# Royal Hospital for Women (RHW)
# NEONATAL BUSINESS RULE
# COVER SHEET

Health
South Eastern Sydney
Local Health District

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| **EXECUTIVE SPONSOR** | Sally Wise, Nursing Co-Director Neonatal Services<br>Srinivas Bolisetty, Medical Co-Director Neonatal Services |
| **AUTHOR** | John Smyth (Neonatologist) |
| **SUMMARY** | To determine a neonate's need for iNO treatment, implement this treatment and wean iNO in a timely and appropriate manner. |
| **Key Words** | Inhaled Nitric Oxide (iNO), Persistent Pulmonary Hypertension (PPHN), neonate |

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## Inhaled Nitric Oxide (iNO) in Neonates — RHW CLIN172

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*Within this document we will use the term woman, this is not to exclude those who give birth and do not identify as female. It is crucial to use the preferred language and terminology as described and guided by each individual person when providing care.*

# 1 BACKGROUND

Use of inhaled nitric oxide (iNO) as a pulmonary vasodilator is well established in term & near-term neonates with hypoxic respiratory failure (HRF) associated with Persistent Pulmonary Hypertension of the Newborn (PPHN)[1]. iNO should ideally be initiated following echocardiographic (ECHO) confirmation of PPHN.

iNO may be considered as a rescue modality in preterm neonates with severe PPHN associated with prolonged preterm rupture of membranes (PPROM), prolonged oligohydramnios and pulmonary hypoplasia. It can also be considered in late-onset HRF in the context of bronchopulmonary dysplasia-associated pulmonary hypertension (PH) with severe right ventricular failure.

# 2 RESPONSIBILITIES

## 2.1 Staff (Medical, Nursing)

2.1.1 Medical – To determine a neonate's need for iNO treatment, perform an ECHO if appropriately trained, prescribe iNO dose on eRIC, inform nursing staff to commence iNO treatment, monitor neonate for iNO response, to wean iNO timely and appropriately, referral to PICU for ECMO consideration.

2.1.2 Nursing – to set up INOmax DSIR Plus, commence iNO treatment under medical supervision, sign iNO prescription with second RN, document iNO treatment, monitor iNO treatment response in neonate, wean iNO when indicated, cease iNO when not required.

# 3 PROCEDURE

## 3.1 Equipment

- INOMax DSIR Plus (refer to NCC CBR Nitric Oxide INOmax DSIR Plus Set up)
- Ultrasound for Echocardiography

## 3.2 Clinical Practice

## 3.3 Indications for iNO therapy

### 3.3.1 General Indications for iNO in Term Neonates and Preterm Neonates >32 weeks gestation

- Clinical and/or ECHO evidence of PPHN
  - Clinical presentation is labile hypoxemia and clinical evidence of right-to-left extrapulmonary shunting demonstrated as a gradient in preductal and post ductal oxygen ($O_2$) saturations of >10%
- Any neonate with severe hypoxic respiratory failure
  - Partial pressure of arterial oxygen ($PaO_2$) < 50mmHg OR
  - $O_2$ saturation < 90% despite optimal ventilation (see note below) with Fraction of Inspired Oxygen ($FiO_2$) > 80%
  - Use of Oxygenation Index (OI) - consider iNO in patients with an OI > 15-25 – for OI calculation see educational notes
- Any ventilated neonate with > 60% $FiO_2$ requirement and echocardiographic evidence of PPHN (i.e. pulmonary artery pressures close to or above systemic pressures).
- Early use of iNO can be considered in neonates with respiratory failure born after prolonged oligohydramnios, congenital diaphragmatic hernia or congenital pulmonary airway malformation.[2-7]

NOTE:
It is important to optimise lung recruitment, systemic hemodynamic and cardiac performance prior to initiation of iNO therapy. For example, target mean systemic arterial blood pressure to be equal to or greater than measured or anticipated pulmonary arterial pressure.

