BlueCross BlueShield of Alabama

Name of Blue Advantage Policy:

Inhaled Nitric Oxide

Policy #: 440
Category: Therapy

Latest Review Date: June 2019
Policy Grade: B

Background:

Blue Advantage *medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:*

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*
   - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
   - *Furnished in a setting appropriate to the patient's medical needs and condition;*
   - *Ordered and furnished by qualified personnel;*
   - *One that meets, but does not exceed, the patient's medical need; and*
   - *At least as beneficial as an existing and available medically appropriate alternative.*

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill* ***Original Medicare* *for covered services that are related to* ***clinical trials*** *that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

Proprietary Information of Blue Cross and Blue Shield of Alabama
An Independent Licensee of the Blue Cross and Blue Shield Association

Description of Procedure or Service:

Inhaled nitric oxide (INO), a treatment for neonates who have hypoxic respiratory failure, is intended to improve oxygenation, reduce mortality rates, and reduce the need for invasive extracorporeal membrane oxygenation (ECMO). It is also proposed as a treatment for premature infants, critically ill children, adults with respiratory failure, in the postoperative management of children undergoing repair of congenital heart disease and in lung transplantation to prevent or reduce reperfusion injury.

Hypoxic Respiratory Failure

Hypoxic respiratory failure may result from respiratory distress syndrome (RDS), persistent pulmonary hypertension, meconium aspiration, pneumonia, or sepsis.

Treatment

Treatment consists of oxygen support, mechanical ventilation, and 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. INO has also been proposed for use in preterm infants less than 34 weeks of gestation and in adults.

In addition, inhaled nitric oxide is proposed for management of 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 post-operative pulmonary hypertension, which can prevent weaning from ventilation and is associated with substantial morbidity and mortality. Another potential surgical application is use of INO in lung transplantation to prevent or reduce reperfusion injury.

Clinical input from academic medical centers and specialty societies obtained by the Blue Cross and Blue Shield Association in 2012 indicated that:

- Prolonged use of INO [inhaled NO] beyond one to two weeks has not been shown to improve outcomes. Use of INO beyond two weeks of treatment is therefore not recommended.
- If ECMO is initiated in near-term neonates, INO should be discontinued as there is no benefit to combined treatment.

Policy:

Effective for dates of service on or after November 8, 2011:

Blue Advantage will treat **inhaled nitric oxide** as a **covered** benefit as a **component of treatment of hypoxic respiratory failure in neonates born at more than 34 weeks of gestation**.

Blue Advantage will treat **other indications for inhaled nitric oxide** as a **non-covered** benefit and as **investigational**, including, but not limited to:

- Treatment of premature neonates born at less than or equal to 34 weeks of gestation with hypoxic respiratory failure;
- Treatment of adults and children with acute hypoxemic respiratory failure;
- Postoperative use in adults and children with congenital heart disease;
- In lung transplantation, during and/or after graft reperfusion.

Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

This policy includes literature found via MEDLINE search through March 21, 2019.

The clinical evidence to determine whether the use of technology improves the net health outcome is assessed by evidence reviews. Health outcomes are assessed by the 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 managing the course of that condition. Outcome measures are validated 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.

The net health outcome of technology is assessed by whether the evidence is sufficient enough to draw conclusions, while examining two domains: the relevance, and 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. In various conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence is determined by study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is favored to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs 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 Near-Term Neonates
Clinical Context and Therapy Purpose
The use of inhaled nitric oxide (INO) provides a treatment option that is an alternative to or an improvement on existing therapies in patients who are neonates, are term or late preterm at birth, and have hypoxic respiratory failure.

This evidence review poses the question: In patients who are neonates, are term or late preterm at birth, and have hypoxic respiratory failure, does INO improve the net health outcome?

The following PICOTS were used to select literature to inform this review.

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

Interventions
The treatment being considered is INO. INO is a natural vasodilator and has been evaluated 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 two 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 linked with INO is higher in premature infants.

Patients who are neonates, are term or late preterm at birth, and have hypoxic respiratory failure are actively managed by pulmonologists and primary care physicians in an outpatient clinical setting.

Comparators
Comparators include standard neonatal specialty care without INO managed by neonatologists and pulmonologists in a tertiary setting.

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

Table 1. Outcomes of Interest

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

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.

