Policy Number	**THE801.038**
Policy Effective Date	**01/01/2025**

Inhaled Nitric Oxide

Table of Contents

Related Policies (if applicable)
None

Disclaimer

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 (ECMO). It is also proposed as a treatment for premature infants, critically ill children, and adults with respiratory failure, as well as in the postoperative management of children undergoing repair of congenital heart disease and 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.

ECMO 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 and in adults.

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

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

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

Rationale

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 neonates who 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 neonates who are term or late preterm at birth and have hypoxic respiratory failure.

Interventions

The therapy being considered is INO. Inhaled nitric oxide is a natural vasodilator and has been studied for a variety of types of respiratory failure. Most commonly, it is used as an initial treatment for neonates with hypoxic respiratory failure to improve oxygenation and reduce the need for invasive extracorporeal membrane oxygenation (ECMO). In late preterm neonates, INO primarily functions as a vasodilator to treat pulmonary hypertension, often due to meconium aspiration or bacterial pneumonia. However, in earlier preterm neonates with respiratory failure, pulmonary hypertension with shunting is less of a risk. Therefore, these 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).

Table 1. Outcomes of Interest

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

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) (2)
CI: confidence interval; ECMO: Extracorporeal membrane oxygenation: INO: inhaled nitric oxide; QOE: quality of evidence.
[a] QOE assessed using the GRADE tool.

Reviewers found that INO in hypoxic infants significantly reduced the incidence of the combined 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 has supported the use of INO in term or late preterm infants to improve the net health outcome. Pooled analyses of RCT data have found that INO leads to a significant reduction in the combined outcome of ECMO or death and a significant reduction of ECMO use before hospital discharge.

Hypoxic Respiratory Failure in Premature Neonates
Clinical Context and Therapy Purpose
The purpose of INO is to provide a treatment option that is an alternative to or an improvement on existing therapies in neonates who 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 neonates who 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).

Table 3. Outcomes of Interest

Outcomes	Details	Timing
Resource utilization	Evaluated through outcomes such as utilization of ECMO before hospital discharge.	1 week to 6 months
Treatment-related morbidity	Evaluated through outcomes such as rates of adverse events including bronchopulmonary dysplasia and severe intracranial hemorrhage.	1 week to 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. (3) The main findings of the meta-analysis are provided in Table 4. Results are reported separately for studies with entry before 3 days based on oxygenation, studies with entry after 3 days based on oxygenation and bronchopulmonary dysplasia (BPD) risk, and studies of routine use of INO in premature infants on respiratory support. Pooled analyses of 3 or more studies are shown.

Table 4. Main Cochrane Findings on INO in Preterm Infants

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

Reviewers found that use of INO in premature infants with respiratory failure did not significantly improve individual outcomes (e.g., death before hospital discharge, BPD at 36 weeks of postmenstrual age) or the combined outcome (BPD or death at 36 weeks of postmenstrual age). Findings were not statistically significant in subgroups of studies that enrolled patients before 3 days old, enrolled patients after 3 days, and that used INO routinely. A fourth primary outcome (intraventricular hemorrhage) was only pooled in studies with entry before 3 days, and again did not find a significant benefit of INO 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. (4) Reviewers did not define “preterm” as used to identify studies, beyond use of the keyword in literature searches. A pooled analysis of all 22 studies did not find a significant difference between groups in mortality (RR=1.00; 95% CI, 0.92 to 1.09). There was also no significant difference between INO and control in the rate of severe intracranial hemorrhage in a pooled analysis of 17 studies (RR=0.99; 95% CI, 0.83 to 1.16). However, a pooled analysis of 20 studies did find a significantly lower rate of BPD in the INO groups than in the control groups (RR=0.88; 95% CI, 0.82 to 0.95). Reviewers noted that their findings on BPD differed from those in other meta-analyses and suggested that the difference might have been due to their inclusion of Chinese-language studies.