### 3.3.2 General Indications for iNO in Preterm Neonates <32 weeks gestation

- Any ventilated preterm neonate with severe hypoxic respiratory failure
  - $PaO_2$ <50 mmHg OR
  - $O_2$ sats <90% despite moderate ventilatory requirements (Moderate ventilator requirements are defined as Mean Airway Pressure 12-14cm$H_2O$ with $FiO_2$ >60%)

#### 3.3.3 Relative Contraindications[8]

- Neonates <26 weeks gestation at time of treatment- lower dose of 5-10parts per million [PPM] suggested
- Known intraventricular haemorrhage
- Evidence of coagulopathy (particularly in preterm neonates <32 weeks)
- HRF and evidence of left ventricular (LV) systolic or diastolic dysfunction without added measures to improve cardiac function may worsen their condition. The presence of LV dysfunction decreases antegrade pulmonary venous flow resulting in pulmonary venous hypertension, or "postcapillary" PH.[21]

### 3.4 iNO Starting Dosage (Appendix 1 Algorithm)

- Neonates >26 weeks gestation:
  - Start at 20ppm (higher doses are unlikely to be of benefit; and doses >40 ppm are associated with methaemoglobinaemia)
- Preterm neonates ≤26 weeks gestation:
  - Start at 5-10ppm (can increase to a maximum of 20ppm depending on response)

### 3.5 Prescribing iNO

- iNO is a schedule 4 medication and must be prescribed on eRIC Medication Prescription Chart.
- Start and stop time and dose changes must be charted accurately.

### 3.6 Response to iNO therapy (Appendix 1 Algorithm)

#### 3.6.1 Evidence of Response to iNO therapy

- $PaO_2$ increase >20mmHg within 30 minutes.
- Fall of $FiO_2$ by 10% or more while maintaining the desired pre-ductal saturation range with or without changes to ventilation strategy (it is advised to try to avoid any changes in therapy while the response to iNO is being evaluated).
- Normalisation of pre/post-ductal arterial oxygen saturation ($SaO_2$) difference.

#### 3.6.2 iNO Lack of Response or Dose Response

- Discontinue iNO if no response is observed within 1 hour.
- Wean iNO dose to the minimal effective dose as able.
- Decrease iNO dose back to original dose if a trial of increasing nitric dose fails to improve oxygenation or haemodynamics.
- Consider whether the neonate is an appropriate candidate for Extracorporeal Membrane Oxygenation (ECMO) if there is no response and/or the OI is 15-25 (see table in Educational Notes below for indications and considerations for ECMO).

#### 3.6.3 Documentation of iNO response

- Document the following iNO parameters in nursing and medical progress notes prior to commencement of iNO:
  - Mean Airway Pressure
  - $FiO_2$

- $PaO_2$
- Pre-ductal oxygen saturation ($SpO_2$)
- Post-ductal $SpO_2$
- Systolic Blood Pressure
- Bi-directional shunt- Medical note ONLY
- Estimated Pulmonary arterial pressure- Medical note ONLY

- Start iNO – try not to change ventilation parameters for the next 15 minutes (only the $FiO_2$)
- At 15 minutes after commencement of iNO therapy, document the following clinical parameters in nursing and medical notes
  - Mean Airway Pressure
  - FiO2
  - PaO2
  - Pre-ductal SpO2
  - Post-ductal SpO2
  - Systolic Blood Pressure
  - Bi-directional shunt- Medical note ONLY
  - Estimated Pulmonary arterial pressure- Medical note ONLY

### 3.7 Weaning iNO (Appendix 2 Algorithm)

- Initiate weaning from iNO when a neonate shows clinical improvement and is stable for a 4-hour period with:
  - $FiO_2$ <60% and preductal $PaO_2$ >60mmHg OR
  - $O_2$ sats >92%
- If starting at 20ppm, decrease iNO:
  - To 10ppm for 1 hour
  - Then reduce to 5ppm for 1-2 hours
  - Followed by decreases of 1ppm every 1-2 hours until ceased
- If weaning from 20ppm to 10ppm results in failure, weaning can be carried out more slowly at the discretion of the senior medical team.
- The aim is to deliver the minimum dose compatible with normal oxygenation and haemodynamics.
- In Term neonates there may be an advantage in maintaining a low dose of iNO (2-5ppm) while $O_2$ and ventilator pressures are weaned, particularly if there is echocardiographic evidence of persistently elevated pulmonary artery pressures
- In preterm neonates the aim should be to wean off iNO as soon as possible

### 3.8 Failure or difficulties with iNO weaning

- While there is no clear definition for failure, iNO weaning can be considered unsuccessful if $FiO_2$ increases by ≥20% and/or persistent requirements of $FiO_2$ >60% (Consider referral for ECMO if appropriate - see education notes)
- If weaning or discontinuation of iNO results in a clinically evident return of PPHN and hypoxaemia (as per criteria above), iNO therapy should be returned to the last effective dose

### 3.9 Methaemoglobin monitoring

- If methaemoglobin levels rise above 3% iNO should be reduced or stopped.[21]

- Methaemoglobin levels are checked regularly (at consultants' discretion) through blood gas analysis.