A number of randomized controlled trials (RCTs) and a Cochrane review of RCT data on inhaled nitric oxide (INO) in infants with hypoxia born at or near-term (>34 weeks of gestation) have been published. The Cochrane review, last updated in 2017, identified 17 trials. Ten trials compared INO to control (placebo or standard neonatal intensive care without INO) in infants with moderately severe illness scores. One of these allowed backup treatment with INO and 2 enrolled only infants with 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 studies, 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 1. Only findings in studies that did not allow backup INO and that were not limited to patients with diaphragmatic hernia are presented; there were too few studies on other subgroups to allow meaningful meta-analysis (n=1 that did not allow backup INO and n=2 that only included patients with diaphragmatic hernia).

Table 2. Main Findings From a 2017 Cochrane Meta-Analysis on INO in Term or Near-Term Infants

Trials	N	Outcome/End Point	RR	95% CI	p	I^2	Quality of Evidence (GRADE)
8	860	Death before hospital discharge	0.89	0.60 to 1.31	0.55	0%	High
7	815	ECMO before hospital discharge	0.60	0.50 to 0.71	<0.001	0%	High
8	859	ECMO before	0.66	0.57 to 0.77	<0.001	0%	High

		hospital discharge					

CI: confidence interval; ECMO: Extracorporeal membrane oxygenation: INO: inhaled nitric oxide.

The investigators found that INO in hypoxic infants significantly reduced the incidence of the combined end point of death or need for extracorporeal membrane oxygenation (ECMO) compared with controls, in studies that did not allow INO backup in controls. INO did not have a statistically significant effect on mortality as a 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 Near-Term Neonates
Evidence from RCTs and a meta-analysis of RCTs support the use of INO in term or near-term 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 use of inhaled nitric oxide (INO) provides a treatment option that is an alternative to or an improvement on existing therapies in patients who are neonates, are term or late preterm at birth, and have hypoxic respiratory failure.

The question addressed in this evidence review is: In patients who are neonates, are premature at birth, and have hypoxic respiratory failure does INO improve the net health outcome?

The following PICOTS were used to select literature to inform this review.

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

Interventions
The treatment being considered is INO. INO is a natural vasodilator and has been evaluated 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 necessity for invasive ECMO.

Comparators
Comparators include standard neonatal intensive care without INO. Patients who are neonates, are premature at birth, and have hypoxic respiratory failure are actively managed by neonatologists and pulmonologists in an inpatient clinical setting.

Outcomes
The outcomes of interest are OS, hospitalizations, resource utilization, and treatment-related morbidity.

Table 3. Outcomes of Interest

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

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.

In near-term neonates, the role of inhaled nitric oxide primarily functions as a vasodilator to treat pulmonary hypertension, often due to meconium aspiration or bacterial pneumonia. However, in preterm neonates with respiratory failure, pulmonary hypertension with shunting is not a clinical problem. Therefore, these two groups of neonates represent distinct clinical issues, and the results of INO in near-term neonates cannot be extrapolated to preterm neonates. In addition, there is concern regarding the possible risk of intraventricular hemorrhage associated with INO in premature infants.

Systematic Reviews

Numerous RCTs and several systematic reviews on INO for treating hypoxic respiratory failure in preterm neonates have been published. Most recently, a 2017 Cochrane review identified 17 RCTs on the efficacy of INO for treating premature infants (i.e., <35 weeks of gestation) with respiratory disease. The main findings of the meta-analysis are provided in Table 2. Results are reported separately for studies with entry before 3 days based on oxygenation, studies with entry after 3 days based on 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 Findings from a 2017 Cochrane Meta-Analysis on INO in Preterm Infants

Trials	N	Outcome/End Point	RR	95% CI	p	I^2	Quality of Evidence (GRADE)
		Death Before Hospital Discharge					

10	1066	Studies with entry before 3 days	1.02	0.89 to 1.18	0.75	3%	High
3	1075	Studies with entry after 3 days	1.18	0.81 to 1.71	0.39	0%	High
4	1924	Studies of routine use	0.90	0.74 to 1.10	0.32	50%	Moderate
		BPD at 36 Weeks					
8	681	Studies with entry before 3 days	0.89	0.76 to 1.04	0.13	29%	NR
3	990	Studies with entry after 3 days	0.91	0.83 to 1.01	0.068	11%	NR
4	1782	Studies of routine use	0.95	0.85 to 1.05	0.32	10%	NR
		BPD or Death at 36 Weeks					
8	957	Studies with entry before 3 days	0.94	0.87 to 1.01	0.084	26%	High
3	1075	Studies with entry after 3 days	0.92	0.85 to 1.01	0.079	51%	High
4	1924	Studies of routine use	0.94	0.87 to 1.02	0.12	11%	High

BPD: bronchopulmonary dysplasia; CI: confidence interval; INO: inhaled nitric oxide; NR: not reported.

