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# NIH Consensus Development Conference Statement: Inhaled Nitric-Oxide Therapy for Premature Infants

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## abstract

Premature birth is a major public health problem in the United States and internationally. Infants born at or before 32 weeks' gestation (2% of all births in the United States in 2007) are at extremely high risk for death in the neonatal period or for pulmonary, visual, and neurodevelopmental morbidities with lifelong consequences including bronchopulmonary dysplasia, retinopathy of prematurity, and brain injury. Risks for adverse outcomes increase with decreasing gestational age. The economic costs to care for these infants are also substantial (estimated at $26 billion in 2005 in the United States). It is clear that the need for strategies to improve outcomes for this high-risk population is great, and this need has prompted testing of new therapies with the potential to decrease pulmonary and other complications of prematurity. Inhaled nitric oxide (iNO) emerged as one such therapy. To provide health care professionals, families, and the general public with a responsible assessment of currently available data regarding the benefits and risks of iNO in premature infants, the Eunice Kennedy Shriver National Institute of Child Health and Human Development, the National Heart, Lung, and Blood Institute, and the Office of Medical Applications of Research of the National Institutes of Health convened a consensus-development conference. Findings from a substantial body of experimental work in developing animals and other model systems suggest that nitric oxide may enhance lung growth and reduce lung inflammation independently of its effects on blood vessel resistance. Although this work demonstrates biological plausibility and the results of randomized controlled trials in term and near-term infants were positive, combined evidence from the 14 randomized controlled trials of iNO treatment in premature infants of ≤34 weeks' gestation shows equivocal effects on pulmonary outcomes, survival, and neurodevelopmental outcomes. *Pediatrics* 2011;127:363–369

*National Institutes of Health (NIH) consensus and state-of-the-science statements are prepared by independent panels of health professionals and public representatives on the basis of (1) the results of a systematic literature review prepared under contract with the Agency for Healthcare Research and Quality, (2) presentations by investigators working in areas relevant to the conference questions during a 2-day public session, (3) questions and statements from conference attendees during open-discussion periods that are part of the public session, and (4) closed deliberations by the panel during the remainder of the second day and morning of the third day. This statement is an independent report of the panel and is not a policy statement of the NIH or the federal government. The statement reflects the panel's as-*

*sessment of medical knowledge available at the time the statement was written. Thus, it provides a "snapshot in time" of the state of knowledge on the conference topic. When reading the statement, keep in mind that new knowledge is inevitably accumulating through medical research.*

Premature birth is a major public health problem in the United States and internationally. Despite clinical, educational, and scientific efforts, the frequency of preterm birth has risen in the United States from 10.6% in 1990 to 12.7% in 2007. Worldwide, ~13 million infants are born prematurely every year. Infants born at or before 32 weeks' gestation (2% of all births in the United States in 2007) are at extremely high risk for death in the neonatal period or for pulmonary, visual, and neurodevelopmental morbidities with lifelong consequences including bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), and brain injury. Risks for adverse outcomes increase with decreasing gestational age. The economic costs to care for these infants are also substantial (estimated at $26 billion in 2005 in the United States). In addition, the emotional and indirect economic costs for families are substantial. It is unfortunate, however, that the multifactorial biological, behavioral, and environmental causes and the heterogeneity of preterm birth make it extremely unlikely that all premature births can be prevented.

Many clinical practices integrated into the care of these infants have been inadequately studied for safety and efficacy, which leads to potentially serious consequences; yet, the smallest and sickest infants are the most vulnerable to adverse effects of the treatments they receive. The broad boundaries of accepted clinical practices in NICUs lead to practice variations among centers. Large variations among centers in outcomes of premature infants, including BPD and adverse neurodevelopmental outcomes, persist after adjusting for risk factors such as gestational age, gender, and disease severity. The extent to which these differences in outcomes are attributable to differences in care practices or in patient characteristics is poorly understood. It is clear that the need for strategies to improve outcomes for this high-risk population is great, and this need has prompted testing of new therapies with the potential to decrease pulmonary and other complications of prematurity. Inhaled nitric oxide (iNO) has emerged as one such therapy.

