health care–related assets or sources of income for myself, my spouse, or my dependent children related to the topic where clinical input is being sought		4) Reportable, more than $350, gifts or travel reimbursements for myself, my spouse, or my dependent children related to the topic where clinical input is being sought	
	YES/NO	Explanation	YES/NO	Explanation	YES/NO	Explanation	YES/NO	Explanation
1	No		No		No		No	
2	No		No		No		No	
3	No		No		No		No	
4	No		No		No		No	

Individual physician respondents answered at individual level. Specialty Society respondents provided aggregate information that may be relevant to the group of clinicians who provided input to the Society-level response. NR=not reported.

Responses

Question 1:

We are seeking your opinion on whether using inhaled nitric oxide for the four indications listed below provides a clinically meaningful improvement in net health outcome. Please respond based on the evidence and your clinical experience. Please address these points in your rationale:

- Relevant clinical scenarios (e.g., a chain of evidence) where the technology is expected to provide a clinically meaningfulimprovement in net health outcome;
- Specific outcomes that are clinically meaningful;
- Any relevant patient inclusion/exclusion criteria or clinical context important to consider in identifying individuals for thisindication;
- Supporting evidence from the authoritative scientific literature (please include PMID).

Indication 1: Individuals who are neonates, are premature at birth, and have hypoxic respiratory failure

#	Rationale
1	Not qualified to comment
2	Nitric Oxide is a critical therapy for neonates with hypoxic respiratory failure and pulmonary hypertension. In this population nitric oxide has been standard care for 20 years and has been shown to decrease the need for extracorporeal life support in newborns with pulmonary hypertension (Neonatal Inhaled Nitric Oxide Study Group. Inhaled nitric oxide in full-term and nearly full-term infants with hypoxic respiratory failure. N Engl J Med. 1997 Feb 27;336(9):597-604. Erratum in: N Engl J Med 1997 Aug 7;337(6):434. PMID: 9036320.)
3	I have no clinical experience with iNO in this patient population.
4	Premature infants <34 weeks: 1. Relevant clinical scenarios where the iNO is expected to provide clinically meaningful net health outcomes a. Infants born premature with severe hypoxemia that is primarily due to persistent pulmonary hypertension (PPHN) physiology b. Infants born Preterm with oligohydramnios and premature prolonged rupture of membrane (PPROM) c. Infants born premature with suspected or proven pulmonary hypoplasia 2. Specific outcomes that are clinically meaningful

#	Rationale
	a. Decreased Fio2 b. Improved PaO2 c. Reduced mortality 3. Any relevant patient inclusion/exclusion criteria or clinical context important to consider in identifying individuals for this indication a. Current evidence suggests that iNO does not improve bronchopulmonary dysplasia b. Current evidence does not support use of iNO for chronic lung disease 1. Abman, S. H., Hansmann, G., Archer, S. L., Ivy, D. D., Adatia, I., Chung, W. K.,... the American Thoracic, S. (2015). Pediatric Pulmonary Hypertension: Guidelines From the American Heart Association and American Thoracic Society. Circulation, 132(21), 2037-2099. doi:10.1161/CIR.0000000000000329. PMID: 26534956 2. Alvarado Socarras, J. L., Monsalve, J. C., & Diaz Quijano, F. A. (2018). Inhaled Nitric Oxide in Preterm Neonates with Refractory Hypoxemia Associated to Oligohydramnios. Curr Drug Discov Technol, 15(2), 156-160. doi:10.2174/1570163814666171017162730. PMID: 29046161 3. Chock, V. Y., Van Meurs, K. P., Hintz, S. R., Ehrenkranz, R. A., Lemons, J. A., Kendrick, D. E.,... Network, N. N. R. (2009). Inhaled nitric oxide for preterm premature rupture of membranes, oligohydramnios, and pulmonary hypoplasia. Am J Perinatol, 26(4), 317-322. doi:10.1055/s-0028-1104743. PMID: 19067285 4. Geary, C., & Whitsett, J. (2002). Inhaled nitric oxide for oligohydramnios-induced pulmonary hypoplasia: a report of two cases and review of the literature. J Perinatol, 22(1), 82-85. doi:10.1038/sj.jp.7210580. PMID: 11840249 5. Kinsella, J. P., Steinhorn, R. H., Krishnan, U. S., Feinstein, J. A., Adatia, I., Austin, E. D.,... Abman, S. H. (2016). Recommendations for the Use of Inhaled Nitric Oxide Therapy in Premature Newborns with Severe Pulmonary Hypertension. J Pediatr, 170, 312-314. doi:10.1016/j.jpeds.2015.11.050. PMID: 26703869 6. Lakshminrusimha, S., Kinsella, J. P., Krishnan, U. S., Van Meurs, K., Edwards, E. M., Bhatt, D. R.,... Abman, S. H. (2020). Just Say No to iNO in Preterms-Really? J Pediatr, 218, 243-252. doi:10.1016/j.jpeds.2019.10.063. PMID: 31810629