The investigators found that INO in premature infants with respiratory failure did not significantly improve outcomes e.g. death before hospital discharge, BPD at 36 weeks' postmenstrual age or the combined outcome of BPD or death at 36 weeks' postmenstrual age. Findings were not statistically significant in subgroups of studies that enrolled patients before three 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 did not find a significant benefit of INO versus control (RR: 0.94, 95% CI: 0.69 to 1.28).

A 2016 meta-analysis by Yang et al identified 22 trials comparing INO to a control intervention in preterm infants. The authors did not report a definition of "preterm" for identifying 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 found a significantly lower rate of BPD in the INO compared with control groups (RR: 0.88, 95% CI: 0.82 to 0.95). The authors noted that their findings on BPD differed from those in other meta-analyses and stated that the difference may be due to their inclusion of Chinese language studies.

Previously, in 2011, an Agency for Healthcare Research and Quality (AHRQ) –sponsored systematic review of randomized trials on INO for premature infants (<35 weeks of gestation) was published. Thirty-one articles were initially selected; they included 14 unique RCTs. Regardless of how mortality was reported or defined (e.g., death within 7 days or 28 days, or death in the neonatal intensive care unit), there was no statistically significant difference between the INO group and control group in any of the 14 RCTs or in pooled analyses of 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 relative risk 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 relative risk of 0.93 (95% CI, 0.86 to 1.00).

Randomized Trials

The largest trial to date was published in 2010 by Mercier and colleagues. This was a multicenter industry-sponsored study known as the European Union Nitric Oxide trial and it evaluated low-dose INO therapy. A total of 792 of 800 (99%) of patients were given 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, overall survival (OS) at 36 weeks of postmenstrual age, and BPD at 36 weeks' postmenstrual age. The percent 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=0.29). The secondary end point of 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=0.23). This end point was attained by 181 (69%) patients in the INO group and 188 (76%) patients in the placebo group. The most common AE was intracranial hemorrhage, which affected 114 (29%) in the INO group and 91 (23%) in the control group (p value not reported).

In 2013, Durrmeyer et al published 2-year outcomes of the European Union Nitric Oxide trial. Of the original 800 patients, 737 (92%) were evaluable at this time point. The evaluable children excluded those who did not receive treatment or who were lost to follow-up. There were also no statistically significant differences between groups in other outcomes such as hospitalization rates, use of respiratory medications, or growth.

Table 5. Summary of Key RCT Characteristics

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Mercier (2010); EUNO	EU	36	2005-2008	Preterm infants (between 24 and 28 weeks GA) weighing ≥500g and requiring surfactant within 24 hr. of birth	INO 5 ppm (n=399)	Placebo-equivalent nitrogen gas (n=401)
Durrmeyer (2013); EUNO	EU	9	2005-2008	Infants born at <29 weeks GA with moderate respiratory failure	INO 5 ppm	Placebo-equivalent nitrogen gas

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

Table 6. Summary of Key RCT Results

Study	Survival Outcomes	Adverse Events
Mercier (2010); EUNO	**OS at 36 wks. PMA**	**Serious AEs[1]**
INO	343 (86%)	158 (40%)
Placebo	359 (90%)	164 (41%)
RR; 95% CI; P-value	0.74; 0.48–1.15; 0.21	NR; NR; 0.72
	Survival without BPD at 36 wks. PMA	
INO	258 (65%)	
Placebo	262 (66%)	
RR; 95% CI; P-value	1.05; 0.78–1.43; 0.73	
Durrmeyer (2013); EUNO	**OS between 36 wks. PMA and 2 yrs.**	
INO	391 (99%)	
Placebo	390 (98.2%)	
RR; 95% CI; P-value	NR; NR; NR	
	Survival without severe or moderate disability at 2 yrs.	
INO	244 (79.7%)	
Placebo	270 (83.3%)	
RR; 95% CI; P-value	NR; NR; 0.29	

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

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

Displaying notable limitations identified in each study is the purpose of the study design and conduct limitation table (see Table 7). This information is generated as a summary of the body of evidence following each table and delivers 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]	Follow-Up[d]	Power[e]	Statistical[f]
Mercier (2010);	3. Allocation concealment					

EUNO[a]	unclear					
Durrmeyer (2013); EUNO	3. Allocation concealment unclear					3. Confidence intervals not reported for all outcomes

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps 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] Follow-Up 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. Intervention is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Intervention 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 difference on primary end points such as mortality and BPD. Meta-analyses of these RCTs have not found better survival rates in patients who receive with INO compared with a control intervention. Most meta-analyses did not find other outcomes e.g. BPD and intracranial hemorrhage were improved by INO.

