Local Guideline

Inhaled Nitric Oxide Therapy in Neonates

Sites where Local Guideline and Procedure applies	Neonatal Intensive Care Unit (NICU) JHCH
This Local Guideline and Procedure applies to:	
1. Adults	No
2. Children up to 16 years	No
3. Neonates – less than 29 days	Yes
Target audience	All clinicians caring for infants in NICU JHCH
Description	Provides guidance for the management of infants requiring inhaled nitric oxide therapy

Go to Guideline

Keywords	NICU, JHCH, neonate, newborn, neonatal, nitric, nitric oxide, inhaled, iNO, PPHN, vasodilation, pulmonary hypertension
Document registration number	JHCH_NICU_
Replaces existing document?	Yes
Registration number and dates of superseded documents	Inhaled nitric oxide (iNO) therapy in NICU for Pulmonary Hypertension JHCH_NICU_12.08

Related Legislation, Australian Standard, NSW Ministry of Health Policy Directive or Guideline, National Safety and Quality Health Service Standard (NSQHSS) and/or other, HNE Health Document, Professional Guideline, Code of Practice or Ethics:

- NSW Health Policy Directive PD2013_043 Medication Handling in NSW Public Health Facilities
- NSW Health Policy Directive PD2017_013 Infection Prevention and Control Policy
- NSW Health Policy Directive PD2017_032 Clinical Procedure Safety
- HNELHD Policy Compliance Procedure PD2019_020:PCP 4 Patient Identification: Medication Prescribing and Administration

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Note: Over time links in this document may cease working. Where this occurs please source the document in the PPG Directory at: http://ppg.hne.health.nsw.gov.au/

PURPOSE AND RISKS

This local guideline has been developed to provide guidance to clinical staff in Neonatal Intensive Care Unit at John Hunter Children's Hospital in the management of infants requiring inhaled nitric oxide therapy. It ensures that the risks of harm to infants, staff and families during set-up and administration are identified and managed.

The risks are:

- *Incorrect set up of nitric oxide therapy circuit causing failure of delivery*
- *Delayed identification of pulmonary hypertension*
- *Exposure to nitrogen dioxide*

These risks are minimised by:

- *Follow pre-procedure set up and safety checks as outlined in this guideline*
- *Early clinical assessment including performance of echocardiogram*
- *Purging of the circuit as required and T-piece device prior to use*

Any unplanned event resulting in, or with the potential for injury, damage or other loss to infants/staff/family as a result of this procedure must be reported through the Incident Management System and managed in accordance with the NSW Health Policy Directive PD2020_020: Incident Management Policy. This would include unintended injury that results in disability, death or prolonged hospital stay.

*It is mandatory for staff to follow relevant: "Five moments of hand hygiene", infection control, moving safely/safe manual handling, documentation practices and to use HAIDET for patient/carer communication: **H**and hygiene **A**cknowledge, **I**ntroduce, **D**uration, **E**xplanation, **T**hank you or closing comment.*

Risk Category: *Clinical Care & Patient Safety*

CLINICAL PROCEDURE SAFETY LEVEL

Every clinician involved in the procedure is responsible for ensuring the processes for clinical procedure safety are followed. The following level applies to this procedure (click on the link for more information):

Level 1 procedure

CONTENT

INHALED NITRIC OXIDE (iNO) THERAPY SUMMARY

- It is vital to optimise patient's respiratory and cardiovascular condition before starting inhaled nitric oxide
- Inhaled nitric oxide can be provided with any form of respiratory support (mechanical ventilation, CPAP, HFNC, nasal cannula)
- In term or near-term infants with significant hypoxic respiratory failure defined as PaO_2 < 100 mmHg on $FiO_2 \geq 80\%$ and/or Oxygenation Index (OI) between 15 and 25, start inhaled nitric oxide at 20 ppm
- Document respiratory, blood gas and cardiovascular parameters at commencement and after 15 to 30 minutes of inhaled nitric oxide (see Table 2)
- Continue inhaled nitric oxide if responder or partial responder; stop if non-responder
- Initiate weaning when FiO_2 < 40% for 6-12 hours. Wean inhaled nitric oxide by 5 ppm every 2 hours until down to 5 ppm, leave on 5 ppm for 2 hours and then wean by 1 ppm every 2 hours
- In preterm infants with evidence of lung hypoplasia and pulmonary hypertension due to prolonged PPROM, start inhaled nitric oxide 10-20 ppm early and monitor response
- In preterm infants with hypoxic respiratory failure due to other reasons, it is not recommended to start inhaled nitric oxide without documenting significant pulmonary hypertension on echocardiogram

GUIDELINE

While not requiring mandatory compliance, staff must have sound reasons for not implementing standards or practices set out within guidelines issued by HNE Health, or for measuring consistent variance in practice.

Introduction

Pulmonary hypertension (PH) can be caused by a broad range of pulmonary and non-pulmonary diseases. The main physiological triggers for PH are (alveolar) hypoxia and acidosis, but PH can also be triggered by other factors such as endotoxins and inflammatory signals. Hypoxic pulmonary vasoconstriction is a physiological response of the body to improve systemic hypoxia, but this process can fail during severe and/or prolonged hypoxia and acidosis. Developmental changes to the pulmonary parenchyma and vasculature (e.g. extreme prematurity, lung hypoplasia, diaphragmatic hernia, chronic lung disease) can also alter this physiological response. With PH, the right ventricle has to work against a high pulmonary vascular resistance (PVR) to have blood flow through the pulmonary circulation. Blood will try to flow through the path of least resistance, in the newborn represented by the fetal shunts (foramen ovale, ductus arteriosus). Those shunts will increase the amount of blood flowing right-to-left (R to L), further diminishing blood flow through the lungs and thus contribute to the persistent hypoxia. The ongoing hypoxia and acidosis, together with closure of the fetal shunts, will eventually lead to right ventricular failure.

PH is a dynamic process in newborns. Its clinical severity will depend on the condition at birth, the extent of the developmental changes, the onset and degree of cardiac dysfunction and how shunts can offer pressure offload for the right ventricle.

Treatment of PH includes a range of measures to address the above mentioned pathophysiology, including the use of inhaled nitric oxide.

Use of Inhaled Nitric Oxide for Pulmonary Hypertension Top

Nitric oxide is an endogenous mediator of smooth muscle relaxation. Nitric oxide is rapidly inactivated once it combines with haemoglobin in the blood stream. Due to this rapid inactivation, inhaled nitric oxide can be administered exogenously as a selective pulmonary vasodilator. When nitric oxide reaches the capillary bed of the lungs, it is inactivated with minimal systemic haemodynamic effects.

Inhaled nitric oxide is approved for treatment for pulmonary hypertension and to support right ventricular function in newborn infants. There are well demonstrated benefits in term infants with hypoxic respiratory failure when ventilation and resuscitation measures alone were not enough. The use of inhaled nitric oxide for pulmonary hypertension can improve oxygenation and reduce the need for ECMO, but does not alter mortality and long-term neurodevelopmental outcomes. Due to the mixed and dynamic nature of PH, up to 40% of infants with hypoxaemic respiratory failure can have either no response or only a transient response to inhaled nitric oxide.

The routine use of inhaled nitric oxide in preterm infants with hypoxaemic respiratory failure and infants with congenital diaphragmatic hernia (CDH) has not shown a reduction in mortality or morbidity.

Treatment of Pulmonary Hypertension Top

The primary treatment for PH is, if possible, to treat the underlying cause. For example, appropriate surfactant therapy for RDS, drainage of moderate to large pneumothoraces, antibiotics for sepsis etc. It is highly desirable to establish arterial access and obtain an arterial blood gas (ABG) before starting treatment for PH. This should, preferably, be post-ductal (umbilical, foot or left hand), but any arterial line is better than none.

The main pillars of treatment for PH are:

- Optimising Lung Volumes
- Lowering Pulmonary Arterial Pressure (PAP)
- Supporting Cardiovascular Function

Optimising Lung Volumes

Top

Before starting inhaled nitric oxide, mean airway pressure (MAP) should be adjusted to provide adequate lung inflation which must be confirmed by chest X-ray. In many, but not all, situations, this might mean using high-frequency oscillatory ventilation (HFOV) particularly if the patient also has high $PaCO_2$ and parenchymal lung disease. MAP can also be optimised on conventional ventilation by appropriate adjustments to PEEP and inspiratory time. Lung recruitment in lung parenchymal disease and substantial PH can be difficult, as oxygenation parameters used to guide recruitment are complicated by intra and extra-pulmonary shunting.