Nitric oxide is a gas that is ubiquitously produced in the human body. It serves as a signaling molecule with numerous regulatory effects on multiple human organ systems, including blood vessels, the lung, the heart, the nervous system, the immune system, and stem cells, and on the development of cancer. Over the past decade, the efficacy of nitric oxide in reducing blood vessel resistance and its easy administration via endotracheal tube to infants with respiratory distress led to trials in term and near-term newborns who were suffering from persistent pulmonary hypertension, a condition that results from failure of normal fetal lung blood vessel relaxation immediately after birth. Large placebo-controlled trials have revealed that nitric oxide decreases the risk of death or the need for extracorporeal membrane oxygenation in term and near-term infants with persistent pulmonary hypertension, and these results have led the US Food and Drug Administration to approve iNO as a therapy for that disease.

Findings from a substantial body of experimental work in developing animals and other model systems suggest that nitric oxide may enhance lung growth and reduce lung inflammation independently of its effects on blood vessel resistance. Although this work demonstrates biological plausibility and the results of randomized controlled trial (RCTs) in term and near-term infants were positive, combined evidence from the 14 RCTs of iNO treatment in premature infants of ≤34 weeks' gestation have shown equivocal effects on pulmonary outcomes, survival, and neurodevelopmental outcomes. Despite these equivocal results, the off-label use of iNO has increased substantially. Controversy about its use in premature infants has been fueled by the refusal of some third-party payers to cover the substantial costs for iNO administration (up to $3000/day).

To provide health care professionals, families, and the general public with a responsible assessment of currently available data regarding the benefits and risks of iNO in premature infants, the Eunice Kennedy Shriver National Institute of Child Health and Human Development, the National Heart, Lung, and Blood Institute, and the Office of Medical Applications of Research of the National Institutes of Health convened a consensus-development panel that included experts in the fields of neonatology, pediatric pulmonology, pediatric neurology, perinatal epidemiology, ethics, neurodevelopmental follow-up, nursing, and family-centered care to review available data, to hear scientific summaries from investigators involved in this field, and to solicit input from the general public. A planning committee developed 6 questions to be addressed by the consensus-development panel.

As part of a comprehensive data review, an independent group, the Johns Hopkins University Evidence-Based Practice Center (JHU EPC), generated a systematic review of all available human studies concerning use of iNO in

premature infants. This review, along with an as-yet-unpublished, updated Cochrane review and an unpublished individual-patient-data (IPD) meta-analysis (the Meta-analysis of Preterm Patients on Inhaled Nitric Oxide [MAPPiNO]) provided the panel with summaries of the available evidence from these trials. One of the published trials, and therefore the JHU EPC systematic review, included infants of 34 weeks' gestation. The panel's review of the published evidence, therefore, is based on infants of ≤34 weeks' gestation. Its recommendations for clinical use of iNO, however, are limited to infants of <34 gestation weeks to avoid contradiction and confusion with the Food and Drug Administration's labeled indications for iNO use. Where applicable, the panel chose to follow the Cochrane-review approach of subdividing the 14 trials into 3 clinically relevant groups on the basis of characteristics of the participating infants and specific treatment strategies: early routine (initiation at <3 days, routine use in intubated infants); early rescue (initiation at <3 days based on oxygenation status); and later rescue (initiation at >3 days based on BPD risk).

Many of the trials and meta-analyses examined results in clinical or demographic subgroups. When treatment effects differ across subgroups, however, as they did in some of the iNO studies, it is unwise to make firm inferences about subgroup differences when those differences are observed post hoc. Posthoc analysis of treatment effects in specific subgroups (eg, dose of iNO, gestational age, early versus late initiation of treatment), whether within or across trials, is prone to false-positive results. The consensus-development panel, therefore, considered the subgroup results of these analyses as hypothesis-generating, rather than hypothesis-testing, and used them as a basis for recommending future research directions.

The 6 questions considered by the consensus-development panel are listed below and addressed in the subsequent sections.

1. Does iNO therapy increase survival rates and/or reduce the occurrence or severity of BPD among premature infants who receive respiratory support?
2. Are there short-term risks of iNO therapy among premature infants who receive respiratory support?
3. Are there effects of iNO therapy on long-term pulmonary and/or neurodevelopmental outcomes among premature infants who receive respiratory support?
4. Does the effect of iNO therapy on BPD and/or death or neurodevelopmental impairment vary across subpopulations of premature infants?
5. Does the effect of iNO therapy on BPD and/or death or neurodevelopmental impairment vary according to timing of initiation, mode of delivery, dose and duration, or concurrent therapies?
6. What are the future research directions needed to better understand the risks, benefits, and alternatives to nitric-oxide therapy for premature infants who receive respiratory support?