Previously, an Agency for Healthcare Research and Quality (AHRQ) - sponsored systematic review by Donohue et al. (2011) of randomized trials on INO for premature infants (<35 weeks

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

Randomized Controlled Trials

The largest trial to date was published by Mercier et al. (2010). (6) This multicenter industry-sponsored study, known as the European Union Nitric Oxide (EUNO) trial, evaluated low-dose INO therapy. Of 800 patients, 792 (99%) received their assigned treatment, and all 800 were included in the intention-to-treat analysis. Primary outcomes were survival without BPD at 36 weeks of postmenstrual age, OS at 36 weeks of postmenstrual age, and BPD at 36 weeks of postmenstrual age. The number of patients with BPD at 36 weeks of postmenstrual age was 81 (24%) in the INO group and 96 (27%) in the control group (RR=0.83; 95% CI, 0.58 to 1.17; p=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. (7) 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. (8) Tables 5 and 6 summarize the key characteristics and results of the EUNO trial and its 2- and 7-year follow-ups.

Table 5. Summary of Key RCT Characteristics

Study; Trial	Country	Sites	Dates	Participants	Interventions	
					Active	**Comparator**
Mercier (2010); EUNO (6)	EU	35	2005-2008	Preterm infants (between 24- and 28-weeks GA) weighing ≥500 g and requiring surfactant within 24 hours of birth	INO 5 ppm (n=399)	Placebo-equivalent nitrogen gas (n=401)

Durrmeyer (2013); EUNO (7)	EU	35	2005-2008	Infants born at <29 weeks GA with moderate respiratory failure	INO 5 ppm (n=306)	Placebo-equivalent nitrogen gas (n=324)
Greenough (2021); EUNO (8)	EU	24	2005-2008	Preterm infants (between 24- and 28-weeks GA) and weighing ≥500 g and requiring surfactant within 24 hours of birth	INO 5 ppm (n=152)	Placebo-equivalent nitrogen gas (n=153)

EU: European Union; EUNO: European Union Nitric Oxide trial; 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 (6)	**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 (7)	**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 (8)	**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; yrs: years.

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

Table 7. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Mercier (2010); EUNO (6)	3. Allocation concealment unclear					
Durrmeyer (2013); EUNO (7)	3. Allocation concealment unclear					3. Confidence intervals not reported for all outcomes
Greenough (2021); EUNO (8)	3. Allocation concealment unclear					3. Confidence intervals not reported

EUNO: European Union Nitric Oxide trial.

The evidence limitations stated in this table are those notable in the current 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] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing

data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. 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 adults or children in acute hypoxemic respiratory failure.

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

Populations
The relevant population of interest is 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).

Table 8. Outcomes of Interest

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Systematic Reviews

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

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

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) (9)

ARDS: acute respiratory distress syndrome: CI: confidence interval; INO: inhaled nitric oxide; NR: not reported; QOE: quality of evidence.

[a] QOE assessed using the GRADE tool.

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. (10, 11) For example, a systematic review by Adhikari et al. (2014) identified 9 RCTs conducted with adults or children (other than neonates) in which at least 80% of patients, or a separately reported subgroup, had ARDS. (10) The trials selected compared INO with placebo or no gas, used INO as a treatment of ARDS (i.e., not a preventive measure), and had less than 50% crossover between groups. Findings were not stratified by adult and pediatric populations. A

pooled analysis of data from the 9 trials (N=1142 patients) found no statistically significant benefit of INO on mortality (RR=1.10; 95% CI, 0.94 to 1.29; p=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 the 2019 Coronavirus disease (COVID-19). (12). The review included 14 retrospective or prospective studies including 423 patients (range, 5 to 169). Racial and ethnic demographics of patients included in these studies were not described. Across these studies, INO demonstrated a slight increase in oxygenation, but appeared to have no impact on mortality.

Adverse Events

A cohort study by Ruan et al. (2016) evaluated the risk of renal dysfunction in patients with ARDS treated using INO. (13) 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). (14)

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 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 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).

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 to 6 months
Resource utilization	Evaluated through outcomes such as mean number of days on mechanical ventilation, length of stay in intensive care unit or hospital.	1 to 6 weeks

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. (15) 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

Systematic Reviews

A Cochrane review by Bizzarro et al. (2014) identified 4 RCTs (N=210 patients) comparing postoperative INO with placebo or usual care in the management of children who had congenital heart disease. (16) 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.

Randomized Controlled Trials

The RCT assessing the largest sample was published by Miller et al. (2000). (17) 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 individuals with lung transplant.

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

Populations

The relevant population of interest is individuals with a 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).