Indication 2: Individuals who are adults or children in acute hypoxemic respiratory failure

#	Rationale
1	Not qualified to comment
2	For adults and children with profound hypoxemia, iNO often improves oxygenation. iNO helps dilate the pulmonary arteries so that V/Q mismatch is improved and RV afterload is reduced. It is often used as a rescue therapy and as a bridge to ECMO.
3	For adults with profound hypoxemia, iNO often improves oxygenation. iNO helps dilate the pulmonary arteries so that V/Q mismatch is improved and RV afterload is reduced.
4	1. Specific outcomes that are clinically meaningful; a. iNO for acute respiratory distress syndrome and acute lung injury in adults and children i. 14 RCTs with total of 1303 participants (Afshari, Brok, Moller, & Wetterslev, 2011) 1. iNO showed no statistically significant effect on overall mortality 2. Limited data demonstrated a statistically insignificant effect of iNO on duration of ventilation, ventilator-free days, and length of stay in the intensive care unit and hospital 3. statistically significant but transient improvement in oxygenation in the first 24 hours ii. concerns with increased risk of renal failure b. iNO for Acute hypoxemic respiratory failure (Gebistorf, Karam, Wetterslev, & Afshari, 2016) i. i. There appears to be a statistically significant improvement in oxygenation at 24 hours ii. There was no statistically significant improvement in ventilator days iii. No statistically significant effects of iNO on mortality in adults iv. No statistically significant effects of iNO on mortality in children v. There was a statistically significant increase in renal failure in the iNO group 2. Any relevant patient inclusion/exclusion criteria or clinical context important to consider in identifying individuals for this indication; a. Patients at risk for renal failure b. Patients with renal failure

#	Rationale
	i. There appears to be a statistically significant risk for increased renal failure in patients who received iNO c. Could be considered as a temporary measure prior to initiating ECMO or starting Sildinofil for severe pulmonary hypertension 1. Afshari, A., Brok, J., Moller, A. M., & Wetterslev, J. (2011). Inhaled nitric oxide for acute respiratory distress syndrome and acute lung injury in adults and children: a systematic review with meta-analysis and trial sequential analysis. Anesth Analg, 112(6), 1411-1421. doi:10.1213/ANE.0b013e31820bd185. PMID:20614430 2. Gebistorf, F., Karam, O., Wetterslev, J., & Afshari, A. (2016). Inhaled nitric oxide for acute respiratory distress syndrome (ARDS) in children and adults. Cochrane Database Syst Rev(6), CD002787. doi:10.1002/14651858.CD002787.pub3. PMID:27347773

Indication 3: Individuals who are adults and children with congenital heart disease who have had heart surgery