Acute Hypoxemic Respiratory Failure in Adults and Children

Clinical Context and Therapy Purpose

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

The question addressed in this evidence review is: In various pediatric and adult populations with acute hypoxemic respiratory failure, does INO improve the net health outcome?

The following PICOTS were used to select literature to inform this review.

Patients

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

Interventions

INO is a natural vasodilator and has been studied for a variety of types of respiratory failure and is the therapy being considered.

Comparators

Comparators include standard medical intensive care without INO. This is managed by pulmonologists and primary care providers in an inpatient clinical setting.

Outcomes

The outcomes of interest are OS, hospitalizations, resource utilization, and treatment-related morbidity.

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 – 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.

Systematic Reviews

A number of RCTs and several meta-analyses of RCTs have been published on the efficacy of INO for treating acute respiratory distress syndrome (ARDS) and acute lung injury (together known as acute hypoxemic respiratory failure [AHRF]). Most recently, 2016 Cochrane review identified 14 RCTs comparing INO with control in adults and children with ARDS. 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 Findings from a 2017 Cochrane Meta-Analysis on INO in Patients with ARDS

Trials	N	Outcome/End Point	RR	95% CI	p	I^2	Quality of Evidence (GRADE)
11	1243	Overall mortality	1.04	0.90 to 1.19	0.63	0%	Moderate
9	1105	Mortality at 28 to 30 days	1.08	0.92 to 1.27	0.36	0%	Moderate
		Overall mortality stratified by age group					
3	185	Pediatric	0.78	0.51 to 1.18	0.24	22%	Moderate
10	1085	Adult	1.09	0.93 to 1.25	0.32	0%	NR

ARDS: acute respiratory distress syndrome: CI: confidence interval; INO: inhaled nitric oxide: Not reported.

INO was not found to significantly improve mortality when used to treat ARDS. Other outcomes e.g., mean number of ventilator days and duration of mechanical ventilation also did

not differ significantly between groups. In terms of 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 versus control (RR: 1.59, 95% CI: 1.17 to 2.16).

Other systematic reviews and meta-analyses had similar findings on mortality. For example, a 2014 meta-analysis by Adhikari et al 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. Moreover, the trials included in the review 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. A pooled analysis of data from the 9 trials (total N=1142) found no statistically significant benefit of INO on mortality (RR=1.10, 95% CI, 0.94 to 1.29, p=0.24). In a preplanned subgroup analysis, INO did not reduce mortality in patients with severe ARDS (baseline PaO_2/ fraction of expired oxygen [FiO_2] ≤100 mmHg) or in patients with mild to moderate ARDS (baseline PaO2/FiO_2 >100mgHg).

Cohort Studies on Adverse Events

A 2016 cohort study by Ruan et al evaluated the risk of renal dysfunction in patients with ARDS treated with INO. Using electronic medical record data from a teaching hospital, 547 patients with ARDS were identified. Among these patients, 216 had been treated with INO and 331 had not received INO. The 30-day incidence of renal replacement therapy (RRT) 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 RRT in the INO versus the non-INO group (hazard ratio [HR]: 1.59 (95% CI: 1.08 to 2.34, p=0.02).

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. Meta-analyses of these RCTs have not found that INO significant reduces mortality or shortens the duration of mechanical ventilation. Moreover, a subanalysis 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 that INO increases the risk of renal impairment in patients with ARDS.

Adults and Children with Congenital Heart Disease Who Have Undergone Heart Surgery
Adults

A 2011 trial by Potapov et al evaluated the prophylactic use of INO in adult patients undergoing left ventricular assist device (LVAD) implantation for congestive heart failure. This double-blind trial was conducted at 8 centers in the United States 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 study 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 study treatment. In addition, 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 was not statistically significant (p=0.33). Other outcomes also did not differ significantly between groups. For example, mean number of days on mechanical ventilation (5.4 in the INO group vs 11.1 in the placebo group; p=0.77) and mean number of days in the hospital (41 in each group).