Targets for PaO_2 and SpO_2

Animal studies have shown that PVR rises steeply if PaO_2 falls below 50 mmHg, but only decreases gradually if PaO_2 is above 60 mmHg. The lowest PVR could be maintained with pre-ductal peripheral SpO_2 in the 90% to 97% range; with pre-ductal PaO_2 between 60 and 80 mmHg. Thus, normal saturation targets should be maintained for newborns with PH (i.e. SpO_2 between 90 and 94%).

Targets for $PaCO_2$ and pH

The physiological response to increased $PaCO_2$ is pulmonary vasodilatation. However, the accompanying acidosis is a stronger trigger for pulmonary vasoconstriction. Hence, the focus for pulmonary hypertension treatment should be on pH, not $PaCO_2$. If possible, target a pH between 7.30 to 7.40 and not less than 7.25. Permissive hypercapnia is allowed; to minimise ventilator associated lung damage.

Targets for spontaneous breathing

In most cases, some spontaneous breathing motion is beneficial for the cardiorespiratory balance. However, especially in distressed and agitated patients, asynchronous spontaneous breathing can also be a significant contributor to a high PVR. Optimise sedation to ensure the patient is as comfortable as possible. Routine paralysis is not recommended, but sometimes muscle relaxants are needed to optimise ventilation and sedation. Be aware of side effects of the medications used. Sedation with narcotics and/or benzodiazepines can reduce systemic vascular resistance and thus lower systemic blood pressure. Paralysis can alter venous capacitance and venous return.

Lowering Pulmonary Arterial Pressure

Top

There are various pharmacological preparations that can lower PAP. This guideline will primarily focus on the use of inhaled nitric oxide to help lower pulmonary arterial pressures.

Starting Inhaled Nitric Oxide

Top

The indication to start inhaled nitric oxide is:

- Any infant ≥ 34 week gestation with severe respiratory failure
    - Defined as PaO_2 < 100 mmHg on FiO_2 ≥ 80% and/or an Oxygenation Index (OI) between 15 and 25

Start at 20 ppm in a term infant. Consider starting inhaled nitric oxide at 10 ppm in preterm infants (see below).

Aim to not make any ventilatory/FiO_2 changes or disconnect infant from ventilator for at least 30 minutes after inhaled nitric oxide has been started (unless a positive response is already established) to be able to confirm patient's response to treatment. In cases of no response, it may be appropriate to continue a 'trial' of therapy for a maximum of one hour.

Assessing Response

Top

The inhaled nitric oxide responsiveness must be assessed within 30 minutes of initiation. It is preferable to obtain an ABG and establish response using PaO_2 but in cases where arterial access is not available, post-ductal SpO_2 may be used.

Positive response:

- Rise in post-ductal PaO_2 of ≥ 20 mmHg or ≥ SpO_2 by 10% or able to drop FiO_2 by at least 20%
- Significant reduction in R to L shunt and improved left ventricular filling on echocardiogram

Partial response:

- Rise in post-ductal PaO_2 by 10-12 mmHg or SpO_2 between 5 and 10% or able to drop FiO_2 by 10% to 20%
- Reduction in R to L shunt on echocardiogram

Negative response:

- No change or minimal rise in post-ductal PaO_2 (≤ 10 mmHg) or SpO2 (< 5%) or only able to drop FiO_2 by < 10%
- No reduction in R to L shunt on echocardiogram

If there is a positive or partial response, continue inhaled nitric oxide and subsequently wean according to the schedule below. If there is no significant improvement in oxygenation after 30 minutes of treatment with 20 ppm of inhaled nitric oxide (negative response) then inhaled nitric oxide therapy should be discontinued and details of lack of response documented. There is no need to wean inhaled nitric oxide in this situation. It is important that during the trial period of inhaled nitric oxide, no additional ventilator changes are made as it can make interpretation of 'response to inhaled nitric oxide therapy' difficult. Be aware that, if the inhaled nitric oxide trial was longer than 30 minutes, the patient might experience deterioration in oxygenation in spite of a negative response. This deterioration is usually transient (from 30 minutes to 4 hours) and is secondary to suppression of endogenous nitric oxide production. This should not be considered as an indication for restarting inhaled nitric oxide therapy if there was a confirmed negative response.

Weaning Inhaled Nitric Oxide

Top

After a sustained positive response is established and oxygenation improved, gradually but frequently wean FiO_2 to minimum required concentration (generally < 40%). Once FiO_2 has been weaned to a clinically appropriate concentration, it is desirable to maintain inhaled nitric oxide for a period of 6 to 12 hours. This is to ensure a period of stability is provided, following which the weaning process can start based on the infant's FiO_2 requirement.

- Wean inhaled nitric oxide by 5 ppm every 2 hours until down to 5 ppm
- Leave on 5 ppm for 2 hours
- Then wean by 1 ppm every 2 hours to zero

Discontinue weaning if, at any point, one or more of the following occur:

- FiO_2 rises by > 20%
- Pre-ductal saturation returns to > 10% higher than post-ductal

If weaning had to be discontinued, then increase inhaled nitric oxide *by one step at a time until infant returns to pre-deterioration status and then leave for at least 12 hours before recommencing weaning. This time, the weaning strategy should be slower than the earlier attempt and should be decided on an individual basis by the attending team*

* Note; some infants may still develop a transient hypoxaemia once inhaled nitric oxide therapy is discontinued. This is due to suppression of endogenous nitric oxide by exogenous therapy. The hypoxaemia is usually moderate (needing increase in FiO_2 by 20%) and short-lasting (up to an hour). This should not be a reason to restart inhaled nitric oxide therapy but should be treated by increasing FiO_2.

Monitoring During Treatment

Top

Nitrogen dioxide is continuously monitored and concentration displayed on the delivery system. Aim should be to ensure concentrations below 2 ppm.

Significant methaemoglobinaemia has never been reported with the use of inhaled nitric oxide at ≤ 20 ppm. If Met Hb level is ≥ 3%, then medical team should be notified and weaning of inhaled nitric oxide should be considered. Subsequent levels should be checked every 24 hours. A Met Hb level ≥ 5% should prompt discontinuation of inhaled nitric oxide.

In any infant with hypoxaemic respiratory failure, the possibility of structural heart defect should be strongly considered if one or more of the following occurs in addition to inhaled nitric oxide non-responsiveness:

- Lack of symptoms of respiratory distress
- Lack of lability, haemodynamic stability in spite of extreme hypoxaemia of prolonged duration
- Pre-ductal SpO_2 lower than post-ductal
- Presence of a heart murmur or abnormal cardiac silhouette on CXR

If inhaled nitric oxide therapy is needed for longer than 7 days, an alternative diagnosis should be considered (e.g. capillary alveolar dysplasia, surfactant deficiency).

Supporting Cardiovascular Function

Top

The main haemodynamic feature of PH is increased PAP. However, this physiological state is not different from the fetal situation. With persistent hypoxia, the increased PAP and thus afterload for the RV will eventually lead to RV dysfunction. Reduced pulmonary blood flow will lead to reduced preload for the left LV and lead to systemic hypoperfusion and shock (see Figure 1).

