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Inhaled Nitric Oxide

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Related Policies (if applicable)
None

Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current peer-reviewed scientific literature. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and acceptable standards of medical practice. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For Illinois only: Illinois Public Act 103-0458 [Insurance Code 215 ILCS 5/356z.61] (HB3809 Impaired Children) states all group or individual fully insured PPO, HMO, POS plans amended, delivered, issued, or renewed on or after January 1, 2025 shall provide coverage for therapy, diagnostic testing, and equipment necessary to increase quality of life for children who have been clinically or genetically diagnosed with any disease, syndrome, or disorder that includes low tone neuromuscular impairment, neurological impairment, or cognitive impairment.

Coverage

Inhaled nitric oxide **may be considered medically necessary** as a component of treatment of hypoxic respiratory failure (see **NOTE 1**) in neonates born at 34 weeks and 0 days of gestation or greater when both of the following criteria are met:

- Conventional therapies have failed or are expected to fail, for example, administration of high concentrations of oxygen, hyperventilation, high frequency ventilation, the induction of alkalosis, neuromuscular blockade and sedation; **and**
- Neonate does not have a congenital diaphragmatic hernia (CDH).

The diagnostic use of inhaled nitric oxide **may be considered medically necessary** as a method of assessing pulmonary vasoreactivity in persons with pulmonary hypertension.

Other indications for inhaled nitric oxide **are considered experimental, investigational, and/or unproven**, including but not limited to:

- Treatment of premature neonates born at less than 34 weeks and 0 days 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.

NOTE 1: 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.)

Policy Guidelines

None.

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. It is also proposed as a method of assessing pulmonary vasoreactivity in individuals with pulmonary hypertension, and 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 patients after lung transplantation to prevent or reduce reperfusion injury.

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 is an invasive technique that may be considered in neonates when other therapies fail. 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.

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 use of INO in lung transplantation to prevent or reduce reperfusion injury.

Diagnostic Testing for Pulmonary Hypertension

INO has also been used as a diagnostic method of assessing pulmonary reactivity in persons with pulmonary hypertension. Pulmonary vasodilator testing results can identify patients who may benefit from long-term medical treatment, transplantation, and if a patient may be an appropriate surgical candidate.

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

Rationale

This medical policy was created in February 2017 and has been updated regularly with searches of the PubMed database. The most recent literature update was performed through December 2022.

Medical policies 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. 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 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 patients who are neonates, are term or late preterm at birth, and have hypoxic respiratory failure.

The question addressed in this medical policy is: Does INO improve the net health outcome in patients 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 policy.

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. 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 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 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. 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 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 back-up 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

Number 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	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 hospital discharge	0.66	0.57 to 0.77	<0.001	0%	High

Adapted from Barrington et al. (2017) (1)
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 end point of death or the need for ECMO compared with controls, in studies that did not allow INO backup in controls. INO 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 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 patients who are neonates, are premature at birth, and have hypoxic respiratory failure.

The question addressed in this medical policy is: Does INO improve the net health outcome in patients who are neonates, are premature at birth, and have hypoxic respiratory failure?

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

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. 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 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. 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.

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. (2) 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

Number 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	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 of gestation							
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 1.01	0.32	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	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

Adapted from Barrington et al. (2017) (2)
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 on the 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 vs 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. (3) 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 (AHRQ) - sponsored systematic review by Donohue et al. (2011) of randomized trials on INO for premature infants (<35 weeks of gestation) was published. (4) Thirty-one articles were initially selected; they included 14 unique RCTs. Regardless of how mortality was reported or defined (e.g., death $\leq$7 days or $\leq$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 Trials

The largest trial to date was published by Mercier et al. (2010). (5) 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=0.29). The secondary end point (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 adverse event was intracranial hemorrhage, which affected 114 (29%) in the INO group and 91 (23%) in the control group (p value not reported).

Durrmeyer et al. (2013) published 2-year outcomes of the EUNO trial. (6) Of the original 800 patients, 737 (92%) were evaluable at this time point. There were 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. (7) 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	Country	Sites	Dates	Participants	Interventions	
					Active	**Comparator**
Mercier (2010); EUNO (5)	EU	35	2005-2008	Preterm infants (between 24 and 28 weeks GA) weighing ≥500g and requiring surfactant within 24 hours of birth	INO 5 ppm (n=399)	Placebo-equivalent nitrogen gas (n=401)
Durrmeyer (2013); EUNO (6)	EU	35	2005-2008	Infants born at ≤29 weeks GA with moderate respiratory failure	INO 5 ppm (n=306)	Placebo-equivalent nitrogen gas (n=324)
Greenough (2021); EUNO (7)	EU	24	2005-2008	Preterm infants (between 24 and 28 weeks GA) and weighing ≥500g 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; GA: gestational age; INO: inhaled nitric oxide; RCT: randomized controlled trial.