## 3.10 Documentation

- eRIC

## 3.11 Education Notes

### 3.11.1 General Notes

- PPHN commonly presents with labile hypoxemia and clinical evidence of right-to-left extrapulmonary shunting, demonstrated as a gradient in preductal and post ductal $O_2$ >10%.
- In term or near-term neonates with hypoxic respiratory failure, iNO has reduced the combined incidence of death or use of ECMO; (typical risk ratio (RR) 0.66, 95% CI 0.57-0.77; 859 neonates in 8 RCT's).[1] This reduction was due to less use of ECMO, mortality was not affected. It did not reduce length of hospitalisation or the risk of neurodevelopmental impairment. There is no evidence of adverse effects, either in the short- or long-term.[8]

### 3.11.2 iNO in Preterm Neonates

- The benefits of iNO in Preterm neonates are not proven. A Cochrane review of 8 trials of early rescue treatment based on oxygenation criteria demonstrated no effect on mortality or BPD (RR 0.94, 95% CI 0.87-1.01; 958 neonates).[9] In addition iNO was associated with a non-significant 20% increase in severe intraventricular haemorrhage (IVH). When used at studied doses of 5-10 ppm, RCT's have not demonstrated an increased risk for severe intraventricular haemorrhage or bleeding, with some showing a significant reduction in severe IVH.[21]
- Despite the above iNO is widely used in preterm neonates with hypoxic respiratory failure and it has a good safety profile. Kinsella et al and others[2-7,10-12] argue using several case series[2-7,11,12] that there may be a place for iNO in the subgroup of preterm neonates (< 34 weeks) with severe PPHN associated with PPROM, prolonged oligohydramnios and pulmonary hypoplasia. It is important in these cases that PPHN is identified on Echocardiography.[7]
- Preterms with severe hypoxemic respiratory failure and PPHN presenting on the first day of life with marked improvement in oxygenation after treatment with iNO are seen as having a very similar to the response to that seen in term newborns with idiopathic PPHN.

**Recommendations for the use of iNO in Preterm Infants**

- iNO therapy while not recommended routinely for respiratory distress syndrome in premature neonates is safe and it can be considered with caution in cases with a concurrent diagnosis of PPHN.[7]
- The Pediatric Pulmonary Hypertension Network has proposed the following recommendations for the role of iNO in premature newborns:[10]

- iNO therapy should not be used in premature neonates for the prevention of bronchopulmonary dysplasia, as data from multicentre studies have failed to consistently demonstrate efficacy for this purpose.
- iNO therapy can be beneficial for preterm neonates with severe hypoxemia that is primarily due to PPHN physiology rather than parenchymal lung disease, particularly if associated with PPROM and oligohydramnios.
- iNO is preferred over other pulmonary vasodilators in preterm neonates based on a strong safety signal from short and long-term follow-up of large numbers of patients from multicentre randomised clinical trials for BPD prevention.

- iNO needs to be used appropriately and safely in both term and preterm neonates and it is important the dose and duration of treatment is minimised.[14] Up to 40% of neonates will not respond to iNO, with the most common reason for an inadequate response being poor alveolar delivery secondary to an underrecruited lung.

**Echocardiography in PPHN and the use of iNO**

- Echocardiography can assist in directing appropriate use of iNO. The best response is often seen in neonates with a relatively normal chest x-ray but ECHO evidence of marked PPHN suggesting primary PPHN.

| Cardiac ECHO features of PPHN include | |
|---|---|
| DA shunt pattern | R → L > 30% (moderate)<br>R→ L > 50% (severe) |
| Pulmonary blood flow | RVO < 150ml/kg/min<br>(PA velocity < 0.25cm/sec) |
| RV pressure | TR jet > 30mmHg<br>LPA pattern<br>Ventricular septum deviation |
| RV function | RVO < 150ml/kg/min |
| LV function | LVO < 150ml/kg/min |