## DOES iNO THERAPY INCREASE SURVIVAL RATES AND/OR REDUCE THE OCCURRENCE OR SEVERITY OF BPD AMONG PREMATURE INFANTS WHO RECEIVE RESPIRATORY SUPPORT?

The panel addressed this question by including all of the trials onto which premature infants of ≤34 weeks' gestation were enrolled irrespective of the timing, dosing regimen, duration of iNO therapy, or subcategorization of the subjects. None of the individual trials included in the systematic reviews revealed a statistically significant effect of iNO on survival in this population. Meta-analysis by the JHU EPC of 11 RCTs revealed that treatment with iNO did not increase survival rates. The IPD approach used in the IPD MAPPiNO of pooled data from 11 RCTs revealed no statistically significant effect of iNO on death at any time, death by 36 weeks' postmenstrual age (PMA), or death before discharge. Inclusion or exclusion of the 1 trial with enrollment exclusively after 1 week did not affect the results of the meta-analysis. Thus, overall, in premature infants of ≤34 weeks' gestation who require respiratory support, current evidence shows that treatment with iNO in the neonatal period does not increase survival rates.

Interpretation of results from RCTs was complicated by different studies that calculated BPD rates by using survivors versus the total group as the denominator, and by the competing risks of death and BPD. In other words, an infant who dies in the first weeks of life is not at risk for developing BPD, which is usually based on criteria at 28 days. Because most of the trials and the JHU EPC systematic review included analyses of BPD alone, however, the panel also examined that evidence. None of the individual trials included in the systematic reviews showed statistically significant differences in BPD at 36 weeks' PMA in those who received iNO compared with controls. The JHU EPC meta-analysis (8 RCTs) of BPD among surviving infants at 36 weeks' PMA revealed no statistically significant differences in rates of BPD between the iNO and control groups. With the approach it used, the IPD MAPPiNO did not report on BPD as a sole outcome variable. Thus, among premature infants who require respiratory support and are surviving at 36 weeks' PMA, current evidence does not support the

hypothesis that treatment with iNO in the neonatal period reduces the occurrence of BPD.

The composite outcome of "death or BPD at 36 weeks' PMA" was reported, although not always as a primary outcome, from 11 iNO RCTs. Two individual trials revealed statistically significant reductions in the composite outcome of death or BPD in the iNO-treated group. The JHU EPC meta-analysis of 11 RCTs found a small, statistically significant reduction in the composite variable death or BPD at 36 weeks' PMA. Exclusion of the 1 trial with enrollment after 1 week of age did not change the results of the meta-analysis. The IPD MAPPiNO of pooled data from 10 trials showed a similarly small effect size for BPD or death as the JHU EPC analysis, but it did not achieve statistical significance. The small effect on this composite outcome should be interpreted cautiously.

The JHU EPC systematic review of the effect of iNO on the severity of BPD in the RCTs was compromised by the wide variation in BPD definitions and other study parameters. The JHU EPC analysis concluded that insufficient data are available to perform a meta-analysis for any measure of severity because of the lack of uniformity in definitions and study measures used. There is insufficient evidence to support the hypothesis that treatment with iNO in the neonatal period reduces the severity of BPD. The authors of 2 individual trials reported a statistically significant favorable effect of iNO on pulmonary outcomes reflecting severity of BPD; rates of hospitalization and respiratory support at 40 and 44 weeks' PMA; and a statistically significant reduction in the average duration of supplemental oxygen. Although these trials raise intriguing questions, the effects of iNO on the severity of BPD have not been studied adequately in subpopulations.

The available evidence, therefore, is insufficient to recommend the routine use of iNO in clinical care of premature infants of <34 weeks' gestation who require respiratory support.

## ARE THERE SHORT-TERM RISKS OF iNO THERAPY AMONG PREMATURE INFANTS WHO RECEIVE RESPIRATORY SUPPORT?

Premature infants are at risk for short-term complications including patent ductus arteriosus, late-onset (>7 days) sepsis, necrotizing enterocolitis, ROP, pulmonary complications (eg, air leak, pulmonary hemorrhage), and brain injury (eg, intraventricular hemorrhage [IVH], intraparenchymal hemorrhage, and periventricular leukomalacia [PVL]). In addition, iNO may lead to accumulation of methemoglobin formed by the reaction of nitric oxide with hemoglobin.