Table 6. Summary of Key RCT Results

Study	Survival Outcomes	Adverse Events
Mercier (2010); EUNO (5)	**OS at 36 wks PMA**	**Serious AEs[a]**
INO	343 (86%)	158 (40%)
Placebo	359 (90%)	164 (41%)
RR; 95% CI; P-value	0.74; 0.48 to 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 to 1.43; 0.73	
Durrmeyer (2013); EUNO (6)	**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	
Greenough (2021); EUNO (7)	**Hospitalization rates – end of 2 yrs 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 yrs	
INO	10 (6.5%)	
Placebo	14 (9.2%)	
P-value	.40	

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

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

The purpose of the study design and conduct limitation table (see 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]	Follow-Up[d]	Power[e]	Statistical[f]
Mercier (2010); EUNO (5)	3. Allocation concealment unclear					
Durrmeyer (2013); EUNO (6)	3. Allocation concealment unclear					3. Confidence intervals not reported for all outcomes
Greenough (2021); EUNO (7)	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 policy 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 differences in primary end points 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 patients who are adults or children in acute hypoxemic respiratory failure.

The question addressed in this medical policy is: Does INO improve the net health outcome in various pediatric and adult populations with acute hypoxemic respiratory failure?

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

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. INO 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. 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
Several meta-analyses of 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. (8) 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

Number of Trials	N	Outcomes	Relative Risk	95% CI	p	I^2	QOE[a]
11	1243	Overall Mortality	1.04	0.90 to 1.19	0.63	0%	Moderate
9	1105	Mortality at 28-30 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

Adapted from Gebistorf et al. (2016). (8)
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.

INO 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. (9, 10) 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. (9) 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 (total N=1142 patients) 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 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 COVID-19. (11). The review included 14 retrospective or prospective studies including 423 patients (range, 5 to 169). Racial and ethnic demographics of patients includes in these studies were not described. Across these studies, INO demonstrated a slight increase in oxygenation, but appeared to have no impact on mortality.

Adverse Events
A cohort study by Ruan et al. (2016) evaluated the risk of renal dysfunction in patients with ARDS treated using INO. (12) 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=0.02). 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). (13)

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 patients who are adults and children with congenital heart disease who have had heart surgery.

The question addressed in this medical policy is: Does INO improve the net health outcome in patients who are adults and children with congenital heart disease who have had heart surgery?

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

Populations

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

Interventions

The therapy being considered is INO. INO 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. Outcomes of Interest

Outcomes	Details	Timing
Treatment-related morbidity	Evaluated through outcomes such as right ventricular dysfunction, pulmonary arterial hypertension, mean arterial pressure, and neurodevelopmental disability.	1 week – 6 months
Resource utilization	Evaluated through outcomes such as mean number of days on mechanical	1 – 6 weeks

	ventilation, length of stay in intensive care unit or hospital.	

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.

Adults

A trial by Potapov et al. (2011) evaluated the prophylactic use of INO in adults undergoing left ventricular assist device (LVAD) implantation for congestive heart failure. (14) 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 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=0.33). Other outcomes also did not differ significantly between groups; e.g., mean number of days on mechanical ventilation (5.4 days of INO group vs 11.1 days of placebo group; p=0.77) and mean number of days in the hospital (41 in each group).

Children

A Cochrane review by Bizzarro et al. (2014) identified 4 RCTs (total N=210 patients) comparing postoperative INO with placebo or usual care in the management of children who had congenital heart disease. (15) All trials included participants 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 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 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 of 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 data available for each outcome.

The RCT assessing the largest sample was published by Miller et al. (2000). (16) The 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 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; $p<0.001$). 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 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 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 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 LVAD surgery.

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 patients with lung transplant.

The question addressed in this medical policy is: Does INO improve the net health outcome in patients with lung transplant?