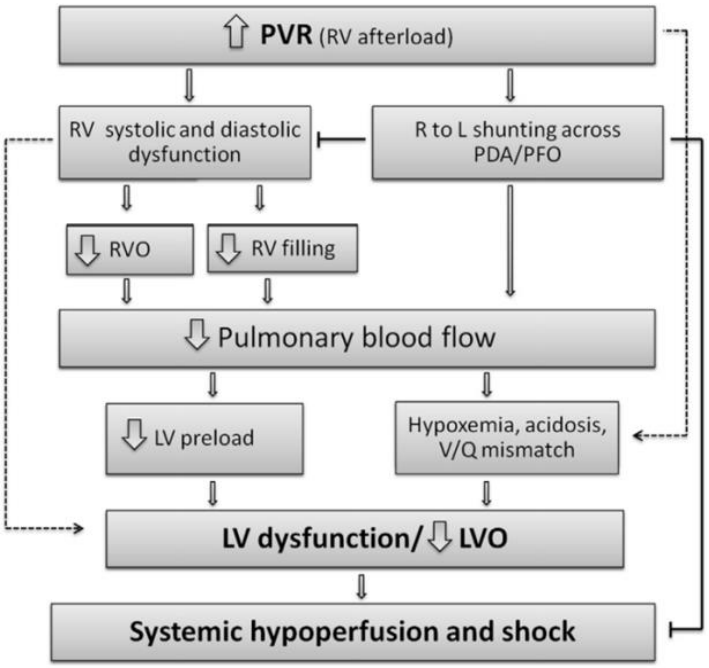


Figure 1: *Circulatory pathophysiology in neonates with pulmonary hypertension (Image from Jain & McNamara 2015)*

PH is a dynamic process, and the degree of PH does not correlate well with the degree of right ventricular dysfunction or clinical outcomes

Repeat assessments of the systemic arterial blood pressure, estimates of pulmonary arterial pressure, shunt and shunt direction and right and left ventricular function are needed to target cardiovascular treatments

Cardiovascular support during PH and inhaled nitric oxide treatment should be guided by the systemic arterial blood pressure (SAP), estimates of pulmonary arterial pressure and the PAP:SAP ratio (see Table 1).
Significant systemic hypotension should be corrected before inhaled nitric oxide is started.
Medications that increase the PAP:SAP ratio (e.g. dopamine) should be avoided.
There is no evidence that increasing the systemic blood pressure to 'supranormal' levels improves outcomes. Pursuing this approach often leads to catecholamine overload (> 2 cardiovascular medications running simultaneously) which can lead to tachycardia and increased PAP: SAP ratio and should be avoided.

Cardiovascular Support Agent	Expected Actions	Comments	Physiological Target
Noradrenaline (norepinephrine)	Pressor, improves contractility	Increases afterload Decreases PAP:SAP ratio	Low contractility, systemic hypotension, PH
Dobutamine	Pressor, improves contractility	Tachycardia May decrease PAP:SAP ratio	Low contractility, low blood flow, PH
Adrenaline (epinephrine)	Pressor, improves contractility	Tachycardia Beta-adrenergic stimulation with hyperglycaemia and increased lactate May decrease PAP:SAP ratio	Low contractility, low blood flow, systemic hypotension
Dopamine	Pressor	Increases afterload Increases PAP:SAP ratio	Systemic hypotension, normal blood flow
Milrinone	Phosphodiesterase inhibitor, improves contractility	Reduces afterload Tachycardia, systemic hypotension May exacerbate right-to-left shunting	Low contractility, low blood flow, high afterload, PH with right ventricular failure
Vasopressin (argipressin)	Neurohormone, increases peripheral vascular resistance	May decrease PAP:SAP ratio	Systemic hypotension, PH
Alprostadil	Prostaglandin E_1, opening of the ductus arteriosus (DA)	May cause systemic hypotension	High PAP with right ventricular failure due to closing of the DA
Sildenafil	Phosphodiesterase type 5 inhibitor, reduces PAP	Oral, slow onset of action May cause systemic hypotension	High PAP

Hydrocortisone	Corticosteroid	Increases SAP	Inotrope-resistant, systemic hypotension
Volume	Improves cardiac input		Low preload, collapsed systemic veins

Table 1: *Cardiovascular support agents, mechanism of action and physiological targets*

Specific Clinical Situations and Other Considerations for Use Top

Preterm infants with hypoxic respiratory failure

Trials of prophylactic or early (within first 2 postnatal days) rescue use of inhaled nitric oxide to prevent chronic lung disease (CLD), decrease mortality & improve long-term neurodevelopmental outcomes have yielded conflicting results, with most showing no improvement in morbidity or mortality. It must be remembered that these trials did not evaluate infants for presence of PPHN prior to inclusion. It is possible that many patients included in these trials had exclusively parenchymal lung disease which, for obvious reasons, would fail to respond to inhaled nitric oxide. One trial in preterm infants, only included patients with a higher likelihood of PH (infants with oligohydramnios and prolonged premature rupture of membranes) and demonstrated improved survival and CLD rates. When used, inhaled nitric oxide exposure must be kept to lowest duration possible as there are unresolved concerns of possible adverse long-term effects associated with use of inhaled nitric oxide in preterm infants.

Inhaled nitric oxide should not routinely be used in preterm infants with hypoxic respiratory failure.

In preterm infants with evidence of lung hypoplasia and pulmonary hypertension due to prolonged PPROM, start inhaled nitric oxide 10-20 ppm early and monitor response. Obtain an echocardiogram before treatment or as soon as possible after initiation.

In preterm infants with hypoxic respiratory failure due to other reasons, it is not recommended to start inhaled nitric oxide without documenting significant pulmonary hypertension on echocardiogram.

In preterm infants with severe CLD and associated significant PH documented on echocardiogram, inhaled nitric oxide may be appropriate when clear clinical goals are defined prior to initiation of inhaled nitric oxide therapy (for example, acute stabilisation while infant is being started on intravenous steroids; therapy for a predefined period in an attempt to reverse pulmonary hypertension).

Infants with congenital diaphragmatic hernia (CDH)

Inhaled nitric oxide treatment in infants with CDH did not improve morbidity or mortality nor reduce the need for ECMO. However, inhaled nitric oxide therapy is commonly started in most infants with CDH and PH. CDH affects not only the pulmonary vascular system, but is often associated with reduced left ventricular size and altered function. Pulmonary vasodilatation in the setting of increased pulmonary venous pressure due to poor left ventricular function will lead to pulmonary congestion and will worsen pulmonary function.

Inhaled nitric oxide should be used cautiously in infants with CDH and it is recommend to start only after echocardiogram has documented a reasonable LV size, acceptable LV function and the presence of significant pulmonary hypertension or right ventricular dysfunction

Inhaled Nitric Oxide Administration Top

Inhaled nitric oxide is a schedule 4 drug. When not in use it must be stored in a locked area that cannot be accessed by the public.

Prescribing inhaled nitric oxide (example in Appendix 5)

- Inhaled nitric oxide must be prescribed on a Paediatric Medication chart in the as required "PRN" medications section
- The prescription must include;
  - Patient label
  - Patient weight
  - Date of prescription
  - Medicine (generic name in full – i.e. nitric oxide)
  - Route of administration (inhaled)
  - Dosing range
  - Maximum Dose
  - Indication
  - Prescriber print name and signature
- The prescription must be co-signed by two Registered Nurses;
  - Upon commencement and
  - With any inhaled nitric oxide dose change
- Always match INOblender dose to treatment dose
- Inhaled nitric oxide should be weaned gradually once the desired effect has been achieved (see weaning)

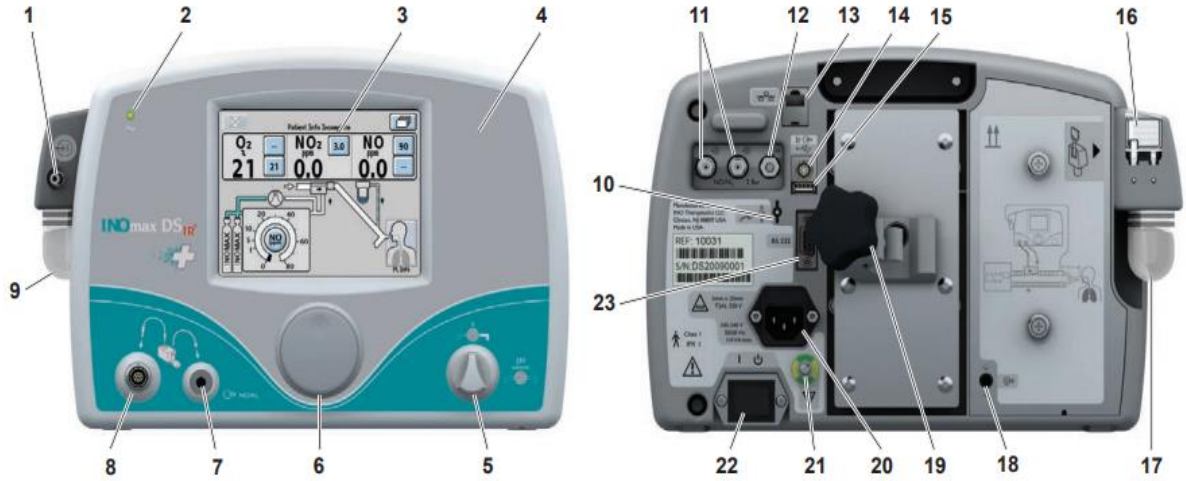
When inhaled nitric oxide ceased and not re-used within 10 minutes, remove from the respiratory circuit and depressurise