Table 11. Outcomes of Interest

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

Systematic Reviews

Tavare and Tsakok (2011) reviewed the literature to assess whether the use of prophylactic INO in patients undergoing a lung transplant reduces morbidity and mortality. (18) They identified 6 studies, 2 RCTs (Meade et al. [2003] [19], Perrin et al. [2006] [20]) and 4 uncontrolled cohort studies. They also identified a third RCT (Botha et al. [2007] [21]), 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) (19)	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-day mortality).
Perrin et al. (2006) (20)	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) (21)	20	Prophylactic INO 20 parts per million versus standard gas mixture for 30 minutes 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; h: hours.

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. (29) 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. (30) 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. (31) 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 (RHC) 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.

Acute vasoreactivity test with INO is performed during diagnostic RHC to identify patients with pulmonary arterial hypertension (PAH) who respond to calcium channel blockers (CCB). Ishii and colleagues (2023) investigated the prognostic importance of follow-up vasoreactivity test after treatment, which has yet to be established. (32) Researchers retrospectively analyzed 36 PAH patients (mean age, 47 years; 61 % treatment-naïve) who underwent diagnostic and follow-up RHC and vasoreactivity tests at a single center in Japan. The primary outcome was all-cause mortality. The median time between baseline and follow-up RHC was 9.7 months.

Absolute change in mean pulmonary arterial pressure (ΔmPAP) during NO challenge was less pronounced after treatment, but there was great variability among patients. Overall cohort was dichotomized into two groups: preserved vasoreactivity (ΔmPAP ≤ −1 mmHg) and less vasoreactivity (ΔmPAP ≥0 mmHg) at follow-up RHC. Less vasoreactivity group had higher usage rate of endothelin receptor antagonists and parenteral prostacyclin analogues. During a median observation period of 6.3 years after follow-up RHC, 7 patients died, of which 6 showed less vasoreactivity at follow-up. Absolute ΔmPAP ≥0 at follow-up RHC was associated with all-cause mortality in univariable Cox regression analysis (hazard ratio, 8.728; 95 % CI, 1.045–72.887; p=0.045), whereas other hemodynamic parameters were not. Absolute ΔmPAP ≥0 at follow-up RHC was associated with all-cause mortality in multivariable Cox analysis adjusted for age and known PAH prognostic factors (HR, 12.814; 95 % CI, 1.088–150.891; p=0.043). Kaplan-Meier survival analysis revealed a significantly worse survival of less vasoreactivity group compared to preserved vasoreactivity group (log-rank test, p = 0.016). Authors concluded that this study demonstrated that the pulmonary vascular reactivity decreased over time; however, the remaining vascular dilatory reserve at the follow-up test after treatment could predict the subsequent all-cause mortality, whereas regularly measured hemodynamic parameters obtained simultaneously did not.

Satoh et al. (2023) investigated INO vasoreactivity tests for patients with Group 2 PH and hypothesized that these changes may have a prognostic impact. (33) This was a single-centre, retrospective study with a median follow-up of 365 days. From January 2011 to December 2015, researchers studied 69 patients with Group 2 PH [age, 61.5 ± 13.0 (standard deviation) years; male:female, 49:20; left ventricular ejection fraction, 50.1 ± 20.4%; mean pulmonary arterial pressure, ≥25 mmHg; and pulmonary arterial wedge pressure (PAWP), >15 mmHg]. Patients with significant valvular heart disease (moderate-to-severe stenosis and moderate-to-severe regurgitation) and heart transplant within 1 year were excluded. Follow-up began on the day of the vasoreactivity test (right heart catheterization and NO inhalation) and was tracked through outpatient visits by cardiologists at Tohoku University Hospital or its satellite hospitals over a period of 1 year. No adverse events were observed after NO inhalation. Thirty-four patients with Group 2 PH showed increased PAWP (ΔPAWP: 3.26 ± 2.22 mmHg), while the remaining 35 patients did not (ΔPAWP: −2.11 ± 2.29 mmHg). Multivariate analysis revealed that increased PAWP was the only significant predictor of all-cause death or hospitalization for heart failure (HF) after 1 year (hazard ratio 4.35; 95% CI, 1.27–14.83; P=0.019). The acute response of PAWP to NO differed between HF with preserved and reduced ejection fractions. Investigators focused on alterations in the hemodynamics of the left side of the heart following NO inhalation. NO inhalation shifts the pressure from the right ventricle to the left ventricle via selective pulmonary arterial dilation, in which patients with potential or manifest LV dysfunction would be intolerant to the change, resulting in increased LV filling pressure, while preserved left ventricle can compensate. Patients with Group 2 PH are likely to tolerate the inhaled NO vasoreactivity test. Investigators determined that increased PAWP after NO inhalation indicates reserve capacity of cardiac function and is a novel and significantly correlated factor of prognosis in patients with Group 2 PH indicating NO-induced PAWP is a novel prognostic indicator. The NO vasoreactivity test is expected to be like a ‘Merk'Mal’, which makes the administration of NO-treatment safer and more effective in clinical practice.