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

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

Interventions
The therapy being considered is INO. INO 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. 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 hours after ICU admission, development of grade II-III primary graft dysfunction or gas exchange.	1 week – 6 months

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 (2011) reviewed the literature to assess whether the use of prophylactic INO in patients undergoing a lung transplant reduces morbidity and mortality. (17) They identified 6 studies, 2 RCTs (Meade et al. [2003] [18] Perrin et al. [2006] [19]) and 4 uncontrolled cohort studies. They also identified a third RCT (Botha et al. [2007] [20]), 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 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 End Points	Results
Meade et al. (2003) (18)	84	INO 20 parts per million 10 minutes after reperfusion versus 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 versus 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, 30-d mortality).
Perrin et al. (2006) (19)	30	INO 20 parts per million at reperfusion for 12 h versus no intervention.	Not specified.	No statistically significant differences between groups in outcomes (e.g., ICU length of stay, duration of ventilation, fluid balance during 24 h after ICU admission).
Botha et al. (2007) (20)	20	Prophylactic INO 20 parts per million versus standard gas mixture for 30	Not specified.	No statistically significant differences between groups in development of grade II-III primary graft

		minutes of reperfusion.		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 available evidence did not support the routine use of INO after lung transplant.

Assessment of Pulmonary Vasoreactivity

Randomized controlled trials (RCTs), case series, and nonrandomized comparative studies have been published regarding the diagnostic use of inhaled nitric oxide as a method of assessing pulmonary vasoreactivity in persons with pulmonary hypertension.

In 2002, Balzar et al., in a small, randomized trial investigated whether preoperative hemodynamic evaluation with O_2 and INO could identify individuals with pulmonary hypertension who may be appropriate candidates for heart transplantation or corrective cardiac surgery, more accurately than an evaluation with O_2 alone. (21) The ratio of pulmonary and systemic vascular resistance (Rp:Rs) was determined at baseline while breathing 21% to 30% O_2, and in 100% O_2 and 100% O_2 with 10 to 80 parts per million (ppm) nitric oxide to evaluate pulmonary vascular reactivity. A total of 78 individuals were determined to be operable. Of those, 74 had undergone surgery at the time data was collected. Twelve persons died or developed right heart failure secondary to pulmonary hypertension following surgery. Survivors were followed for a median duration of 26 months. Rp:Rs 0.33 and a 20% decrease in Rp:Rs from baseline had been chosen as two criteria for operability to retrospectively determine the efficacy of preoperative testing in selecting surgical candidates. In comparison to an evaluation with oxygen alone, sensitivity (64% versus 97%) and accuracy (68% versus 90%) were increased by an evaluation with O_2 and NO when Rp:Rs 0.33 was used as the criterion for surgery. Specificity was only 8% when a 20% decrease in Rp:Rs from baseline was used as the criterion for operability. The authors indicated that a preoperative hemodynamic evaluation with a combination of supplemental O_2 and INO may identify a greater number of candidates for corrective surgery or transplantation than a preoperative evaluation with O_2 alone.

In 2011, Krasuski et al., evaluated the ability of vasodilator response to predict survival in a heterogeneous group of individuals with pulmonary hypertension. (22) A total of 214 treatment-naive subjects with pulmonary hypertension were enrolled in the study between November 1998 and December 2008. Vasoreactivity was assessed during inhalation of INO. There were 51 deaths (25.9%) over a mean follow-up period of 2.3 years. Kaplan-Meier analysis demonstrated that vasodilator responders had significantly improved survival ($p<0.01$). The authors concluded that "vasodilator responsiveness to INO is an important method of risk stratifying PH patients, with results that apply regardless of clinical etiology."

In 2010, Barst et al., in an industry sponsored study, investigated whether a combination of INO and O_2 was more effective than 100% O_2 or INO alone for acute vasodilator testing in children. (23) An open, prospective, randomized, controlled trial was conducted at 16 centers. A total of 136 children were enrolled and 121 completed the study. Children 4 weeks to 18 years of age with pulmonary hypertension (PH) and increased pulmonary vascular resistance (PVR) underwent right heart catheterization for acute vasodilator testing. All subjects were tested with each of three agents (80 ppm INO, 100% O_2 and a combination of 80 ppm INO/100% O_2) in three 10-minute treatment periods. Primary outcome measures were percentages of acute responders to each agent. Changes in PVR index and mean pulmonary arterial pressure vs baseline were greater with INO/O_2 vs either O_2 or INO alone ($p<0.001$). Survival at 1-year follow-up included 1) 90.9% of acute responders to the combination, compared with 77.8% of nonresponders to the combination, and 2) 85.7% of acute responders to O_2 alone, compared with 80.6% of nonresponders to O_2. There was no significant difference in acute responder rate with INO alone versus INO/O_2; however, it was reported that the combination improved pulmonary hemodynamics acutely better than INO alone. One-year survival data show similar rates between the INO/O_2 and the O_2 alone groups.

Section Summary: Assessment of Pulmonary Vasoreactivity

Available evidence from RCTs, case series, and nonrandomized comparative studies found INO a safe and effective screening agent for pulmonary vasoreactivity.