INOmax DS_{IR} Plus Set up

Top

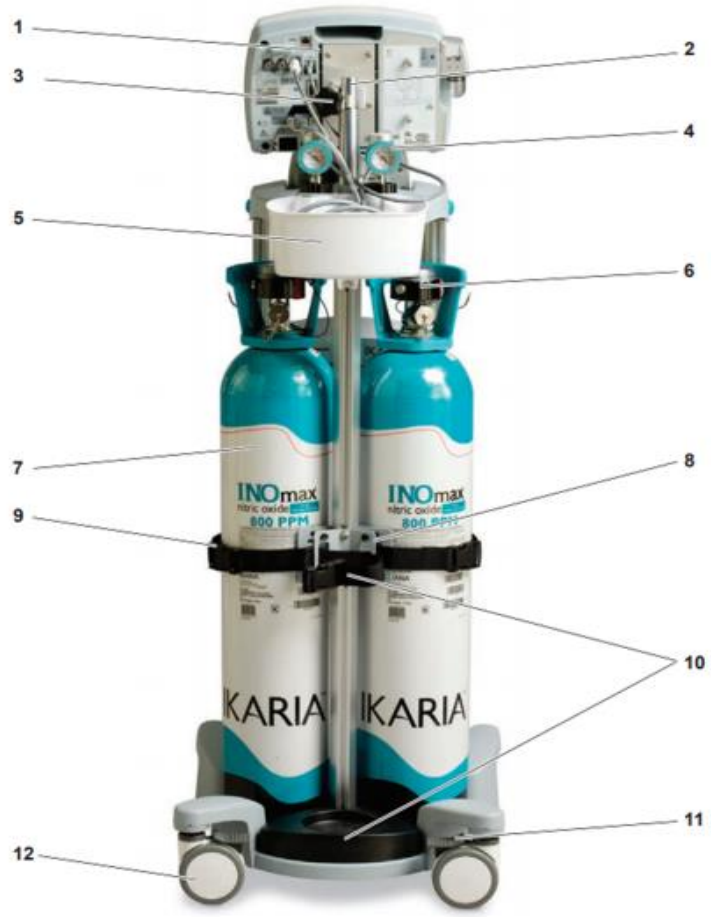
In JHCH NICU the INOmax DS_{IR} Plus system is used for inhaled nitric oxide delivery. This system delivers a constant set concentration of nitric oxide gas via the inspiratory limb of the patient breathing circuit and deliver to the patient through the inspired breath whilst tracking the ventilator waveform via the injector module. The system also includes an INOblender. The INOblender is used independently of the INOmax DS_{IR} Plus. It allows nitric oxide delivery via a T-piece device or self-inflating bag.

The INOmax DS_{IR} Plus system set up is displayed in Figures 2 & 3.



1. Sample Line Inlet
2. Main Power Indicator
3. Display Screen
4. Alarm Speaker (under front label)
5. Integrated Pneumatic Backup Switch
6. Control Wheel
7. Injector Module Tubing Outlet
8. Injector Module Cable Inlet
9. Water Bottle
10. Purge Port
11. INOMAX Gas Inlets
12. INOblender Gas Outlet
13. Ethernet Port
14. Infrared Connector
15. USB Port
16. Water Separator Cartridge
17. Water Bottle
18. Sample Gas Outlet Port
19. Clamp Assembly
20. Electrical Cord Inlet
21. Equipotential Terminal
22. ON/Standby Switch
23. RS 232 Port

Figure 2: *INOmax DS_{IR} Plus front and rear view (Image from Ikaria operational manual)*



1. INOmax DS_{IR} Plus
2. INOmax DS_{IR} Plus Mounting Post
3. Clamp Assembly
4. INOMAX Regulator (2)
5. Small Part Bin
6. INOmeter
7. INOMAX Cylinder
8. Cylinder Holding Bracket
9. Cylinder Mounting Strap
10. Oxygen Cylinder Bracket
11. Caster Lock Lever
12. Caster (4)

Figure 3: *INOmax DS_{IR} Plus and cart (Image from Ikaria operational manual)*

Pre-use Connection Equipment and Set up (see Figure 4) Top

1. Sample T-piece (with blue cap; for pre use testing set up only)
2. Blue corrugated tubing
3. Injector module (ensure direction of arrow always directed to patient)
4. Clear adaptor
5. T-piece device adaptor
6. Oxygen tubing
7. Sample line
8. Clear sample tubing
9. Injector module electrical cable (ensure red dots are aligned)
10. Plastic elbow (inspiratory limb ventilatory attachment; may be grey or green in colour)
11. Sample T-piece (to attach to inspiratory limb of the respiratory circuit at patient end)

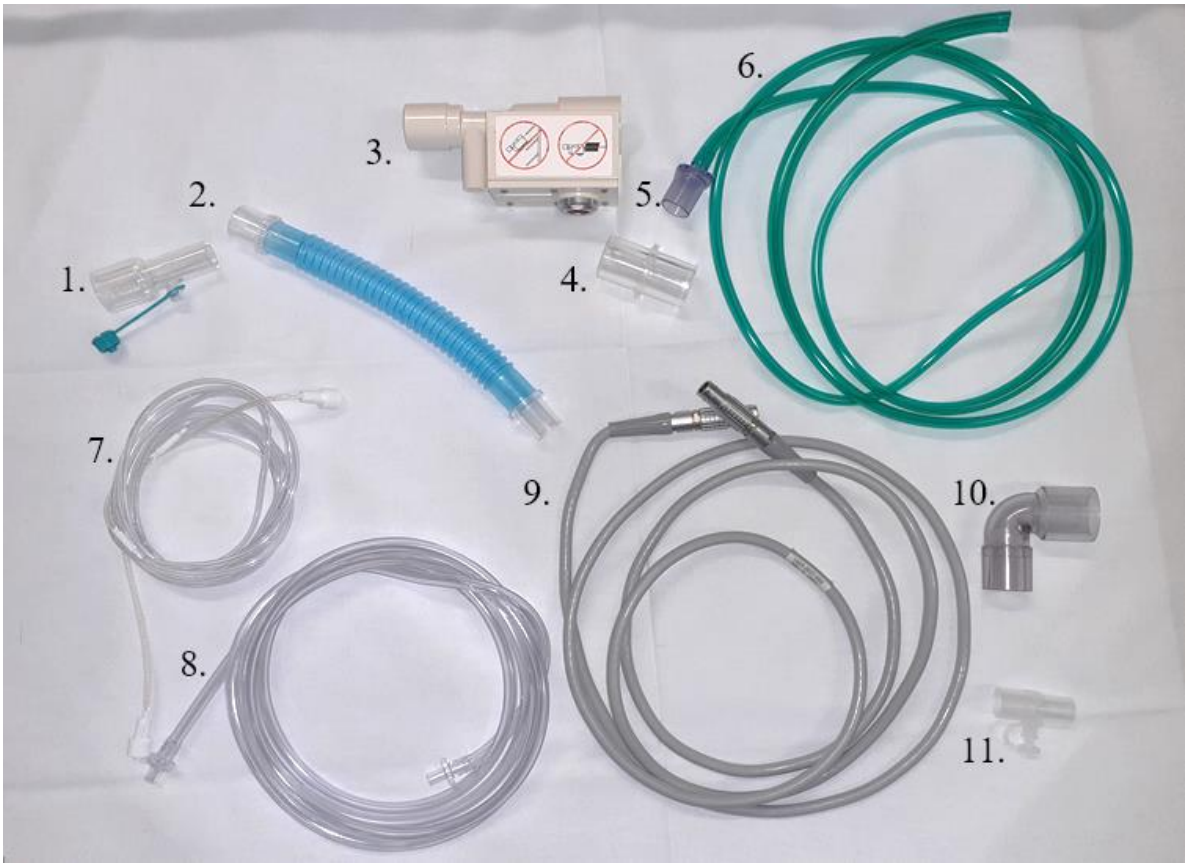


Figure 4: *Equipment required for pre use set up (Image from NICU JHCH)*

Complete Connection Set up of Injector Module for Pre Use Testing (see Figure 3)