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 an improvement in the net health outcomes.

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 that the technology results in an improvement in the net 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 acute respiratory distress syndrome. The evidence is insufficient to determine that the technology results in an improvement in the net health outcomes.

For individuals who are adults or 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 that the technology results in an improvement in the net health outcomes.

For individuals who have a 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 that the technology results in an improvement in the net health outcomes.

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.

Practice Guidelines and Position Statements

American Academy of Pediatrics

In 2014, the American Academy of Pediatrics provided the following recommendations on the use of INO in premature infants (Table 13). (22)

Table 13. Guidelines on Use of INO for Premature Infants

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

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

American Heart Association/American Thoracic Society

In 2015, the American Heart Association and American Thoracic Society published guidelines on the management of pediatric pulmonary hypertension. (23) Relevant recommendations related to INO included:

- "Inhaled nitric oxide (iNO) is indicated to reduce the need for extracorporeal membrane

oxygenation (ECMO) support in term and near-term infants with persistent pulmonary hypertension of the newborn (PPHN) or hypoxemic respiratory failure who have an oxygenation index that exceeds 25 (Class I; Level of Evidence A)."
- "iNO can be beneficial for preterm infants with severe hypoxemia that is due primarily to PPHN physiology rather than parenchymal lung disease, particularly if associated with prolonged rupture of membranes and oligohydramnios (Class IIa; Level of Evidence B)."

National Institute for Health and Care Excellence (NICE)

In April 2019, NICE issued a guidance on specialist neonatal respiratory care for preterm infants. (24) The guidance recommends against the routine use of INO for preterm infants who need respiratory support for respiratory distress syndrome, unless there are other indications such as pulmonary hypoplasia or pulmonary hypertension.

National Institutes of Health

The National Institutes of Health (2011) published a consensus development conference statement on INO for premature infants, (25) which was based on the Agency for Healthcare Research and Quality–sponsored systematic review of the literature, previously described. (5) Conclusions included:

- "Taken as a whole, the available evidence does not support use of INO (inhaled NO) in early-routine, early-rescue, or later-rescue regimens in the care of premature infants of <34 weeks' gestation who require respiratory support."
- "There are rare clinical situations, including pulmonary hypertension or hypoplasia, that have been inadequately studied in which INO may have benefit in infants of <34 weeks' gestation. In such situations, clinicians should communicate with families regarding the current evidence on its risks and benefits as well as remaining uncertainties."

The National Institutes for Health guidelines for COVID-19 treatment recommended against the routine use of INO in pediatric or adult patients who are mechanically ventilated; however, they suggest that INO may be used after other options have failed. (26)

Pediatric Academic Society

In April 2019, the Pediatric Academic Society convened a workshop regarding the role of INO in infants born preterm. (27) The controversy surrounding its use in this patient population was reviewed by established experts in the field. The experts at the workshop concluded that the "rate of INO use in the infant born preterm is not declining, despite the publication of RCTs and related consensus statements that discourage its routine use due to lack of evidence for bronchopulmonary dysplasia prevention." These experts stated that "none of these studies or recommendations are based on its role in the management of persistent primary hypertension of the newborn in infants born preterm." In this setting, "extensive case series, guidelines, and others recommend the selective use of INO in infants born preterm with documented persistent primary hypertension of the newborn physiology as a contributing cause of hypoxemia, as best confirmed by echocardiography."

Pediatric Pulmonary Hypertension Network

In 2016, the Pediatric Pulmonary Hypertension Network (a network of clinicians, researchers, and centers) published recommendations on the use of INO in premature infants with severe pulmonary hypertension. (28) 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..."