- The use of iNO for neonates with HRF and evidence of left ventricular (LV) systolic or diastolic dysfunction without added measures to improve cardiac function may worsen their condition. The presence of LV dysfunction decreases antegrade pulmonary venous flow resulting in pulmonary venous hypertension, or “postcapillary” PH.[21]

  Those at risk for LV dysfunction include neonates with CDH, HIE, Sepsis, and in postcardiac arrest populations. ECHO signs suggestive of poor LV function include right-to-left ductal shunting but with left-to-right atrial shunting, mitral valve regurgitation and left atrial dilation

**iNO Toxicity and side effects**

- Toxicity of iNO may result from direct inhibitory effects on platelet function, or via its products and reactive metabolites, including methaemoglobin, nitrogen dioxide, and peroxynitrite.[15,16] At the dose range applied clinically (20 ppm), iNO rarely causes clinically significant bleeding, or leads to potentially toxic levels of either methaemoglobin or nitrogen dioxide. iNO has not been demonstrated to increase peroxynitrite formation in the lungs or other tissues of human newborns.[15,16]

- Preclinical work supports the fact oxidative stress incurred by prolonged oxygen exposure directly impairs sCG activity and increases phosphodiesterase 5 (PDE5) activity, contributing to increased vascular tone in the absence of iNO. Given the risk of reduced endogenous signaling, constant reassessment of the clinical benefit gained from iNO is essential to promote active weaning and to reduce cost
- iNO can theoretically cause methaemoglobinaemia although none of the RCTs using doses of 20 ppm or less have reported any increase in the incidence of methaemoglobinemia.[8] Preterm neonates are more susceptible because of relatively low levels of the enzyme methaemoglobin reductase.

### 3.11.3 Oxygenation Index

- The severity of respiratory failure can be estimated by calculating Oxygenation Index (OI).

$$\text{Oxygenation Index (OI)} = \frac{\text{Mean Airway Pressure (cm } H_2O\text{) x } FiO_2 \text{ (as a fraction) x 100}}{PaO_2 \text{ (mmHg)}}$$

### 3.12 Consideration for referral for ECMO

- ECMO is not performed in Newborn Care and a Paediatric Intensive Care referral is required
- The Cochrane review of 4 RCT's shows strong benefit of ECMO on mortality (typical RR 0.44; 95% CI 0.31 to 0.61), especially for babies without congenital diaphragmatic hernia (typical RR 0.33, 95% CI 0.21 to 0.53).[17]
- Controversy exists regarding the degree of HRF severity at which to initiate iNO therapy. The incidence of death or ECMO appears to be strongly correlated with the OI at trial enrolment. Neonates in the early RCTs, where iNO was initiated at a mean OI of >40, had a mortality or ECMO rate of >40%, while neonates who received iNO at an OI of 15-20 had a mortality or ECMO rate of 10.2% [3,21]
- A strategy of early institution of ECMO therapy is likely to result in better outcomes for newborns with hypoxemic respiratory failure.[18] At present, there are few markers that predict which neonates need ECMO therapy and which can be safely managed with non-ECMO therapies.[19]
- Although RCT's have not supported decreased extracorporeal membrane oxygenation (ECMO) or death when initiated at a lower OI, it is reasonable to trial iNO with less-severe HRF but only with concurrent ECHO evidence of PH.[21]

| **Consideration for ECMO** | **ECMO Exclusion Criteria** | |
|---|---|---|
| | **Absolute** | **Relative** |
| • Birthweight >2000 g<br>• Gestation ≥34+0 weeks<br>• Potentially reversible disease<br>• Failing conventional treatment<br>• Oxygenation Index 15-25<br>• Uncompensated hypercapnoea ($pCO_2$ | • Major congenital / chromosomal anomaly<br>• Irreversible lung disease<br>• Major intracranial bleed (grade 3-4 IVH)<br>• Severe encephalopathy | • Gestation < 34 wks<br>• Birth weight <2 kg<br>• Ventilation >10-12 days |

| | | |
|---|---|---|
| >90 mmHg with pH <7.25)<br>• Less than 10 days ventilation<br>• No reason to stop treatment | • Cardiac arrest (other than at birth)<br>• Severe non-treatable congenital heart disease | |