Although different trials monitored different combinations of these complications and used differing study designs (eg, timing dose of iNO), the JHU EPC (which examined patent ductus arteriosus, late-onset sepsis, necrotizing enterocolitis, ROP, pulmonary complications, IVH, PVL, intraparenchymal hemorrhage, or toxic levels of methemoglobin), the updated Cochrane meta-analysis (which examined severe IVH and combined outcomes of severe IVH or PVL), and the IPD MAPPiNO (which examined air leak, pulmonary hemorrhage, and severe ROP) showed no evidence for an increased risk of any of these complications or methemoglobin levels considered toxic in term infants and adults at doses up to 20 ppm.

The updated Cochrane meta-analysis did show that early rescue administration of iNO was associated with a nonsignificant trend toward increased severe IVH, and the IPD MAPPiNO showed a nonsignificant trend toward increased severe neurologic events (eg, IVH, intraparenchymal hemorrhage, cystic PVL) with iNO treatment.

Although these morbidities might be exacerbated by iNO, there may be other important indicators specific to premature infants that have not been examined.

In summary, there is no evidence that treatment with iNO either increases or decreases the risk of several short-term complications of prematurity, including patent ductus arteriosus, late-onset sepsis, severe ROP, and pulmonary complications (eg, air leaks, pulmonary hemorrhage).

## ARE THERE EFFECTS OF iNO THERAPY ON LONG-TERM PULMONARY AND/OR NEURODEVELOPMENTAL OUTCOMES AMONG PREMATURE INFANTS WHO RECEIVE RESPIRATORY SUPPORT?

### Long-term Pulmonary Outcomes

The JHU EPC reported on 2 RCTs that examined long-term pulmonary outcomes. One large study demonstrated a statistically significant decrease in use of lung-related medications and fewer parental reports of respiratory symptoms at 12 months in children who received iNO compared with controls; a smaller study revealed no statistically significant difference in reported use of lung medications or reports of symptoms at 12 months. Neither study found a statistically significant difference in rates of hospitalization for lung problems or wheezing at 12 months. The lack of a difference in hospitalization or wheezing casts doubt on the clinical importance of a difference in medication use between those who received iNO and the controls.

The panel concludes, as did the JHU EPC, that there is evidence in 1 trial of an advantage in long-term pulmonary outcome for the use of iNO, but this evidence is not strong enough to justify

the widespread use of iNO to prevent long-term pulmonary disease.

### Long-term Neurodevelopmental Outcomes

None of the trials that examined long-term neurodevelopmental outcomes in children have convincingly demonstrated a long-term neurodevelopmental effect of iNO. Individually, none of the trials found a statistically significant difference in the incidence of motor delay between those who had received iNO and controls. For cerebral palsy, the 2 trials that did show associations conflicted in the direction of association. There is insufficient evidence to determine if there is an effect of iNO on motor impairment or if it differs according to the birth weight of the treated infants. There also were no significant differences between the iNO and control groups in the proportion of children with visual or hearing impairment. Few individual trials and none of the meta-analyses revealed a statistically significant association between neonatal iNO treatment and any neurodevelopmental outcome at up to 5 years of age.

Studies of long-term neurodevelopment in preterm infants of ≤34 weeks' gestation treated with iNO have been hampered by variation in measures used to assess neurodevelopmental status and the ages at which outcomes are measured and by the lack of physiologic, radiologic, functional, or quality-of-life measures used as outcomes. Most studies of long-term effects typically have used overly broad measures of development in the absence of physiologic or anatomic examinations; many also have used the measure at too young an age. Although 18 to 24 months is appropriate for detecting cerebral palsy, testing at school age is more appropriate for diagnosing intellectual disability. Newer methods of assessment, including correlated neuroimaging and standardized behavioral testing, should be included in any future assessments of the long-term neurodevelopmental consequences of iNO.

## DOES THE EFFECT OF iNO THERAPY ON BPD AND/OR DEATH OR NEURODEVELOPMENTAL IMPAIRMENT VARY ACROSS SUBPOPULATIONS OF PREMATURE INFANTS?

The panel elected to review common clinical variables that may interact with iNO treatment apart from timing or duration of treatment (see response in "Does the Effect of iNO Therapy on BPD and/or Death or Neurodevelopmental Impairment Vary According to Timing of Initiation, Mode of Delivery, Dose and Duration, or Concurrent Therapies?"). Analysis of subpopulations is limited by the fact that few trials have identified subgroups, subgrouping results in small sample sizes in each subcategory, and trials are often not powered to detect subgroup differences. In addition, when trials did define subgroups, definitions varied across trials and were usually post hoc.