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			
NCT05757557	Perioperative Nitric oxiDE-conditioning, Produced by Plasma-chemical Synthesis Technology, For prevEnt Acute kidNey Injury During carDiac surgEry in Patients With chRonic Kidney Disease (DEFENDER-trial)	136	Jan 2025
NCT04305457	Nitric Oxide Gas Inhalation Therapy for Mild/Moderate COVID-19 (NoCovid)	70	Apr 2025
Unpublished			
NCT02836899	Effect of Nitric Oxide in Cardiac Surgery Patients With Endothelial Dysfunction (MGHK23)	250	Nov 2023 (unknown status)

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®) ©2023 American Medical Association: Chicago, IL.

References

1. U.S. Food and Drug Administration (FDA). Medical Device Recalls: Vero Biotech Recalls GENOSYL DS; Nitric Oxide Delivery System Due to Software Error. 2021; Available at: <https://www.fda.gov> (accessed March 30, 2024).
2. Barrington KJ, Finer N, Pennaforte T, et al. Nitric oxide for respiratory failure in infants born at or near term. Cochrane Database Syst Rev. Jan 05 2017; 1(1):CD000399. PMID 28056166
3. Barrington KJ, Finer N, Pennaforte T. Inhaled nitric oxide for respiratory failure in preterm infants. Cochrane Database Syst Rev. Jan 03 2017; 1(1):CD000509. PMID 28045472
4. Yang Y, Feng Y, Zhou XG, et al. Inhaled nitric oxide in preterm infants: An updated meta-analysis. J Res Med Sci. 2016; 21:41. PMID 27904587
5. Donohue PK, Gilmore MM, Cristofalo E, et al. Inhaled nitric oxide in preterm infants: a systematic review. Pediatrics. Feb 2011; 127(2):e414-422. PMID 21220391
6. Mercier JC, Hummler H, Durrmeyer X, et al. Inhaled nitric oxide for prevention of bronchopulmonary dysplasia in premature babies (EUNO): a randomised controlled trial. Lancet. Jul 31 2010; 376(9738):346-354. PMID 20655106
7. Durrmeyer X, Hummler H, Sanchez-Luna M, et al. Two-year outcomes of a randomized controlled trial of inhaled nitric oxide in premature infants. Pediatrics. Sep 2013; 132(3):e695-703. PMID 23940237
8. Greenough A, Decobert F, Field D, et al. Inhaled nitric oxide (iNO) for preventing prematurity-related bronchopulmonary dysplasia (BPD): 7-year follow-up of the European Union Nitric Oxide (EUNO) trial. J Perinat Med. Sep 07 2020; 49(1):104-110. PMID 32892178
9. Gebistorf F, Karam O, Wetterslev J, et al. Inhaled nitric oxide for acute respiratory distress syndrome (ARDS) in children and adults. Cochrane Database Syst Rev. Jun 27 2016; 2016(6):CD002787. PMID 27347773
10. Adhikari NK, Dellinger RP, Lundin S, et al. Inhaled nitric oxide does not reduce mortality in patients with acute respiratory distress syndrome regardless of severity: systematic review and meta-analysis. Crit Care Med. Feb 2014; 42(2):404-412. PMID 24132038
11. Afshari A, Brok J, Moller AM, et al. Inhaled nitric oxide for acute respiratory distress syndrome and acute lung injury in adults and children: a systematic review with meta-analysis and trial sequential analysis. Anesth Analg. Jun 2011; 112(6):1411-1421. PMID 21372277
12. Prakash A, Kaur S, Kaur C, et al. Efficacy and safety of inhaled nitric oxide in the treatment of severe/critical COVID-19 patients: A systematic review. Indian J Pharmacol. 2021; 53(3):236-243. PMID 34169911
13. Ruan SY, Wu HY, Lin HH, et al. Inhaled nitric oxide and the risk of renal dysfunction in patients with acute respiratory distress syndrome: a propensity-matched cohort study. Crit Care. Nov 30 2016; 20(1):389. PMID 27903300
14. Wang J, Cong X, Miao M, et al. Inhaled nitric oxide and acute kidney injury risk: a meta-