### 3.13 Abbreviations

| | | | |
|---|---|---|---|
| iNO | Inhaled Nitric Oxide | HRF | Hypoxic Respiratory Failure |
| PPHN | Persistent Pulmonary Hypertension of the Newborn | ECHO | Echocardiographic |
| PPROM | prolonged preterm rupture of membranes | PH | Pulmonary Hypertension |
| $O_2$ | Oxygen | $PaO_2$ | Partial pressure of arterial oxygen |
| $FiO_2$ | Fraction of Inspired Oxygen | OI | Oxygenation Index |
| PPM | Parts per Million | LV | Left ventricular |
| $SaO_2$ | Arterial oxygen saturation | ECMO | Extracorporeal Membrane Oxygenation |
| $SpO_2$ | Oxygen Saturation | IVH | intraventricular haemorrhage |

### 3.14 Related Policies/procedures

- NSW Health PD PD2012_069 Health Care Records- Documentation and Management
- NSW Health PD PD2022_032 Medication Handling
- RHW NCC CBR- Arterial line - Blood sampling
- RHW NCC CBR- Continuous Positive Airway Pressure (CPAP) Therapy
- RHW NCC CBR- Deteriorating neonate - Recognition and management inside newborn care centre
- RHW NCC CBR- Drager Babylog VN 500 set up
- RHW NCC CBR- High Flow Nasal Cannula Therapy
- RHW NCC CBR – Nitric Oxide INOMax DS IR Plus set up
- RHW NCC CBR- Kangaroo Care - Non-ventilated and ventilated neonate
- RHW NCC CBR- NAVA
- RHW NCC CBR- NAVA Nursing Management for Invasive Mode
- RHW NCC CBR- NAVA Nursing Management for Non-Invasive Mode
- RHW NCC CBR- Neonatal CERS - Management of the Deteriorating NEONATAL inpatient (CERS)

- RHW NCC CBR- Transcutaneous CO2 monitoring - Sentec Device
- RHW NCC CBR- Transfer of neonate on Non-Invasive respiratory support outside of newborn care centre
- RHW NCC CBR- Transfer of ventilated neonate outside of newborn care centre

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## 4 ABORIGINAL HEALTH IMPACT STATEMENT DOCUMENTATION

- Considerations for culturally safe and appropriate care provision have been made in the development of this Business Rule and will be accounted for in its implementation.
- When clinical risks are identified for an Aboriginal and/or Torres Strait Islander woman or family, they may require additional supports. This may include Aboriginal health professionals such as Aboriginal liaison officers, health workers or other culturally specific services

## 5 CULTURAL SUPPORT

- For a Culturally and Linguistically Diverse CALD woman, notify the nominated cross-cultural health worker during Monday to Friday business hours
- If the woman is from a non-English speaking background, call the interpreter service: NSW Ministry of Health Policy Directive PD2017_044-Interpreters Standard Procedures for Working with Health Care Interpreters.