#	Rationale
1	Not qualified to comment
2	iNO is widely used in children and adults with congenital heart disease. In patients with pulmonary hypertension, iNO can improve outcomes by improving perioperative pulmonary hypertension. However, even absent pulmonary hypertension, the right ventricle is frequently dysfunctional following cardiac surgery due to surgical approaches. At times, reducing afterload to the right ventricle by reducing pulmonary pressures can significantly improve a patients condition perioperatively.
3	iNO helps dilate the pulmonary arteries so that V/Q mismatch is improved and RV afterload is reduced.
4	1. Relevant clinical scenarios where the iNO is expected to provide clinically meaningful net health outcomes 1. Pediatric cardiac population 2. Adult patients with congenital heart disease 2. Specific outcomes that are clinically meaningful a. Decreased mean pulmonary artery pressure b. Length of stay remained unchanged with iNO c. Use of iNO associated with increased mortality in patients WITHOUT pulmonary hypertension d. Use of iNO appears to be associated with increased length of stay in patients WITHOUT pulmonary hypertension (length of stay increased by 10 days compared to 3 days for patients with pulmonary hypertension)-(Wong, et.al. 2019) e. Use of iNO does not impact mortality in patients WITH pulmonary hypertension f. Routine use of iNO after congenital heart surgery can lessen the risk of pulmonary hypertensive crises and shorten postoperative course with no toxic effects. g. Better mid-term survival is obtained, in adult patent with congenital heart disease an pulmonary arterial hypertension, when pulmonary vascular reactivity, defined as responsiveness to iNO, is preserved (Post, Janssens, Van de Werf, & Budts, 2004) 3. Any relevant patient inclusion/exclusion criteria or clinical context important to consider in identifying individuals for this indication a. There is no benefit of iNO for patients without pulmonary hypertension 1. Bizzarro, M., Gross, I., & Barbosa, F. T. (2014). Inhaled nitric oxide for the postoperative management of pulmonary hypertension in infants and children with congenital heart disease. Cochrane Database Syst Rev(7), CD005055. doi:10.1002/14651858.CD005055.pub3. PMID: 24991723 2. Curran, R. D., Mavroudis, C., Backer, C. L., Sautel, M., Zales, V. R., & Wessel, D. L. (1995). Inhaled nitric oxide for children with congenital heart disease and pulmonary hypertension. Ann Thorac Surg, 60(6), 1765-1771. doi:10.1016/0003-4975(95)00812-8. PMID: 8787478 3. Miller, O. I., Tang, S. F., Keech, A., Pigott, N. B., Beller, E., & Celermajer, D. S. (2000). Inhaled nitric oxide and prevention of pulmonary hypertension after congenital heart surgery: a randomised double-blind study. Lancet, 356(9240), 1464-1469. doi:10.1016/S0140-6736(00)02869-5. PMID: 11081528 4. Post, M. C., Janssens, S., Van de Werf, F., & Budts, W. (2004). Responsiveness to inhaled nitric oxide is a predictor for mid-term survival in adult patients with congenital heart defects and pulmonary arterial hypertension. Eur Heart J, 25(18), 1651-1656. doi:10.1016/j.ehj.2004.07.005. PMID: 15351165 5. Sardo, S., Osawa, E. A., Finco, G., Gomes Galas, F. R. B., de Almeida, J. P., Cutuli, S. L.,... Hajjar, L. A. (2018). Nitric Oxide in Cardiac Surgery: A Meta-Analysis of Randomized Controlled Trials. J Cardiothorac Vasc Anesth, 32(6), 2512-2519. doi:10.1053/j.jvca.2018.02.003. PMID: 29703580

#	Rationale
	6. Wong, J., Loomba, R. S., Evey, L., Bronicki, R. A., & Flores, S. (2019). Postoperative Inhaled Nitric Oxide Does Not Decrease Length of Stay in Pediatric Cardiac Surgery Admissions. Pediatr Cardiol, 40(8), 1559-1568. doi:10.1007/s00246-019-02187-z PMID:31446473

Indication 4: Individuals with lung transplant

#	Rationale
1	Nitric oxide is commonly used in patients with acute, chronic or acute and chronic right heart failure in the immediate perioperative period during lung transplantation. High pulmonary vascular resistance prior to transplant is common due to severe hypoxia from severe end stage lung disease, which results in right heart failure. Bilateral lung transplantation is usually sequential single lung transplant, which requires the right heart to handle single lung ventilation while the new contralateral lung graft is being grafted. At this point, the right ventricle needs to handle rapid shifts in pulmonary vascular resistance. Right heart failure is extremely common in the immediate perioperative period (within 0-5 days after transplantation) but eventually recovers after engraftment of the transplant. Furthermore, the new lung graft undergoes a period of ischemia during transport that producs hypoxic pulmonary vasoconstriction that compounds the issue. Nitric oxide is the shortest acting agent that can handle the rapid shifts in pulmonary vascular resistance and right heart pressure during the highest risk critical period. It is usually delivered inhaled to the target organ, and unlike IV prostacyclins has minimal systemic effect. Inhaled prostacyclins can also be given but due to its mechanism of effect (intermediate physiologic effect causing increase in NO), NO is usually given when rapid adjustments are required.
2	I have no clinical experience with iNO in this patient population.
3	I have no clinical experience with iNO in this patient population.
4	1. Relevant clinical scenarios where the iNO is expected to provide clinically meaningful net health outcomes a. While none of the studies reviewed was large enough to provide conclusive evidence, many suggest a benefit/utility in the use of iNO for individuals with lung transplantation i. Perioperative lung transplantation 1. iNO improves gas exchange and decreases pulmonary pressure in patients who develop reperfusion injury (Ardehali, et.al. 2001) 2. iNO protective against ischemia and repursion injury in the clinical setting of lung transplantation (Thabut, 2001) 3. Patients receiving iNO were discharged from hospital more quickly (Cornfield, et. Al. 2003) 4. iNO at the beginning of lung transplant and continued for first 48 hours decreases the incidence of primary graft dysfunction. 5. iNO continues to be recommended by ISHLT as vasoactive agent when acute vasodilator challenge is unsuccessful 6. ISHLT also recommends iNO for patients on waiting list for transplant to identify development of irreversible pulmonary vasoconstriction 2. Specific outcomes that are clinically meaningful a. Decreased Fio2, thus minimizing oxygen toxicity b. Improved PaO2, thus improved oxygenation c. Decreased reperfusion injury after lung transplantation d. Reduces mean Pulmonary arterial pressure