analysis of randomized controlled trials. Ren Fail. Dec 2021; 43(1):281-290. PMID 33494652
15. Potapov E, Meyer D, Swaminathan M, et al. Inhaled nitric oxide after left ventricular assist device implantation: a prospective, randomized, double-blind, multicenter, placebo-controlled trial. J Heart Lung Transplant. Aug 2011; 30(8):870-878. PMID 21530317
16. Bizzarro M, Gross I, Barbosa FT. Inhaled nitric oxide for the postoperative management of pulmonary hypertension in infants and children with congenital heart disease. Cochrane Database Syst Rev. Jul 3 2014; 2014(7):CD005055. PMID 24991723
17. Miller OI, Tang SF, Keech A, et al. Inhaled nitric oxide and prevention of pulmonary hypertension after congenital heart surgery: a randomised double-blind study. Lancet. Oct 28 2000; 356(9240):1464-1469. PMID 11081528
18. Tavare AN, Tsakok T. Does prophylactic inhaled nitric oxide reduce morbidity and mortality after lung transplantation? Interact Cardiovasc Thorac Surg. Nov 2011; 13(5):516-520. PMID 21791520
19. Meade MO, Granton JT, Matte-Martyn A, et al. A randomized trial of inhaled nitric oxide to prevent ischemia-reperfusion injury after lung transplantation. Am J Respir Crit Care Med. Jun 1 2003; 167(11):1483-1489. PMID 12770854
20. Perrin G, Roch A, Michelet P, et al. Inhaled nitric oxide does not prevent pulmonary edema after lung transplantation measured by lung water content: a randomized clinical study. Chest. Apr 2006; 129(4):1024-1030. PMID 16608953
21. Botha P, Jeyakanthan M, Rao JN, et al. Inhaled nitric oxide for modulation of ischemia-reperfusion injury in lung transplantation. J Heart Lung Transplant. Nov 2007; 26(11):1199-1205. PMID 18022088
22. Kumar P, Committee on F, Newborn, et al. Use of inhaled nitric oxide in preterm infants. Pediatrics. Jan 2014; 133(1):164-170. PMID 24379225
23. Abman SH, Hansmann G, Archer SL, et al. Pediatric pulmonary hypertension: Guidelines from the American Heart Association and American Thoracic Society. Circulation. Nov 24 2015; 132(21):2037-2099. PMID 26534956
24. National Institute for Health and Care Excellence (NICE). NICE Guideline: Specialist neonatal respiratory care for babies born preterm [NG124]. April 2019. Available at <https://www.nice.org.uk> (accessed March 30, 2024).
25. Cole FS, Alleyne C, Barks JD, et al. National Institutes of Health (NIH) Consensus Development Conference statement: inhaled nitric-oxide therapy for premature infants. Pediatrics. Feb 2011; 127(2):363-369. PMID 21220405
26. National Institutes of Health. COVID-19 Treatment Guidelines. Updated February 29, 2024. Available at <https://www.covid19treatmentguidelines.nih.gov> (accessed April 1, 2024).
27. Lakshminrusimha S, Kinsella JP, Krishnan US, et al. Just say no to iNO in preterms – really? J Pediatr. Mar 2020; 218:243-252. PMID 31810629
28. Kinsella JP, Steinhorn RH, Krishnan US, et al. Recommendations for the use of inhaled nitric oxide therapy in premature newborns with severe pulmonary hypertension. J Pediatr. Mar 2016; 170:312-314. PMID 26703869
29. Balzer DT, Kort HW, Day RW, et al. Inhaled nitric oxide as a preoperative test (INOP Test I): the INOP Test Study Group. Circulation. 2002; 106(12 Suppl 1):76-81. PMID 12354713
30. Krasuski RA, Devendra GP, Hart SA, et al. Response to inhaled nitric oxide predicts survival in patients with pulmonary hypertension. J Card Fail. 2011; 17(4):265-271. PMID 21440863

31. Barst RJ, Agnoletti G, Fraisse A, et al.; NO Diagnostic Study Group. Vasodilator testing with nitric oxide and/or oxygen in pediatric pulmonary hypertension. Pediatr Cardiol. 2010; 31(5):598-606. PMID 20405117
32. Ishii S, Hatano M, Maki H, et al. Prognostic value of follow-up vasoreactivity test in pulmonary arterial hypertension. J Cardiol. Jul 2023; 82(1):69-75. PMID 36682710
33. Satoh T, Yaoita N, Nochioka K, et al. Inhaled nitric oxide testing in predicting prognosis in pulmonary hypertension due to left-sided heart diseases. ESC Heart Failure. 2023; 10:3592-3603. PMID 37775984

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 <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
01/01/2025	Document updated with literature review. Coverage unchanged. Added references 1, 26, and 32-33.
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.)