Children

A 2014 Cochrane review by Bizzarro et al identified 4 RCTs (total N=210 patients) comparing postoperative INO and placebo or usual care in the management of children with congenital heart disease. All trials included participants who were identified as having pulmonary hypertension in the preoperative or postoperative period. Three trials were parallel group, and 1 was a crossover. Mortality was the primary outcome of the Cochrane 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 (OR=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), 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). Insufficient data were available for pooled analyses of other outcomes. The reviewers noted the lack of data on long-term mortality, length of stay in an intensive care unit or hospital, and neurodevelopmental disability, and also had 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 confidence intervals around the pooled treatment effects reflect the relative paucity of data available for each outcome.

The RCT with the largest sample size was published by Miller et al in Australia in 2000. The trial included 124 infants (median age, 3 months) who were candidates for corrective heart surgery. Eligibility requirements included 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 presence (45/124 [36%]) or absence (79/124 [64%]) of Down syndrome. The primary outcome was reduction of pulmonary hypertensive crisis (PHTC) episodes, defined as a pulmonary/systemic artery pressure ratio more 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 study found that infants who received INO after surgery had significantly fewer PHTC episodes (median, 4) than those who received placebo (median, 7; unadjusted RR=0.66; 95% CI, 0.59 to 0.74; p<0.001). 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=0.019). There were 5 deaths in the INO group and 3 deaths in the placebo group; this difference was not statistically significant (p=0.49). Similarly, there was no significant difference in median time to discharge from intensive care (138 hours for INO vs 162 hours for placebo; p>0.05). 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 study was likely underpowered to detect differences in these more clinically relevant secondary outcomes.

Section Summary: Children and Adults With Congenital Heart Disease Who Have Undergone Heart Surgery
Evidence from a number of small RCTs, and one systematic review 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 did not find a significant effect of treatment with INO on reduction of postoperative outcomes in adults with congestive heart failure who had LVAD surgery.

Lung Transplantation

Clinical Context and Therapy Purpose

The treatment of INO provides an option that is an alternative to or an improvement on existing therapies in patients with lung transplant.

The question addressed in this evidence review is: In lung transplant recipients, does INO improve the net health outcome?
The following PICOTS were used to select literature to inform this review.
Patients
The patient population of interest are individuals with lung transplant.

Interventions
INO is a natural vasodilator and has been studied for a variety of types of respiratory failure and is the therapy being considered.

Comparators
Comparators include standard post-transplant care without INO. This is managed by transplant surgeons, pulmonologists, and primary care providers in an inpatient clinical setting.

Outcomes
The outcomes of interest are OS, hospitalizations, resource utilization, and treatment-related morbidity.

Table 11. Outcomes of Interest

Outcomes	Details		Timing
Resource utilization	Evaluated through outcomes such as length of hospital or ICU stay		1 – 6 weeks
Treatment-related morbidity	Evaluated through outcomes such as time to extubation, duration of ventilation, fluid balance during 24		1 week – 6 months

	hours after ICU admission, development of grade II-III primary graft dysfunction or gas exchange		

ICU: intensive care unit.

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.

Tavare and Tsakok reviewed the literature on whether prophylactic INO in patients undergoing a lung transplant reduces morbidity and mortality. They identified 6 relevant studies, 2 RCTs (Meade et al, Perrin et al) and 4 uncontrolled cohort studies. They also identified a third RCT (Botha et al), which they excluded from the review because they did not view the outcomes in that study as clinically useful. The reviewers observed that there are few controlled studies and all published studies, including the RCTs, had small sample sizes. Moreover, they noted that no RCTs found that INO reduced mortality or morbidity (e.g., time to extubation, length of hospital stay) and thus concluded that "it is difficult to currently recommend the routine use of prophylactic inhaled NO in lung transplant surgery." Published RCTs are summarized in the following table.

Table 12. Summary of RCTs Evaluating INO after Lung Transplantation

Study	N	Interventions	Primary End Points	Synopsis of Findings
Meade et al (2003)	84	INO 20 ppm 10 min after reperfusion vs placebo gas mixture	Duration of mechanical ventilation from admission to ICU to first successful extubation	No statistically significant difference in time to successful extubation (mean, 25.7 h in INO group vs 27.3 h in control group; p=0.76). No statistically significant differences in secondary outcomes (e.g., severe reperfusion injury, time to hospital discharge, hospital mortality, 30d mortality).
Perrin et al (2006)	30	INO 20 ppm at reperfusion for 12 h vs no intervention	Not specified	No statistically significant differences between groups on outcomes (eg, ICU length of stay, duration of ventilation, fluid balance during 24 h after ICU admission)
Botha et al (2007)	20	Prophylactic INO 20 ppm vs standard gas mixture during 30 min of reperfusion	Not specified	No statistically significant differences between groups in development of grade II-III primary graft dysfunction or gas exchange

ICU: intensive care unit; 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 there is insufficient evidence to support routine use of INO after lung transplant.