1. Ardehali, A., Laks, H., Levine, M., Shpiner, R., Ross, D., Watson, L. D.,... Waters, P. F. (2001). A prospective trial of inhaled nitric oxide in clinical lung transplantation. Transplantation, 72(1), 112-115. doi:10.1097/00007890-200107150-00022. PMID: 11468544
2. Cornfield, D. N., Milla, C. E., Haddad, I. Y., Barbato, J. E., & Park, S. J. (2003). Safety of inhaled nitric oxide after lung transplantation. J Heart Lung Transplant, 22(8), 903-907. doi:10.1016/s1053-2498(02)00809-4.PMID: 12909471
3. Mehra, M. R., Canter, C. E., Hannan, M. M., Semigran, M. J., Uber, P. A., Baran, D. A.,... Transplantation, C. (2016). The 2016 International Society for Heart Lung Transplantation listing criteria for heart transplantation: A 10-year update. J Heart Lung Transplant, 35(1), 1-23. doi:10.1016/j.healun.2015.10.023. PMID26776864
4. Moreno, I., Vicente, R., Mir, A., Leon, I., Ramos, F., Vicente, J. L., & Barbera, M. (2009). Effects of inhaled nitric oxide on primary graft dysfunction in lung transplantation. Transplant Proc, 41(6), 2210-2212. doi:10.1016/j.transproceed.2009.05.019. PMID: 19715875

#	Rationale
	5. Thabut, G., Brugiere, O., Leseche, G., Stern, J. B., Fradj, K., Herve, P.,... Mal, H. (2001). Preventive effect of inhaled nitric oxide and pentoxifylline on ischemia/reperfusion injury after lung transplantation. Transplantation, 71(9), 1295-1300. doi:10.1097/00007890-200105150-00019. PMID:11397965
	6. Yerebakan, C., Ugurlucan, M., Bayraktar, S., Bethea, B. T., & Conte, J. V. (2009). Effects of inhaled nitric oxide following lung transplantation. J Card Surg, 24(3), 269-274. doi:10.1111/j.1540-8191.2009.00833.x. PMID: 19438780

Question 2:
Would you agree that the following criterion for hypoxic respiratory failure is clinically appropriate? An oxygenation index (OI) of at least 25 on 2 measurements made at least 15 minutes apart.
(The OI is calculated as the mean airway pressure times the fraction of inspired oxygen divided by the partial pressure of arterial oxygen times 100. An OI of 25 is associated with a 50% risk of requiring extracorporeal membrane oxygenation [ECMO] or dying. An OI of 40 or more is often used as a criterion to initiate ECMO therapy.)

- Respond YES or NO; AND
- Please provide any supporting comments below.