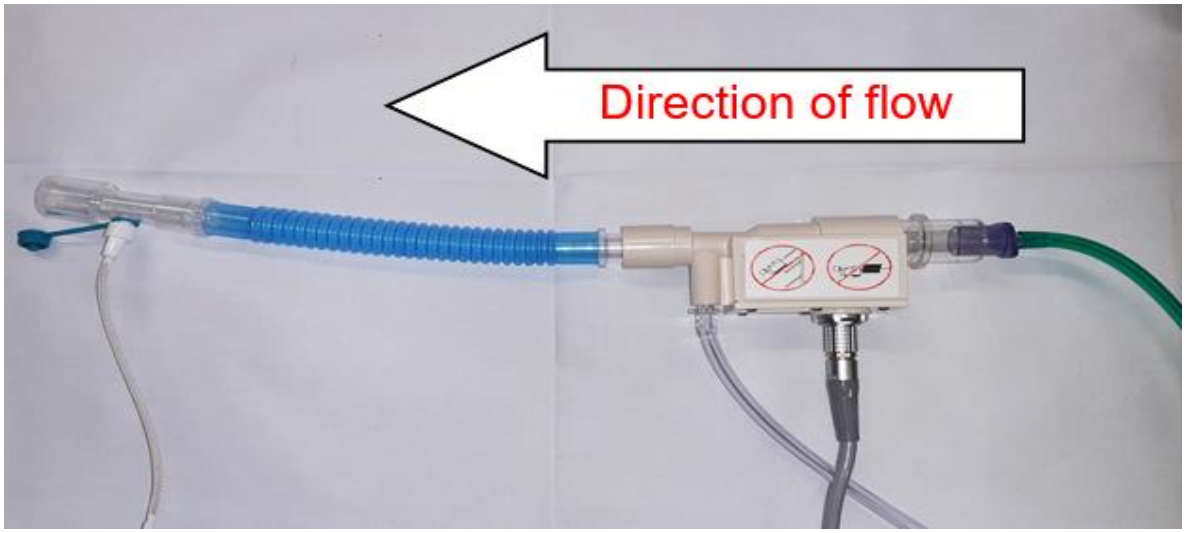


Figure 3: *Injector module set up for testing (Image from NICU JHCH)*

Start-up Connection Set up Procedure

Top

- Plug in power cord and verify green AC power light is on
- Attach the dual oxygen outlet to the wall oxygen (see Figure 4)
- Attach the free end of the green oxygen tubing to the dual oxygen flowmeter outlet
- Check expiry date and dose of gas on cylinder
- Remove INOMAX regulator and pressure gauge from back of cart and verify that the white Kel-F tip is in place and not damaged (see Figure 5) (The regulator may already be inserted into the INOMAX treatment cylinder, if so there is no need to remove it)
- Connect high pressure regulator to INOMAX cylinder (where applicable) (see Figure 6)

Figure 4: *Dual oxygen set up*

Figure 5: *Kel-F tip (white tip)*

Figure 6: *High pressure regulator*

(All images from NICU JHCH)

- Ensure INOblender dose setting dial is off
- Turn the INOmax DS_{IR} Plus delivery system on (located at the back of the machine)
- Low calibration will automatically begin and complete when the system is turned on
- Connect regulator hose to the inlet on the back of the device
- Note; each gas cylinder has an INOMAX regulator hose. Only the hose attached to the cylinder in use needs to be inserted into the back of the INOmax DS_{IR} Plus
- Check grey INOblender hose is in situ
- Check black infrared cable is in situ
- Check oxygen supply hose is connected to the INOblender
- Ensure the water trap and water separation cartridge are in place
- Ensure the sample line is connected to the port above the water trap bottle
- Ensure the injector module cable and electrical cable are in place
- Ensure the backup switch is off (dial set at zero when in the off position)

INOmax DS_{IR} Plus Pre-use Tests

Top

Step 1

High-pressure leak test

- Make sure INOMAX cylinder icon is present
- Open/close INOMAX cylinder valve (verify cylinder is >500 psi)
- Wait 30 seconds and ensure there is no pressure drop
- If no pressure decrease observed, the high pressure leak test is complete

Step 2

Manual purge and alarm verification

- Most commonly, an automated purge is performed by using the touch screen wizard. If a manual purge is required, then the information below outlines how to do this.
- Press cancel to exit pre-use wizard
- Ensure INOMAX cylinder valve is closed
- Connect green oxygen tubing to wall oxygen
- Set O_2 flowmeter to 10 L/min
- Set the INOMAX dose to 40 ppm
- 'Cylinder Valve Closed' alarm will occur and cylinder pressure should drop to zero
- Purge is complete when 'Low Cylinder Pressure' alarm activates
- Open cylinder valve
- Turn INOMAX dose to zero

Note: The 'Set Dose is Zero, Close cylinder Valve' indicator will appear; at this point do not close the cylinder valve. Please ignore this indicator at all times during the pre-use procedure

Automated purge:

- Ensure injector module is not attached to a patient circuit
- Press next button to commence purge
- Alarm will sound
- Automated purge complete
- Open the cylinder valve

Step 3

Backup delivery test

- Ensure pre-use setup connectors and tubing are set up correctly (If uncertain press 'show diagram' button for an immediate image and ensure the injector module arrow is in the direction of the gas flow)
- Set oxygen flow to 10 L/min
- Turn integrated backup on (250 mL/min)
- Verify backup alarm occurs
- Allow values to stabilise;
    - Nitrogen dioxide ≤1.0 ppm
    - Nitric oxide 14-26 ppm
- Backup delivery test complete; turn backup off

Step 4

Performance test

- Verify oxygen flow set at 10 L/min
- Press next button to automatically set dose to 40 ppm
- Verify monitor values;
    - Nitrogen dioxide <1.5 ppm
    - Nitric oxide 35-45 ppm
    - FiO_2 92-98%
- Performance test complete

Step 5

INOblender test

- Turn oxygen flowmeter off and remove green oxygen tubing from flowmeter and attach to front of INOblender
- Remove injector module from pre-use setup and re-connect connectors (see Figure 7)
- Set INOblender to 40 ppm of nitric oxide and oxygen flow to 10 L/min
- Allow values to stabilise with nitric oxide 32-48 ppm
- Turn nitric oxide dose and flow to off
- INOblender test is complete
- Ready to apply to respiratory circuit

Figure 7: *INOblender test set up (Image from NICU JHCH)*

If the nitric oxide is not going to be used within 10 minutes then:

- Close cylinder valve until you get the '- - -' symbol (Note; the disappearance of the green head of the cylinder on the screen which confirms that the cylinder is off)
- Depressurise the regulator hose via the labelled purge port at the back of the machine

- Return the injector module to the setup as for pre-use procedure setup
- No need to depressurise if the INOmax DS_{IR} Plus is to be used immediately
- If the INOmax DS_{IR} Plus has been checked and not depressurised within 10 minutes repeat automated or manual purge procedure
- The INOMAX DS_{IR} Plus if not used, must have the pre-use procedure repeated 12 hourly

Prior to commencement:

- An echocardiogram is recommended prior to commencing inhaled nitric oxide to assess pulmonary pressures and haemodynamic status of the infant, assist in establishing the diagnosis, review left and right ventricular function and optimise circulatory support
- Before attachment to the infant, ensure correct setup procedure has occurred
- Determine when the last 'pre-use' procedure check was completed. It must be performed 24^{th} hourly or will need to go through pre use procedure check prior to commencement
- Sample T-piece should be approximately 15 cm from the ETT. If closer than this, both the inspiratory and expiratory gases will be sampled possibly resulting in an under-reading i.e. set dose of 20 ppm may read 16 ppm
- Only one regulator hose can be plugged in at any time as two can cause a leak of nitric oxide
- Ensure that ventilator trigger setting is accurate as the commencement of nitric oxide can affect trigger sensitivity
- The injector module must have the arrow pointing in the direction of the gas flow from the ventilator (or CPAP circuit) towards the patient.
- The injector module must be placed between the ventilator inspiratory gas outlet and the ventilator circuit