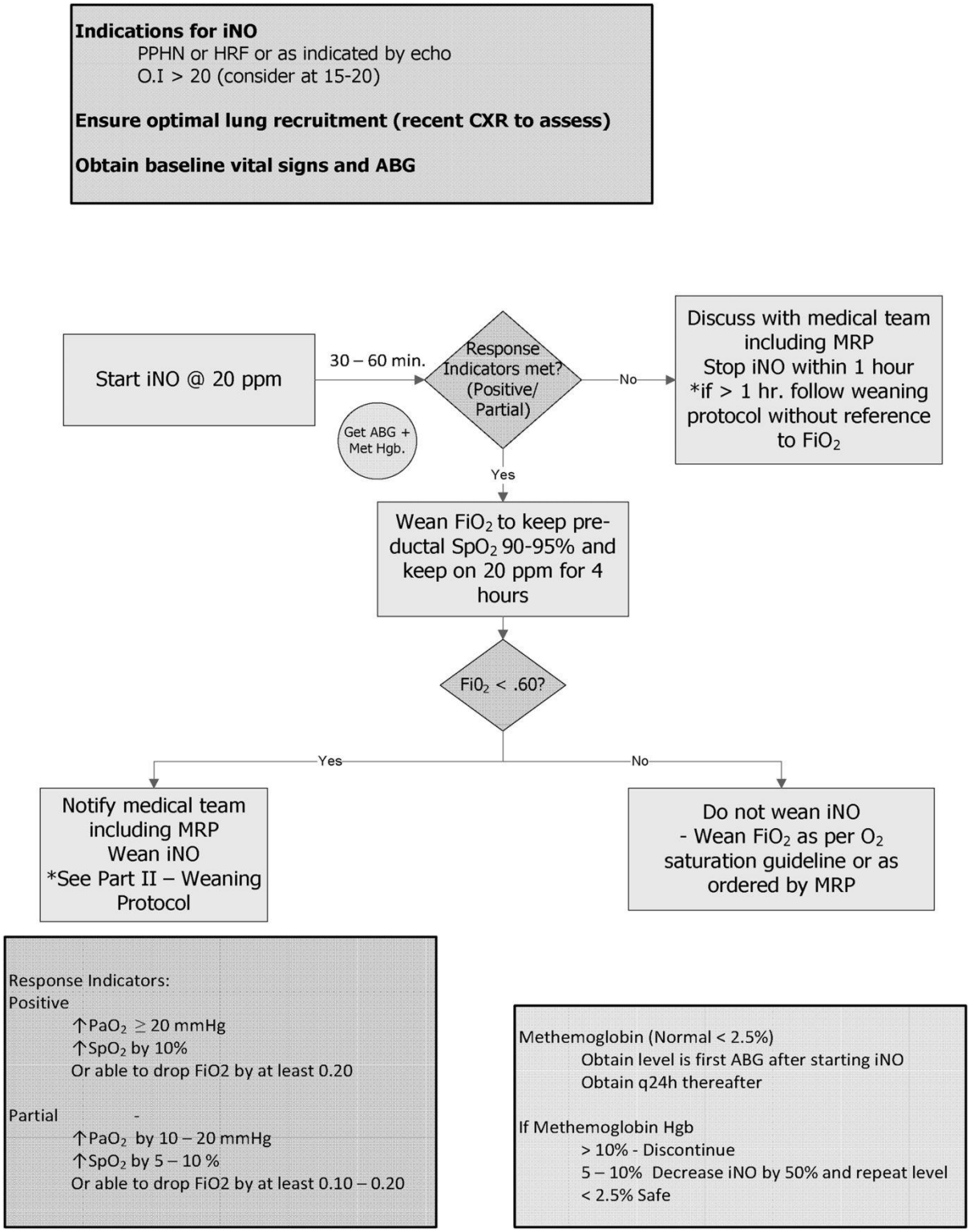
## 6 NATIONAL STANDARDS

- Standard 1 Clinical Governance
- Standard 2 Partnering with Consumers
- Standard 4 Medication Safety
- Standard 5 Comprehensive Care
- Standard 6 Communicating for Safety
- Standard 8 Recognising and Responding to Acute Deterioration