#	YES / NO	Comments
1	Yes	Hypoxemic respiratory failure is commonly multifactorial. It may be a combination of volume overload, and non-cardiogenic edema(inflammatory extravasation of fluid). Although ECMO is increasingly used as rescue therapy, it is not available in most centers. Furthermore, ECMO is typically recommended only in 2 situations: as a bridge to transplant, and as a bridge to recovery. In many situations, improving ventilation-perfusion mismatch by abrogating inappropriate hypoxic vasoconstriction may buy enough time for the clinician to help reverse the hypoxemia. ARDS is the culmination of multiple factors but is a spectrum. Many studies of NO in ARDS or hypoxic respiratory failure do not show survival advantage, but there is literature to show at least transient improvement in hypoxia. This may sometimes buy enough time to bridge the patient to more advanced treatments such as lung transplant or ECMO.
2	Yes	This is a reasonable definition. For profound hypoxemia, iNO often improves oxygenation. iNO helps dilate the pulmonary arteries so that V/Q mismatch is improved and RV afterload is reduced.
3	Yes	For profound hypoxemia, iNO often improves oxygenation. iNO helps dilate the pulmonary arteries so that V/Q mismatch is improved and RV afterload is reduced.
4	No	This statement is not entirely accurate and is somewhat dependent on scenario, age of the patient and other factors that suggest impaired tissue oxygenation. In newborns who meet criteria for ECMO, an OI of >40 is predictive of a mortality risk of 80-90%. OI >40, PaO2 < 50 for 4 hours often used to as criteria for initiation of ECMO. Patients with an OI of 25-40 are predicted to have a 50-80% mortality (data from the University of MI retrieved from: http://www.med.umich.edu/ecmo/physicians/neonatal.html on 1/31/2021.) For Pediatric respiratory failure; OI > 25 and not improving combined with one sign of impaired tissue oxygenation such as: 1) rising serum lactate; 2) widening arterial-venous saturation gradient; 3) diminishing urine output; 5) increasing need for vasoactive support; 6) worsening metabolic acidosis. Therefore, multiple factors and not OI alone should be used in determining need for ECMO and risk of dying. 1)Friedman, M., & Hobson, M. (2018). Extracorporeal Membrane Oxygenation for Acute Pediatric Respiratory Failure. Pediatric Critical Care: Current Controversies, 17–41. https://doi.org/10.1007/978-3-319-96499-7_2. PMCID: PMC7119989

Question 3:
Prolonged use (>1-2 weeks) of inhaled nitric oxide has not been shown to improve outcomes. Use of inhaled nitric oxide beyond 2 weeks of treatment is therefore not recommended.

- Respond YES or NO; AND

- Please provide any supporting comments below.

#	YES / NO	Rationale
1	Yes	Tachyphylaxis to inhaled NO is well documented after 4-5 days. Therefore, prolonged use such as the situation stated without correcting the underlying reason for the respiratory failure likely will not produce additional effect.
2	No	Although I agree that prolonged use of inhaled nitric oxide has not been shown to improve outcomes, one cannot predict before starting the medication which patients will respond to nitric oxide and improve and wean off, and which patients will not. Frequently, it is challenging to wean off nitric oxide once started, so an arbitrary cutoff would be difficult to adhere to.
3	No	I know of no data to support this statement.
4	No	I disagree with this statement both from personal clinical experience with infants (unpublished) in the NICU and from review of the literature in both pediatric and adult medicine. Ivy et. Al. 1998, reported experience with 8 children with pulmonary hypertension who received short-term pulsed nasal delivery of iNO and found that iNO was effective in lowering pulmonary artery pressure and pulmonary vascular resistance. Inhaled Nitric oxide was found to have utility as a bridge to heart-lung transplantation in patients with end-stage pulmonary hypertension. (Snell, et. Al. 1995) Perez-Penate, et. Al. 2008, found that long-term treatment with ambulatory iNO, after 1 month of treatment improved walking distance, mean pulmonary artery pressure, pulmonary vascular resistance and cardiac index; these findings were sustained at 1 year. There were no reports of changes in metHb levels, adverse reactions, nitric oxide toxicity or rebound pulmonary hypertension from sudden withdrawal. Importantly, 8 of the 11 patients in the Perez-Penata cohort, who led a nonsendentary life were able to leave their home daily, with 4 returning to work while on long-term iNO therapy. In a second case report, Perez-Penata, et.al, 2001, followed a 32 year old male with primary hypertension and found that after prolonged NO mono-therapy, improved dyspnea, gas exchange and PaO2 levels with no signs of toxicity or tachyphylaxis. 1. Barst, R. J., Channick, R., Ivy, D., & Goldstein, B. (2012). Clinical perspectives with long-term pulsed inhaled nitric oxide for the treatment of pulmonary arterial hypertension. Pulm Circ, 2(2), 139-147. doi:10.4103/2045-8932.97589. PMID: 22837854 2. Ivy, D. D., Griebel, J. L., Kinsella, J. P., & Abman, S. H. (1998). Acute hemodynamic effects of pulsed delivery of low flow nasal nitric oxide in children with pulmonary hypertension. J Pediatr, 133(3), 453-456. doi:10.1016/s0022-3476(98)70287-2. PMID: 9738734 3. Perez-Penate, G., Julia-Serda, G., Pulido-Duque, J. M., Gorriz-Gomez, E., & Cabrera-Navarro, P. (2001). One-year continuous inhaled nitric oxide for primary pulmonary hypertension. Chest, 119(3), 970-973. doi:10.1378/chest.119.3.970. PMID: 11243987 4. Perez-Penate, G. M., Julia-Serda, G., Ojeda-Betancort, N., Garcia-Quintana, A., Pulido-Duque, J., Rodriguez-Perez, A.,... Gomez-Sanchez, M. A. (2008). Long-term inhaled nitric oxide plus phosphodiesterase 5 inhibitors for severe pulmonary hypertension. J Heart Lung Transplant, 27(12), 1326-1332. doi:10.1016/j.healun.2008.08.007. PMID: 19059113 5. Snell, G. I., Salamonsen, R. F., Bergin, P., Esmore, D. S., Khan, S., & Williams, T. J. (1995). Inhaled nitric oxide used as a bridge to heart-lung transplantation in a patient with end-stage pulmonary hypertension. Am J Respir Crit Care Med, 151(4), 1263-1266. doi:10.1164/ajrccm/151.4.1263. PMID: 7697264