Alarms:

- Yellow is a low-priority alarm
- Red is a high-priority alarm
- If the low-pressure alarm warning is signaling you really have no gas remaining
- Always change when at 500 psi
- Alarm help key is available to direct you through steps to fix a problem
- Alarm history can store 2000 entries and all is deleted when INOmax DS_{IR} Plus rebooted
- Alarm limits default to 50 above and below what is being delivered and are automatically confirmed when initial dose set. Any other dose changes require the high and low alarms to be altered manually
- Expiratory date on cylinder is underneath bar code, machine will not deliver if expired (first day of the month is the expiry date not the last day)

Positive pressure ventilation with inhaled nitric oxide:

- Connect oxygen tubing with the T-piece adaptor, from INOblender outlet to the T-piece device
- Check inspiratory and expiratory pressure settings of the T-piece device (i.e. Neopuff™) are at appropriate settings prior to use
- Ensure flow is at 10 L/min on inhaled nitric oxide flowmeter and nitric dose set appropriately on the nitric oxide (ppm) dose dial
- Prior to use, purge nitrogen dioxide from the T-piece device circuit by running system for 10 seconds
- Ensure INOblender flow is off when not in use

Maintenance and Troubleshooting Top

Calibration

- High-range calibration is completed every 30 days and can be done whilst on the patient
- During calibration, monitoring values show zero and grey bars appear under numeric windows as the machine calibrates to air
- A low-range calibration is automatic and will occur at setup and then repeat automatically dependent on the use of the nitric oxide
- Cancelling the low-range calibration is possible; once cancelled, calibration will automatically occur again in 15 minutes
- Low calibration will occur automatically when in use. The system delivers the set parts per million (ppm) of nitric oxide; however, during calibration the values will read as zero

Back up delivery system

- The INOmax DS_{IR} Plus has a battery life of 6 hours
- The back-up switch is provided in case of INOmax DS_{IR} Plus circuit power board failure. The backup system will need to be activated to ensure a continued supply of nitric oxide to the infant until an alternate INOmax DS_{IR} Plus can be provided
- If the backup system is switched on whilst the INOmax DS_{IR} Plus is running, it will deliver 250 mL/min of nitric oxide in addition to the prescribed dose of nitric oxide. A high priority alarm will be present

Water filter

- Sample error may occur; the most common reason is an issue with the water filter which needs to be replaced. Be aware that the nitric oxide dose will read zero, however the set dose is still being delivered while the cartridge is out
- Emptying the water trap requires the use of PPE. Note; the nitric oxide dose will read zero, however the set dose is still being delivered while the water trap is disconnected. To empty the water trap, pull down on the trap and wipe out with clean cloth, return trap and discard cloth into waste bin whilst still wearing PPE. Wash hands after

Nursing Management of Infants Receiving Inhaled Nitric Oxide Top

- Infants receiving inhaled nitric oxide are extremely fragile and require intensive care support
- Infants requiring increasing inhaled nitric oxide are very sensitive to changes in inhaled nitric oxide delivery, refrain from disconnecting ventilation circuit
- The half-life of nitric oxide is 5 seconds; abrupt disconnections or interruptions to the circuit should be avoided as it may lead to increased pulmonary vascular resistance and worsening hypoxia
- Minimal handling must be considered; these infants are often haemodynamically unstable, they may require significant pacing through cares and cares intervals may be required up to 12^{th} hourly with consideration to pressure injury prevention strategies
- Adapt the environment for the infant; provide a noise and light-reduced setting as these infants are also highly sensitive to noxious stimuli
- Nitric oxide is an inhibitor of platelet function, therefore, caution is needed when an infant has thrombocytopenia or other bleeding irregularities
- Nitrogen dioxide may cause airway inflammation and damage to lung tissues and should not exceed 2 ppm

Monitoring considerations:

- All infants receiving inhaled nitric oxide must have pre and post-ductal saturation monitoring, and continuous heart rate and arterial blood pressure monitoring
- Arterial blood gas analysis is performed PRN and requires consultation, consideration to transcutaneous monitoring should be employed
- Methaemoglobin levels are dose dependent and should be maintained at < 3%; levels of 3-5% are rare at doses ≤ 20 ppm; however, if 5%, the Neonatologist must be informed
- FiO_2 is monitored from the INOmax DS_{IR} Plus (not the respiratory device)
- Oxygen index calculation should be calculated once per shift

Safety assessments at handover:

- Check prescribed inhaled nitric oxide dose against set inhaled nitric oxide dose
- Check set inhaled nitric oxide dose against dose being delivered on INOmax monitor
- Check monitored does of nitrogen dioxide (<3 ppm)
- Check position of injector module (i.e. direction of arrow equals direction of respiratory flow)
- Check position of sample T-piece (on inspiratory circuit)
- Check INOblender set up and assess with T-piece device (i.e. Neopuff) settings
- Check pressure gauge on regulator
- Check cylinder concentration (800 ppm) and expiry date on cylinder
- Review alarm settings

Documentation

Top

The managing medical team should document the respiratory, blood gas and cardiovascular parameters at commencement and after 15 to 30 minutes of inhaled nitric oxide therapy as outlined in Table 2.

	At Commencement	After 15–30 minutes of Inhaled Nitric Oxide
Time		
Mean Airway Pressure		
FiO_2		
SpO_2 (post-ductal)		
Arterial PaO_2 (*if available*)		
Oxygen Index ($MAP \times FiO_2 / PaO_2$)		
Systemic Blood Pressure		
Echo R-to-L shunt % (*if available*)		

Table 2: *Inhaled nitric oxide therapy response summary (Table from NICU JHCH)*

IMPLEMENTATION PLAN

The clinical guideline will be:

- Circulated to Head of Department and Managers in NICU
- Circulated to the clinicians via the Children Young People and Families Network and the Women's Health and Maternity Network (where applicable)
- Made available on the intranet (PPG) and HNEKids website
- Presented at facility/unit meetings and tabled for staff to action

MONITORING AND AUDITING PLAN

- The person or leadership team approving the clinical guideline is responsible for ensuring timely and effective review of the guideline.
- Evaluation will require a review of the most current evidence as well as consideration of the experience of Neonatal staff at JHCH in the implementation of the clinical guideline.
- Data derived from monitoring and evaluation should inform the review of the clinical guideline either as required or scheduled.
- Implementation, education support and monitoring compliance be completed by local Clinical Educators and Unit Managers.
- Amendments to the guideline will be ratified by the Clinical Director and Manager of Newborn Services prior to final sign off by the JHCH.

CONSULTATION WITH KEY STAKEHOLDERS

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APPENDICES

1. Glossary & Abbreviations
2. Connections & Set up for inhaled nitric oxide via ventilator
3. Connections & Set up for inhaled nitric oxide via CPAP
4. Changing the Nitric Oxide Cylinder

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FEEDBACK

Any feedback on this document should be sent to the Contact Officer listed on the front page.