On the basis of the JHU EPC systematic review, there is insufficient evidence to evaluate whether factors such as gender, gestational age, ethnic group/race, and socioeconomic status were associated with increased benefit or risk from iNO therapy. There is no information regarding the effects of growth restriction, antenatal steroid use, multiple gestation, chorioamnionitis, or other antenatal factors.

The JHU EPC systematic review revealed insufficient evidence of decreased incidence of death or BPD particular to any subgroup of premature infants treated with iNO. From 5 studies (representing 3 independent clinical trials) outcomes according to birth weight have been reported. Two of the 3 trials demonstrated a significant reduction in the composite outcome of death or BPD when iNO was administered to premature infants born at ≥1000 g but not in those born at <1000 g.

This review raises a concern for the safety of iNO in premature infants born at <1000 g. Three studies of infants of this birth weight treated within 48 hours of delivery revealed an increased risk of death, severe IVH and PVL, neurodevelopmental impairment, BPD, and/or oxygen dependence at 1 year of age. However, in another large study that initiated iNO at 7 days of life, no such safety concerns were noted in this birth-weight category.

On the basis of the JHU EPC systematic review of published studies, there is insufficient evidence of improvement in neurodevelopmental outcomes in any subgroup of premature infants treated with iNO.

Published trial reports have shown insufficient evidence of benefit to premature infants with pulmonary hypoplasia or hypertension, likely because of small numbers of such patients and severity of illness. Additional studies in this population will be difficult to accomplish. Therefore, clinical use in this population should be left to clinical discretion.

On the basis of published data, the panel recommends special caution in studies of early rescue use of iNO in premature infants of <34 weeks' gestation who weigh <1000 g.

## DOES THE EFFECT OF iNO THERAPY ON BPD AND/OR DEATH OR NEURODEVELOPMENTAL IMPAIRMENT VARY ACCORDING TO TIMING OF INITIATION, MODE OF DELIVERY, DOSE AND DURATION, OR CONCURRENT THERAPIES?

Infants treated with early routine and early rescue iNO (see introduction for definitions of these groups) had no significant reduction in deaths, BPD, or the composite outcome of death or BPD. However, infants treated in the later-rescue group, predominantly

represented by 1 large multicenter trial in which the treatment protocol was unique not only in the timing of initiation but also in dosing and duration, had an overall reduction in the composite outcome of death or BPD and a posthoc finding of greater efficacy when treatment was initiated during the second postnatal week as compared with the third postnatal week. The method of treatment allocation and statistical analysis of multiples enrolled in the trial made it difficult to integrate this trial's findings in a conventional meta-analysis. Nevertheless, different statistical approaches to the analysis of multiples did not substantially change the estimate of the effect of iNO.

The effect of mode of ventilation (conventional versus high frequency) on efficacy and safety of iNO was evaluated in 2 trials, in 1 by prospective randomization and in the other by posthoc analysis. No studies have directly compared delivery by continuous positive airway pressure or nasal cannula versus endotracheal positive-pressure ventilation. There is insufficient evidence to determine if mode of ventilation affects outcome from iNO treatment.

To date, none of the trials with published reports randomly assigned subjects according to dose or treatment duration of iNO. Despite this limitation, these trials can be subdivided into 3 broad dosage groups: 5, 10, and 20 ppm. In a dose-stratified meta-analysis by the JHU EPC, which combined all 3 treatment-initiation subgroups, iNO therapy in the group that received a maximum dose of 10 ppm was associated with a statistically significant reduction in the risk of BPD, but not death, or the composite outcome of death or BPD. These results do not form a basis for deciding that 1 dosing regimen was superior, because they were based on posthoc comparisons and there was too much variability among the study designs within each dose group. A more focused examination of dosing and treatment duration within clinically meaningful subgroups is needed.

Little is known about the effect of concurrent therapies on the efficacy and safety of iNO. Only 1 trial directly addressed the effect of iNO with a concurrent therapy (glucocorticoids). Additional research is needed to determine the effect of concurrent therapies (such as antenatal and postnatal glucocorticoids, surfactant, vitamin A, indomethacin, and caffeine) on the efficacy and safety of iNO.

There is no evidence to suggest that variations in these treatment-regimen factors (eg, dose, timing, mode of administration) are harmful in terms of BPD, death, or neurodevelopmental outcome. The design of future trials comparing treatment regimens should include a longer duration of follow-up to ensure long-term safety.