Question 4:
Would you agree that the following statement is clinically appropriate?
If extracorporeal membrane oxygenation is initiated in near-term neonates, inhaled nitric oxide should be discontinued because there is no benefit to combined treatment.

- Respond YES or NO; AND
- Please provide any supporting comments below.

#	YES / NO	Comments
1	NR	Not qualified to answer
2	Yes	NR
3	Yes	Once on ECMO, tidal volumes drop significantly so that the ability to inhale the NO drops dramatically, thus negating its effect.
4	Yes	One study (Muller, et. al. 1996) found utility in continuing iNO during ECMO in 6 out of 10 patients; 4 were non-responders. No data on whether NO shortened ECMO duration or improved survival were reported in this study, additionally, this study was too small to be conclusive. Theoretically, once on ECMO, the lungs are allowed to rest and it is the ECMO circuit that performs the function of ventilation and oxygenation, therefore use of iNO during ECMO seems counterintuitive. It is possible however, that the use of iNO during ECMO might be useful while trialing patients off of ECMO (Tadphale, et. al. 2016). Tadphale, 2016 found that the duration of ECMO, duration of mechanical ventilation, and duration of hospital stay were longer among the patients in the iNO during ECMO group. In a stratified analysis, the authors found worse mortality among patients receiving NO during ECMO. Based on lack of evidence to support continuing iNO during an ECMO run, concerns for increased mortality, I would agree that if extracorporeal membrane oxygenation is initiated in near-term neonates, inhaled nitric oxide should be discontinued because there is no benefit to combined treatment. 1. Muller, W., Kachel, W., Lasch, P., Varnholt, V., & Konig, S. (1996). Inhaled nitric oxide during extracorporeal membrane oxygenation for the treatment of severe persistent pulmonary hypertension of the newborn. Artif Organs, 20(1), 60-63. doi:10.1111/j.1525-1594.1996.tb04420.x. PMID: 8645132 2. Tadphale, S. D., Rettiganti, M., Gossett, J. M., Beam, B. W., Padiyath, A., Schmitz, M. L., & Gupta, P. (2016). Is Administration of Nitric Oxide During Extracorporeal Membrane Oxygenation Associated With Improved Patient Survival? Pediatr Crit Care Med, 17(11), 1080-1087. doi:10.1097/PCC.0000000000000939. PMID: 27632059

NR: not reported.

Question 5:
The benefit of inhaled nitric oxide appears limited in term or near-term infants whose hypoxic respiratory failure is due to diaphragmatic hernia.

- Respond YES or NO; AND
- Please provide any supporting comments below.

#	YES / NO	Comments
1	NR	Not qualified to answer
2	No	This is incorrect. Frequently these infants with diaphragmatic hernias have associated pulmonary hypertension for which iNO is beneficial.
3	NR	I have no clinical response with iNO in this patient population.
4	Yes	While previous studies have suggested no benefit to using iNO in patients with CDH, these studies did not assess severity of pulmonary hypertension or left ventricular function. In a recent study by Lawrence, et. al, 2020, iNO treatment was associated with improved oxygenation and reduced need for ECMO in a subpopulation of neonates with CDH and hypoxic respiratory failure who also had pulmonary hypertension and normal left ventricular systolic function. In contrast, iNO therapy did not improve oxygenation in patients with LV dysfunction, CDH and hypoxic respiratory failure. Patients who responded to treatment were less likely to be treated with ECMO or die from hypoxemic respiratory failure (Lawrence, et.al, 2020). Importantly, Lawrence, et.al, showed that it is