APPENDIX 1

GLOSSARY & ABBREVIATIONS

Acronym or Term	Definition
ABG	Arterial Blood Gas
CDH	Congenital Diaphragmatic Hernia
CLD	Chronic Lung Disease
CPAP	Continuous Positive Airway Pressure
CXR	Chest X-Ray
ECMO	Extracorporeal Membrane Oxygenation
FiO_2	Fraction Of Inspired Oxygen
HFNC	High Flow Nasal Cannula
HFOV	High Frequency Oscillatory Ventilation
HNELHD/HNE Health	Hunter New England Local Health District
INOmax DS_{IR} Plus	Nitric Oxide Delivery System
JHCH	John Hunter Children's Hospital
LV	Left Ventricular
MAP	Mean Arterial Pressure
Met Hb	Methaemoglobin
mmHg	Millimetres of Mercury
NICU	Neonatal Intensive Care Unit
OI	Oxygen Index
$PaCO_2$	Arterial Partial Pressure of Carbon Dioxide
PaO_2	Arterial Partial Pressure of Oxygen
PAP	Pulmonary Arterial Pressure
PEEP	Positive End Expiratory Pressure
PPE	Personal Protective Equipment
pH	Potential of Hydrogen
PH	Pulmonary Hypertension; Increased pulmonary arterial pressure, where the mean pulmonary arterial pressure > ½ mean systemic arterial pressure. It is clinically significant when it produces hypoxia
PPHN	Persistent Pulmonary Hypertension of the Newborn;

	When the normal cardiopulmonary transition fails to occur and there is increased pulmonary vascular resistance and the presence of a right-left shunt at the foramen ovale and/or ductus arteriosus level. The patient may or may not have pulmonary hypertension
ppm	Parts Per Million
PPROM	Preterm Premature Rupture of Membranes / Preterm Prelabour Rupture of Membranes
PRN	Pro Re Nata “when necessary”
psi	Pounds Per Square Inch
PVR	Pulmonary Vascular Resistance
RDS	Respiratory Distress Syndrome
R to L	Right to Left (shunt)
RV	Right Ventricular
SAP	Systemic Arterial Blood Pressure
SpO_2	Peripheral Capillary Oxygen Saturation

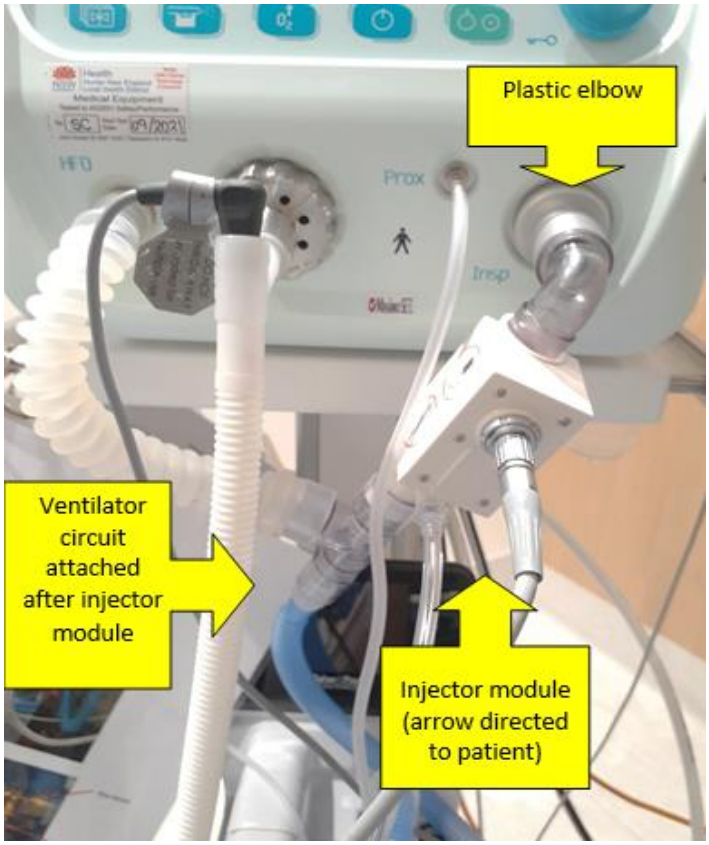
APPENDIX 2

CONNECTIONS & SET UP FOR INHALED NITRIC OXIDE VIA VENTILATOR

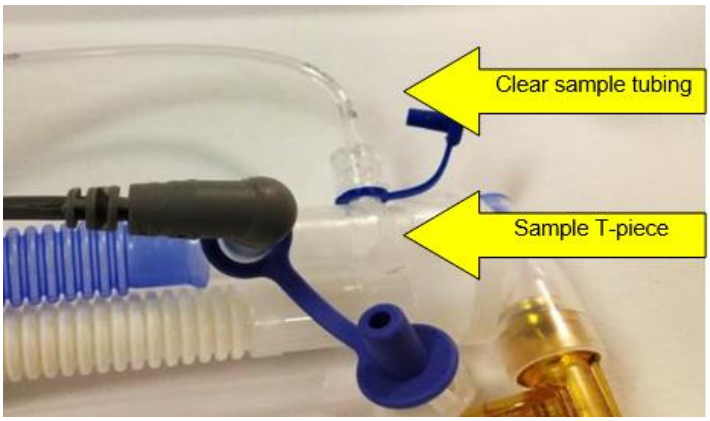
Two connectors; an inspiratory limb sampling port and an inspiratory limb elbow, are required to attach the INOmax DS_{IR} Plus to the Fabian; these are kept with the INOmax DS_{IR} Plus

Attaching the INOmax DS_{IR} Plus to the Ventilator:

- Remove clear sample tubing from the plastic sample T-piece (which is next to the blue corrugated tubing)
- Attach clear sample tubing to inspiratory limb sampling port
- The plastic sample T-piece and blue corrugated tubing are no longer required
- Attach elbow to injector module, insert elbow and injector module to inspiratory outlet and attach ventilator circuit to the bottom of the injector module (see below)