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

For individuals who are neonates and are premature at birth and have hypoxic respiratory failure who receive INO, the evidence includes RCTs and systematic reviews. Relevant outcomes are overall survival, 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 on primary end points such as mortality and bronchopulmonary dysplasia (BPD). Meta-analyses of these RCTs have not found better survival rates in patients who receive with INO compared with a control intervention. Most meta-analyses did not find other outcomes e.g., BPD and intracranial hemorrhage were improved by INO. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have acute hypoxemic respiratory failure (non-neonates) who receive INO, the evidence includes RCTs and systematic reviews. Relevant outcomes are overall survival, 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 significant reduces mortality or shortens the duration of mechanical ventilation. There is some evidence from a meta-analysis of 4 RCTs and from a cohort study 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 the effects of the technology on health outcomes.

For individuals who have congenital heart disease who underwent heart surgery who receive INO, the evidence consists of RCTs and a systematic review. Relevant outcomes are overall survival, hospitalizations, resource utilization, and treatment-related morbidity. Evidence from a number of small RCTs and a systematic review 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 of postoperative outcomes in

adults with congestive heart failure. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have lung transplant who receive INO, the evidence consists of RCTs and a systematic review. Relevant outcomes are overall survival, hospitalizations, resource utilization, and treatment-related morbidity. Several small RCTs have evaluated INO after lung transplantation and have not found statistically significant improvement in health outcomes. A systematic review of RCTs and observational studies concluded that there is insufficient evidence to support routine use of INO after lung transplant. The evidence is insufficient to determine the effects of the technology on health outcomes.

Practice Guidelines and Position Statements

Pediatric Pulmonary Hypertension Network

In 2016, The Pediatric Pulmonary Hypertension Network (a network of clinicians, researchers, and centers) published recommendations for use of INO in premature infants with severe pulmonary hypertension. Key recommendations are:

> "(1) INO therapy should not be used in premature infants for the prevention of BPD [bronchopulmonary dysplasia], 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 [persistent pulmonary hypertension of the newborn] 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…."

National Institutes of Health

The National Institutes of Health (2015) published the following recommendations for the use of INO therapy in premature newborns with severe pulmonary hypertension:

•"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;

•"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;

•"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".

American Academy of Pediatrics

In 2000 (reaffirmed in 2009), the American Academy of Pediatrics (AAP) issued recommendations regarding the use of inhaled nitric oxide in pediatric patients. The

recommendations were reaffirmed on April 1, 2010. They stated that "Inhaled nitric oxide therapy should be given using the indications, dosing, administration and monitoring guidelines outlined on the product label." This recommendation is consistent with the policy statement. In addition, the AAP recommended the following:

- Inhaled nitric oxide should be initiated in centers with extracorporeal membrane oxygenation capability.
- Centers that provide inhaled nitric oxide therapy should provide comprehensive long-term medical and neurodevelopmental follow-up.
- Centers that provide inhaled nitric oxide therapy should establish prospective data collection for treatment time course, toxic effects, treatment failure, and use of alternative therapies and outcomes.
- Administration of INO for indications other than those approved by the U.S. Food and Drug Administration (FDA) or in other neonatal populations, including compassionate use, remains experimental.

The AAP policy statement does not address the use of INO in premature infants.

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.

U.S. Preventive Services Task Force Recommendations

Use of inhaled nitric oxide is not a preventive service.

Key Words:

Inhaled Nitric Oxide, Treatment of Respiratory Failure, Nitric Oxide, Inhaled, Respiratory Failure, INOmax™, INO

Approved by Governing Bodies:

In 1999, INOmax™ (Ikaria®, Clinton, NJ) was approved by the 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 (Dublin, Ireland) 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.

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

Coding:

CPT Codes:
There is not a specific CPT code.

This service is usually billed on the hospital bill with revenue code 412 for inhalation services. The physician component is included in critical care services.

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This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member's plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield's administration of plan contracts.