There is insufficient evidence to conclude that the efficacy of iNO therapy with respect to BPD and/or death, or neurodevelopmental impairment, varies according to timing of initiation, mode of delivery, dose and duration of therapy, or concurrent therapies. Although the evidence suggests that some treatment regimens may provide greater benefit, additional RCTs designed to address these specific hypotheses must be undertaken.

## WHAT ARE THE FUTURE RESEARCH DIRECTIONS NEEDED TO BETTER UNDERSTAND THE RISKS, BENEFITS, AND ALTERNATIVES TO NITRIC-OXIDE THERAPY FOR PREMATURE INFANTS WHO RECEIVE RESPIRATORY SUPPORT?

1. Understanding risks, benefits, and alternatives to iNO therapy for premature infants requires investigation of iNO's mechanisms of action through additional basic research in developmentally relevant experimental models, especially understanding the respective roles of dosing, delivery, and timing of therapy and of accompanying ventilation strategies, oxygen management, and concurrent therapies in optimizing the benefits of iNO, on understanding the pharmacology and toxicology of iNO specifically in premature infants, and on increasing tissue-specific production of endogenous nitric oxide.
2. Future trials for evaluation of safety and efficacy of iNO for premature infants should be informed by previous trials and future studies in premature animals or other model systems, examine both short-term and long-term pulmonary and neurodevelopmental outcomes, and investigate effect-modifying factors (eg, pharmacokinetic, genetic, racial/ethnic, and disease risk factors).
3. Future randomized trials should be designed to assess variations in the timing, dose, and duration of treatment by randomly assigning them separately, to include a placebo control, to ensure a sample size sufficient to detect a significant interaction between gestational-age category and treatment arm, and to consider an appropriate developmental window for efficacy and safety. The positive results of one multicenter trial, which was characterized by later timing, higher dose, and larger duration of treatment, should be confirmed through future trials to understand the effects of each treatment-related variable.
4. Future trials should assess the long-term safety and efficacy of iNO treatment by following study subjects to a minimum of school age with standardized assessments of behavior, cognitive ability, neuroanatomy, and neurophysiology.

5. Design of future efficacy and safety trials of iNO for premature infants should include interdisciplinary teams of experts in high-risk obstetrics, neonatology, pediatric pulmonology, pediatric neurology, neurodevelopmental follow-up, neonatal pharmacology, lung development, brain development, nitric-oxide physiology, biostatistics, and clinical trial design, as well as ethicists, nurses, respiratory therapists, and families.
6. Given the large differences in outcomes of death and BPD among NICUs, comparative effectiveness research strategies should be considered to identify components of care that may have greater impact on improving outcomes than iNO.
7. In addition to the panel's iNO research recommendations, future research should pursue promising strategies other than iNO.
8. Biomarker, neuroimaging, pulmonary function testing, pulmonary imaging, and other techniques with potentially better predictive accuracy should be developed and tested.

## CONCLUSIONS

1. Taken as a whole, the available evidence does not support use of iNO in early-routine, early-rescue, or later-rescue regimens in the care of premature infants of <34 weeks' gestation who require respiratory support.
2. 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.
3. Future research should seek to understand the gap between benefits on lung development and function in infants at high risk of BPD suggested by basic research and animal studies and the results of clinical trials to date.
4. Predefined subgroup and posthoc analyses of previous trials showing potential benefit of iNO have generated hypotheses for future research for clinical trials. Previous strategies shown to be ineffective are discouraged unless new evidence emerges. Future trials should attempt to quantify the individual effects of each of these treatment-related variables (timing, dose, and duration), ideally by randomly assigning them separately.
5. On the basis of assessment of currently available data, hospitals, clinicians, and the pharmaceutical industry should avoid marketing iNO for premature infants of <34 weeks' gestation.

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**KEY WORDS**

premature, inhaled nitric-oxide therapy, bronchopulmonary dysplasia

**ABBREVIATIONS**

BPD—bronchopulmonary dysplasia
ROP—retinopathy of prematurity
iNO—inhaled nitric oxide
RCT—randomized controlled trial
JHU EPC—Johns Hopkins University Evidence-Based Practice Center
MAPPiNO—Meta-analysis of Preterm Patients on Inhaled Nitric Oxide
IPD—individual patient data
PMA—postmenstrual age
IVH—intraventricular hemorrhage
PVL—periventricular leukomalacia

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