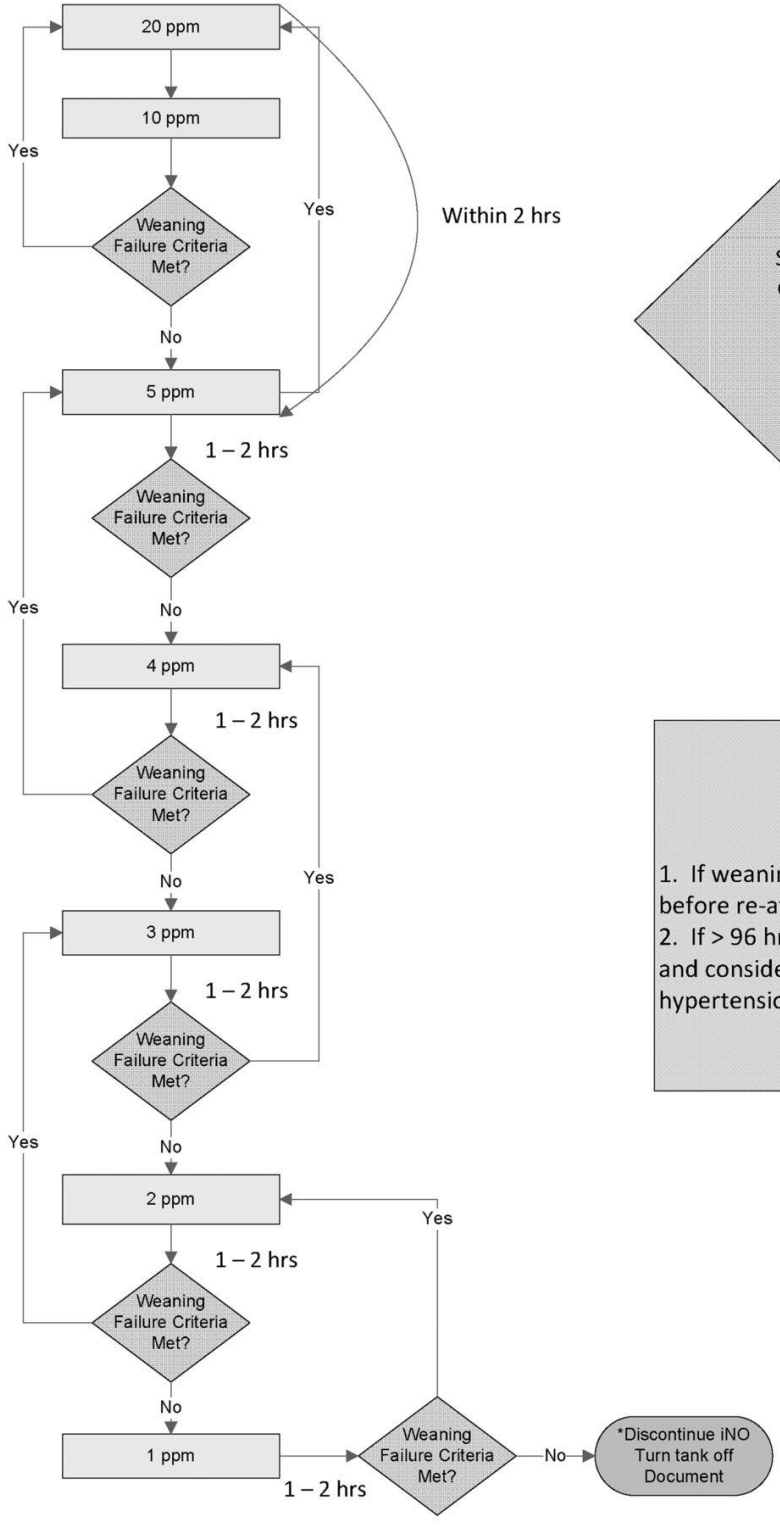
## 7 REVISION AND APPROVAL HISTORY

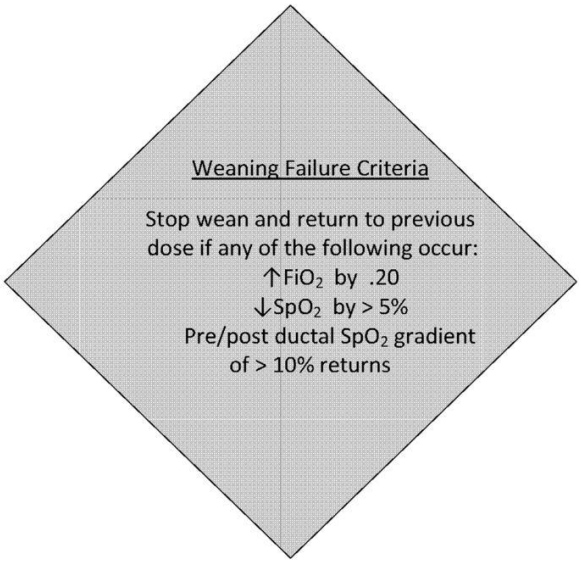
| Date | Revision No. | Author and Approval |
|---|---|---|
| 18/9/2014 | 1 | J Smyth (Neonatologist) Approved by Newborn Care Management Committee and RHW Quality & Patient safety |
| 28/8/2018 | 2 | J Smyth (Neonatologist) Approved by NCC LOPs Committee |
| 25/02/2025<br>11.9.2025 | 3 | J Smyth (Neonatologist)<br>Endorsed by NCC CBR Committee |
| 15.09.25 | 3 | RHW BRGC |

## Appendix 1: Flowchart for Initiation of iNO[14]



## Appendix 2: Flowchart for Weaning iNO[14]




**Weaning Considerations**

1. If weaning failure criteria are met wait 4 hrs before re-attempting wean
2. If > 96 hrs on iNO repeat echocardiography and consider consulting pulmonary hypertension service

*Consider increasing $FiO_2$ by 0.1-0.2 10 min prior to discontinuation