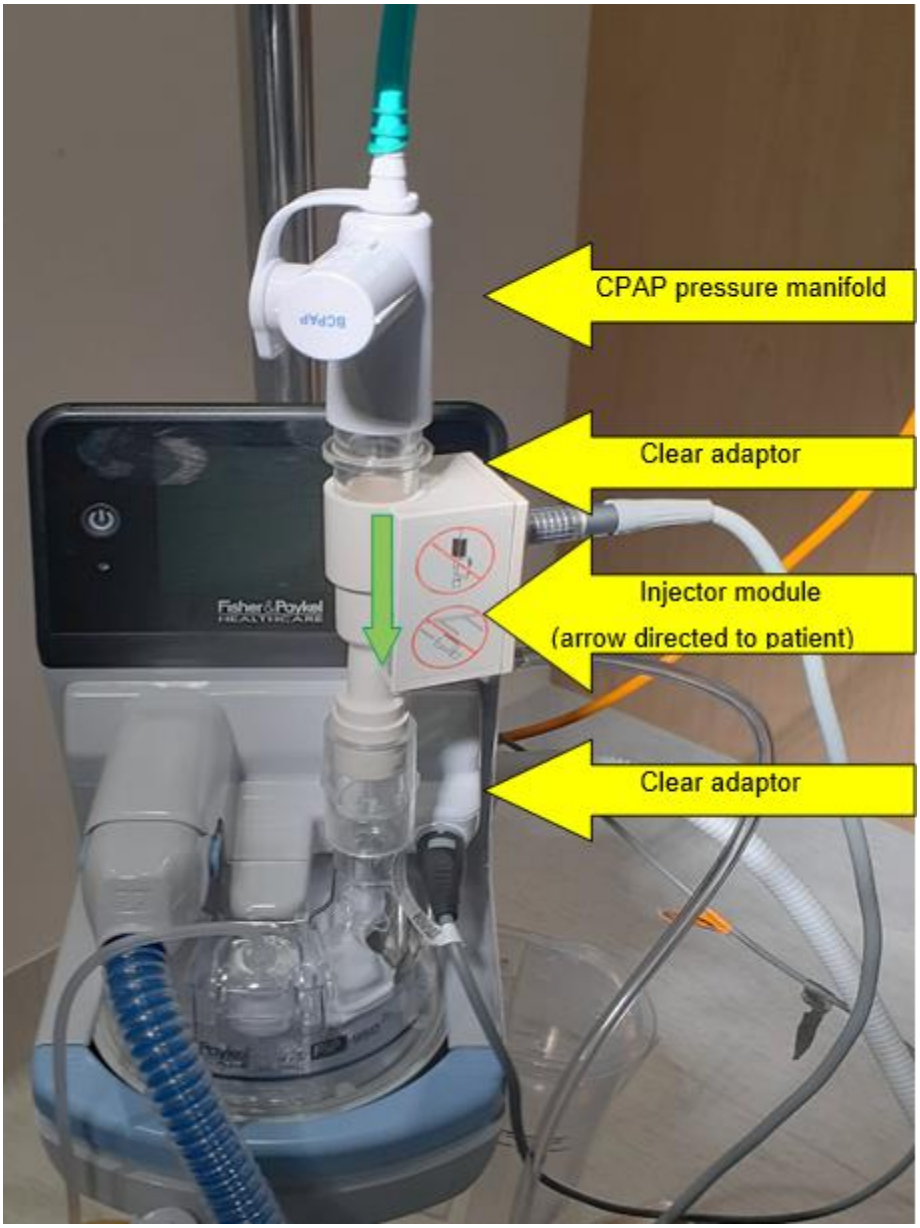
SET UP AT PATIENT END



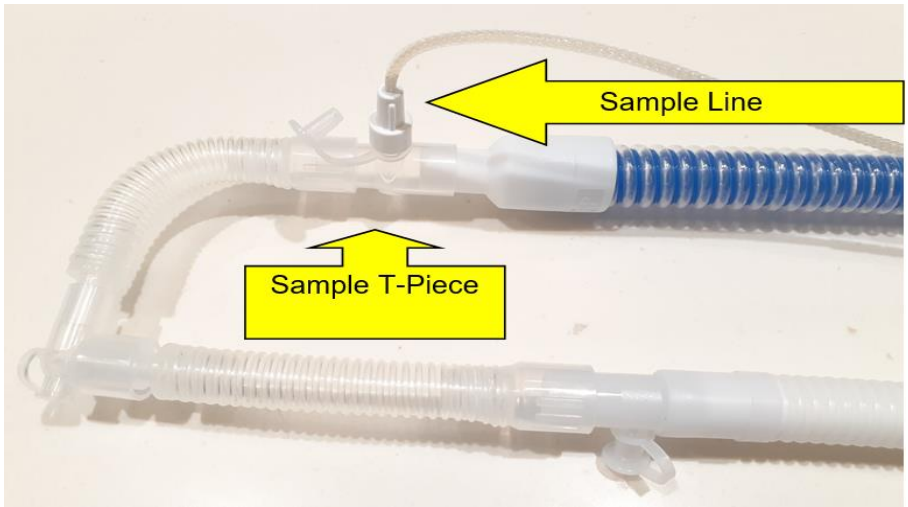
** Sample T-piece and sample line must face upwards once attached to prevent water collection*

APPENDIX 3

CONNECTIONS & SET UP FOR INHALED NITRIC OXIDE VIA CPAP



SET UP AT PATIENT END



**Ensure the sample line and sample T-piece are placed on the inspiratory limb of circuit (blue limb)*

APPENDIX 4

CHANGING THE NITRIC OXIDE CYLINDER

Step 1

- Change the INOMAX cylinder when the pressure gauge shows a pressure of 500 psi or less
- Crack open the new cylinder
- Remove the INOMAX regulator currently not in use from the back of the cart; verify the white Kel-F tip on the regulator is in place and not damaged
- Connect this INOMAX regulator to the new INOMAX treatment cylinder
- Do not insert the INOMAX grey regulator hose into the back of the INOmax DS_{IR} Plus at this point

Step 2

- Open and close the INOMAX cylinder
- Ensure the cylinder shows more than 200 psi on the gauge
- Ensure you are using an INOMAX cylinder that is 800 ppm and check expiry date
- Watch the pressure gauge for 30 seconds to check for leakage

Step 3

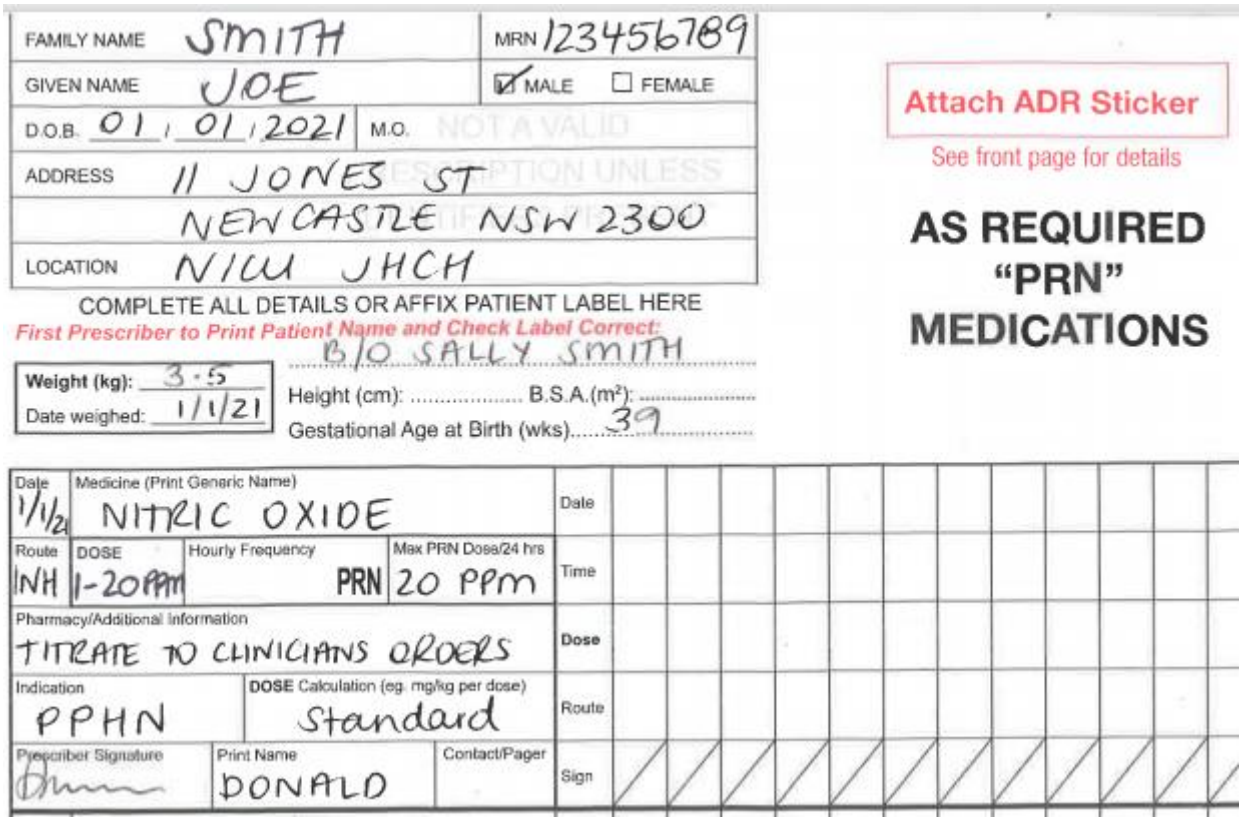
- Take the grey regulator hose which is not currently in use and insert into the purge port (push firmly)
- There will be a sound of escaping gas and a degree of pressure is felt as the hose and gauge are depressurised
- Observe pressure gauge needle drop to zero

Step 4

- Remove the grey regulator hose from the purge port and insert into the gas inlet at the back of the INOmax DS_{IR} Plus
- Turn on the new cylinder. This may activate the ‘two cylinders open‘ alarm until the empty cylinder is closed
- Turn off the old cylinder
- Remove the grey regulator hose which has been in use on the old cylinder from the back of the INOmax DS_{IR} Plus
- Inform the technical assistant team that the cylinder is empty and label as empty
- Remove cylinder from bedside using gas trolley
- Replace with new cylinder if and when possible

APPENDIX 5

PRESCRIPTION OF INHALED NITRIC OXIDE



FAMILY NAME	SMITH
MRN	1234567 89
GIVEN NAME	JOE
☑ MALE ☐ FEMALE	
D.O.B.	01 / 01 / 2021
M.O.	
ADDRESS	11 JONES ST
	NEWCASTLE NSW 2300
LOCATION	NICU JHCH

Attach ADR Sticker

See front page for details

AS REQUIRED "PRN" MEDICATIONS

COMPLETE ALL DETAILS OR AFFIX PATIENT LABEL HERE

First Prescriber to Print Patient Name and Check Label Correct:

B/O SALLY SMITH

Weight (kg): 3.5
Date weighed: 1/1/21

Height (cm): ..... B.S.A.(m²): .....

Gestational Age at Birth (wks) 39

Date	Medicine (Print Generic Name)			Date												
1/1/21	NITRIC OXIDE															
Route	DOSE	Hourly Frequency	Max PRN Dose/24 hrs	Time												
INH	1-20 PPM	PRN	20 PPM													
Pharmacy/Additional Information				Dose												
TITRATE TO CLINICIANS ORDERS																
Indication	DOSE Calculation (eg. mg/kg per dose)			Route												
PPHN	Standard															
Prescriber Signature	Print Name	Contact/Pager		Sign												
	DONALD															