#	YES / NO	Comments
		the LV systolic dysfunction, rather than LV size that was associate with lack of response to treatment and subsequent ECMO treatment, potentially suggesting that pulmonary vasodilation and increased pulmonary venous return could precipitate cardiorespiratory failure in this subset of patients (Lawrence, et al 2020). Both the Canadian CDH collaborative and the American Heart Association guidelines state iNO therapy can be used to treat pulmonary hypertension in neonates with CDH and normal LV function, but should be discontinued if no clinical improvement is seen after 24 hours of treatment. 1. Abman, S. H., Hansmann, G., Archer, S. L., Ivy, D. D., Adatia, I., Chung, W. K.,... the American Thoracic, S. (2015). Pediatric Pulmonary Hypertension: Guidelines From the American Heart Association and American Thoracic Society. Circulation, 132(21), 2037-2099. doi:10.1161/CIR.0000000000000329. PMID: 26534956 2. Canadian Congenital Diaphragmatic Hernia, C., Puligandla, P. S., Skarsgard, E. D., Offringa, M., Adatia, I., Baird, R.,... Traynor, M. (2018). Diagnosis and management of congenital diaphragmatic hernia: a clinical practice guideline. CMAJ, 190(4), E103-E112. doi:10.1503/cmaj.170206. PMID: 29378870 3. Lawrence, K. M., Monos, S., Adams, S., Herkert, L., Peranteau, W. H., Munson, D. A.,... Hedrick, H. L. (2020). Inhaled Nitric Oxide Is Associated with Improved Oxygenation in a Subpopulation of Infants with Congenital Diaphragmatic Hernia and Pulmonary Hypertension. J Pediatr, 219, 167-172. doi:10.1016/j.jpeds.2019.09.052. PMID: 31706636

NR: not reported.

Question 6:

Additional narrative rationale or comments regarding the clinical context or specific clinical pathways for this topic and/or any relevant scientific citations (including the PMID) with evidence that demonstrates health outcomes you would like to highlight.

#	Additional Comments
1	NR
2	NR
3	NR
4	With respect to use of iNO in premature infants (<34 weeks gestational age) with clinically significant pulmonary hypertension, there is evolving literature that suggests that these infants may benefit from use of iNO. Currently, in the clinical setting, premature infants with noted shunting as document by pre/post ductal sats and/or with pulmonary hypertension documented by echo have shown improvement and clinical stability upon initiating iNO. Therefore, its use should not be discounted in this population of patients. Cheng, D. R., Peart, S., Tan, K., & Sehgal, A. (2016). Nitric therapy in preterm infants: rationalised approach based on functional neonatal echocardiography. Acta Paediatr, 105(2), 165-171. doi:10.1111/apa.13238. PMID: 26450016

NR: not reported.

Question 7:

Is there any evidence missing from the attached draft review of evidence that demonstrates clinically meaningful improvement in net health outcome?

#	YES / NO	Citations of Missing Evidence
1	Yes	Yerebakan C, Ugurlucan M, Bayraktar S, Bethea BT, Conte JV. Effects of inhaled nitric oxide following lung transplantation. J Card Surg. 2009 May-Jun;24(3):269-74. doi: 10.1111/j.1540-8191.2009.00833.x. PMID: 19438780. Adatia I, Lillehei C, Arnold JH, Thompson JE, Palazzo R, Fackler JC, Wessel DL. Inhaled nitric oxide in the treatment of postoperative graft dysfunction after lung transplantation. Ann Thorac Surg. 1994 May;57(5):1311-8. doi: 10.1016/0003-4975(94)91382-x. PMID: 8179406.

#	YES / NO	Citations of Missing Evidence
		Cornfield DN, Milla CE, Haddad IY, Barbato JE, Park SJ. Safety of inhaled nitric oxide after lung transplantation. J Heart Lung Transplant. 2003 Aug;22(8):903-7. doi: 10.1016/s1053-2498(02)00809-4. PMID: 12909471. Date H, Triantafillou AN, Trulock EP, Pohl MS, Cooper JD, Patterson GA. Inhaled nitric oxide reduces human lung allograft dysfunction. J Thorac Cardiovasc Surg. 1996 May;111(5):913-9. doi: 10.1016/s0022-5223(96)70364-1. PMID: 8622313.
2	No	NR
3	No	NR
4	No	NR

NR: not reported.