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, 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 leads to a significantly reduced 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 a meaningful improvement in the net health outcome.

For individuals with pulmonary hypertension, the evidence to support the use of INO as a method of assessing pulmonary vasoreactivity includes RCTs, case series, and nonrandomized comparative studies. Available evidence found INO to be a safe and effective screening agent for pulmonary vasoreactivity. Additionally, specialty society guidelines and/or recommendations include the use of INO as an accepted method of vasoreactivity testing. The evidence is sufficient to determine that the technology results in a meaningful 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 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 for primary end points such as mortality and bronchopulmonary dysplasia. 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., bronchopulmonary dysplasia, intracranial hemorrhage). The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are adults and children in acute hypoxemic 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 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 ARDS. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are adults and children with congenital heart disease who have had heart surgery who receive INO, the evidence includes 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 the postoperative outcomes of 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 includes 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; 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 the effects of the technology on health outcomes

Practice Guidelines and Position Statements

Pediatric Academic Society

In April 2019, the Pediatric Academic Society convened a workshop regarding the role of INO in infants born preterm. (24) The controversy surrounding its use in this patient population was reviewed by established experts in the field. The experts at the workshop conclude 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 for use of INO in premature infants with severe pulmonary hypertension. (25) Key recommendations included:

"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 (2011) published a consensus development conference statement on INO for premature infants, (26) which was based on the Agency for Healthcare Research and Quality–sponsored systematic review of the literature, previously described. (4) 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."

American Heart Association and American Thoracic Society

In 2015, the American Heart Association and American Thoracic Society issued guidelines for the treatment of pediatric pulmonary hypertension. (27) 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 failures 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)."

American Academy of Pediatrics

In 2014, the American Academy of Pediatrics provided the following recommendations on the use of INO in premature infants (see Table 13). (28)

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.

National Institute for Health and Care Excellence (NICE)

In April 2019, NICE issued a guidance on specialist neonatal respiratory care for preterm infants. (29) 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.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this medical policy are listed in Table 14.

Table 14. Summary of Key Trials

NCT Number	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT00515281	Inhaled Nitric Oxide and Neuroprotection in Premature Infants	484	Jun 2021
NCT03661385	A Randomised Controlled Trial of Nitric Oxide Administration During Cardiopulmonary Bypass in Infants Undergoing Arterial Switch Operation for Repair of Transposition of the Great Arteries (NASO)	800	Dec 2021 (recruiting)
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	Dec 2022

NCT04306393	Nitric Oxide Gas Inhalation Therapy for Mechanically Ventilated Patients With Severe Acute Respiratory Syndrome Caused by SARS-CoV2: a Randomized Clinical Trial (NOSARSCOVID)	200	Dec 2022
NCT04305457	Nitric Oxide Gas Inhalation Therapy in Spontaneous Breathing Patients With Mild/Moderate COVID-19: a Randomized Clinical Trial (NoCovid)	240	Apr 2022

NCT: national clinical trial.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	93463
HCPCS Codes	None

*Current Procedural Terminology (CPT®) ©2022 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) **does not** have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been **developed** since this medical policy document was written. See Medicare's National Coverage at <http://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
01/01/2024	Reviewed. No changes.
01/15/2023	Document updated with literature review. Coverage unchanged. References 7, 11, 13, 24, 27 and 29 added; some removed.
11/01/2021	Reviewed. No changes.
10/15/2020	Document updated with literature review. Coverage unchanged. No new references added.
11/15/2019	Reviewed. No changes.
01/15/2019	Document updated with literature review. Coverage unchanged. References 2-4, 8, 11, and 25 added. Some references removed.
10/15/2017	Reviewed. No changes.

02/15/2017	New medical document. Inhaled nitric oxide may be considered medically necessary as a component of treatment of hypoxic respiratory failure (see Note) in neonates born at 34 weeks and 0 days of gestation or greater when both of the following criteria are met: 1) Conventional therapies have failed or are expected to fail, for example, administration of high concentrations of oxygen, hyperventilation, high frequency ventilation, the induction of alkalosis, neuromuscular blockade and sedation; and 2) Neonate does not have a congenital diaphragmatic hernia (CDH). The diagnostic use of inhaled nitric oxide may be considered medically necessary as a method of assessing pulmonary vasoreactivity in persons with pulmonary hypertension. Other indications for inhaled nitric oxide are considered experimental, investigational, and/or unproven, including but not limited to: treatment of premature neonates born at less than 34 weeks and 0 days 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; and in lung transplantation, during and/or after graft reperfusion. NOTE: 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.)