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Advanced Specialty Pediatric Hospitals Position Statement August 2, 2012: Nitric Oxide Use for Pulmonary Hypertension in Preterm Neonates

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This statement was originally written to the United States Food and Drug Association in 2012. Despite increasing evidence to support the effectiveness of inhaled Nitric Oxide in premature infants with physiologic pulmonary hypertension, the use of iNO in this population is not routine. Dr. Null submitted this statement on behalf of the original authors of the document, which is included in this submission, along with the letter written by F. Sessions Cole.

The following national network of board-certified Neonatologists and Pediatric Intensivists recognize the administration and charge for inhaled Nitric Oxide (iNO) in neonates less than 34 weeks gestation in the treatment of pulmonary hypertension as both medically appropriate and a community standard of care practiced by Advanced Specialty Pediatric Hospitals across the United States. Insurance company refusal to reimburse for this standard of care reflects inappropriate application of labeling by the Food and Drug Administration (FDA).

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Our national network supports the FDA's labeling of inhaled Nitric Oxide as inappropriate for the treatment of lung disease in infants less than 34 weeks gestational age for bronchopulmonary lung disease. However, we do support the use of Nitric Oxide in neonates less than 34 weeks gestational age with severe respiratory failure with evidence of pulmonary hypertension that have shown no improvement with ventilation strategies. Additionally, we support the use of Nitric Oxide in patients who are older ex-premature infants with severe Chronic Lung Disease (CLD) that developed secondary pulmonary hypertension. Pulmonary hypertension is a condition in which pulmonary artery blood pressure is abnormally high; this can dramatically increase the possibility of requiring heart and lung support via extracorporeal membrane oxygenation (ECMO). Our physician experts and leaders practice under extreme real-life circumstances. They are familiar with this deteriorating condition as they follow advances in technological science, research, clinical practice, and community standards of care when making clinical judgments to treat the patient. Medicine is based upon many diverse sources, and for neonates, these sources involve very few large clinical trials. The large clinical trial used as the basis for the FDA's labeling had gestational limitations inherent in their sampling, which included patients that were 34 weeks gestation and greater. This gestation age limitation was related to criteria for ECMO since one of the major outcome variables being tested was a reduction in the need for ECMO. But the most important outcome was the recognition that iNO is an effective therapy for pulmonary hypertension, and this is the basis for treating any infant with the diagnosis of pulmonary hypertension who is not responding to routine therapy regardless of their gestational or postnatal age. Community standards of care in medical practice evolve due to the extensive period required to methodically study patient groups and obtain regulatory approval.

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Per a review in the Cochrane Collaborative, the U.S and international use of pulse oximetry as "a tool that guides the anesthesiologists in the daily management of patients, in teaching situations, in emergencies and especially in caring for children" is in the absence of scientific evidence supporting such perioperative monitoring. (1) Despite requiring further scientific study, community standards of care are widely accepted and regarded as an integral part of making important medical decisions.

Based upon the National Institutes of Health (NIH) Consensus and utilizing state-of-the-science statements, this practice of utilizing Nitric Oxide on premature newborns is deemed appropriate based upon clinicians' judgment. (2) In rare clinical situations, Nitric Oxide "may have benefit in

infants <34 weeks' gestation." (2) The available evidence is equivocal and, therefore, does not suggest Nitric Oxide "either increases or decreases the risk of several short-term complications of prematurity." (2) In other words, the available early evidence involved a small number of very high-risk patients at high risk for mortality who are extremely difficult to study. This is why independent panelists and public representatives participating in the NIH Consensus conclude that the use of Nitric Oxide in premature infants "should be left to clinical discretion." (2)

"In association with the Child Health Corporation of America (CHCA), a consortium of free-standing pediatric hospitals, it is our position that the use of nitric oxide in infants of less than 34 weeks gestation with pulmonary hypertension is a community standard of practice."

Per the Agency for Healthcare Research and Quality under the U.S. Department of Health and Human Services, "we should not abandon the possibility that iNO may someday become a component of a treatment strategy for some preterm infants receiving respiratory support. Several factors contribute to our recommendation to continue the study of iNO: 1) our finding of a small but statistically significant difference in death or BPD at 36 weeks PMA, the common primary outcome variable of 73% of RCT conducted to-date; 2) the statistically significant finding of a diminished need for chronic pulmonary medication at one year corrected age, suggesting less severe lung disease in those treated with iNO, and 3) no studies have been powered to detect meaningful differences in infant functional outcome or quality of life with iNO treatment compared to standard therapy." (3) Future studies into premature birth in the U.S. and internationally will assist in providing a clearer strategy for the FDA to issue labeling changes.

In association with the Child Health Corporation of America (CHCA), a consortium of free-standing pediatric hospitals, it is our position that the use of nitric oxide in infants of less than 34 weeks gestation with pulmonary hypertension is a community standard of practice. We are a community of recognized leaders in providing the highest quality and excellence in pediatric medicine. We are committed to providing safety, quality performance, education, research, and child health advocacy co11joined with forward-thinking, ethics, and integrity in the vision of transforming healthcare.

In summary, Nitric Oxide use in preterm neonates with pulmonary hypertension is in accordance with 2011 NIH guidelines and not addressed in the current FDA labeling due to the lack of clinical studies. Furthermore, the use of Nitric Oxide in preterm neonates is a standard of practice at free-standing pediatric hospitals across the country. Based on this community standard of practice, we use Nitric Oxide in a medically appropriate manner.

References:

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2. *"NIH Consensus Development Conference Statement: Inhaled Nitric-Oxide Therapy for Premature Infants." Journal of the American Academy of Pediatrics 127.2 (2011): 363- 69. Web. September 28, 2011.*
3. *Allen MC., et al., Inhaled Nitic Oxide in Preterm Infants, Evidence Report/ Technology Assessment No. 195, (Prepared by Johns Hopkins University Evidence-based Practice Center under Contract No. 290-2007-10061-I). AHRQ Publication No. 11-E00l. Rockville, MD: Agency for Healthcare Research and Quality. October 2010.*

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