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Documentation for Clinical Review

Please provide the following documentation:

- History and physical and/or consultation notes including:
  - Reason for needing iNO including diagnosis and circumstances
  - Previous treatment(s) and response(s)

- MD progress notes and orders (specific to inhaled nitric oxide therapy) with documentation of ongoing need for each day of use
- Inhalation/respiratory therapy notes (specific to inhaled nitric oxide therapy) including:
  - Arterial blood gases (ABGs)
  - Nitric oxide administration
  - Oxygenation indices
  - Pulse oximetry records

Post Service (in addition to the above, please include the following):

- Discharge summary (if available)

Coding

The list of codes in this Medical Policy is intended as a general reference and may not cover all codes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy.

Type	Code	Description
CPT®	None	
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
03/30/2012	New Policy adoption
01/11/2013	Policy revision without position change
04/16/2014	Policy revision without position change
06/30/2015	Coding update
07/01/2016	Policy revision without position change
07/01/2017	Policy revision without position change
07/01/2018	Policy revision without position change
08/01/2019	Policy revision without position change
07/01/2020	Annual review. No change to policy statement. Literature review updated.
07/01/2021	Annual review. No change to policy statement. Policy guidelines and literature review updated.
07/01/2022	Annual review. Policy statement, guidelines and literature review updated.
07/01/2023	Annual review. No change to policy statement. Literature review updated.
07/01/2024	Annual review. No change to policy statement. Policy guidelines and literature review updated.
07/01/2025	Annual review. No change to policy statement and policy guidelines. Literature review updated.

Definitions of Decision Determinations

Healthcare Services: For the purpose of this Medical Policy, Healthcare Services means procedures, treatments, supplies, devices, and equipment.

Medically Necessary: Healthcare Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield of California, are: (a) consistent with Blue Shield of California medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the member; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the member's illness, injury, or disease.

Investigational or Experimental: Healthcare Services which do not meet ALL of the following five (5) elements are considered investigational or experimental:

A. The technology must have final approval from the appropriate government regulatory bodies.
   - This criterion applies to drugs, biological products, devices and any other product or procedure that must have final approval to market from the U.S. Food and Drug Administration ("FDA") or any other federal governmental body with authority to regulate the use of the technology.
   - Any approval that is granted as an interim step in the FDA's or any other federal governmental body's regulatory process is not sufficient.
   - The indications for which the technology is approved need not be the same as those which Blue Shield of California is evaluating.

B. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.
   - The evidence should consist of well-designed and well-conducted investigations published in peer-reviewed journals. The quality of the body of studies and the consistency of the results are considered in evaluating the evidence.
   - The evidence should demonstrate that the technology can measure or alter the physiological changes related to a disease, injury, illness, or condition. In addition, there should be evidence, or a convincing argument based on established medical facts that such measurement or alteration affects health outcomes.

C. The technology must improve the net health outcome.
   - The technology's beneficial effects on health outcomes should outweigh any harmful effects on health outcomes.

D. The technology must be as beneficial as any established alternatives.
   - The technology should improve the net health outcome as much as, or more than, established alternatives.

E. The improvement must be attainable outside the investigational setting.
   - When used under the usual conditions of medical practice, the technology should be reasonably expected to satisfy Criteria C and D.

Feedback

Blue Shield of California is interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration. Our medical policies are available to view or download at www.blueshieldca.com/provider.

For medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as member health services contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member health services contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT (No changes)	
BEFORE	AFTER
Inhaled Nitric Oxide 8.01.37 Policy Statement: I. Inhaled nitric oxide (INO) may be considered **medically necessary** as a component of treatment of: A. Hypoxic respiratory failure in neonates born at more than 34 weeks of gestation II. Other indications for inhaled nitric oxide are considered **investigational**, including, but not limited to: A. Treatment of premature neonates born at less than or equal to 34 weeks of gestation with hypoxic respiratory failure B. Treatment of adults and children with acute hypoxemic respiratory failure C. Postoperative use in adults and children with congenital heart disease D. In lung transplantation, during and/or after graft reperfusion	Inhaled Nitric Oxide 8.01.37 Policy Statement: I. Inhaled nitric oxide (INO) may be considered **medically necessary** as a component of treatment of: A. Hypoxic respiratory failure in neonates born at more than 34 weeks of gestation II. Other indications for inhaled nitric oxide are considered **investigational**, including, but not limited to: A. Treatment of premature neonates born at less than or equal to 34 weeks of gestation with hypoxic respiratory failure B. Treatment of adults and children with acute hypoxemic respiratory failure C. Postoperative use in adults and children with congenital heart disease D. In lung transplantation, during and/or after graft reperfusion