Local Guideline

John Hunter Children's Hospital
CHILDREN, YOUNG PEOPLE AND FAMILIES

NSW GOVERNMENT Health
Hunter New England Local Health District

Inhaled nitric oxide (iNO) therapy in NICU for Pulmonary Hypertension

Sites where Local Guideline applies	
This Local Guideline applies to:	
1. Adults	No
2. Children up to 16 years	No
3. Neonates – less than 29 days	Yes
Target audience	NICU clinical staff, which provide care to neonatal patients
Description	The guideline provides information about neonatal assessment to ensure escalation of treatment occurs as necessary
National Standard	Standard 4 Medication Safety

Go to Guideline

Keywords	calibration, half-life, INOMAX, nitric oxide, persistent pulmonary hypertension of the newborn, PPHN, vasodilator
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Replaces existing document?	Yes
Registration number and dates of superseded documents	NITRIC OXIDE (iNO) THERAPY in NICU for Persistent Pulmonary Hypertension of the Newborn 26/05/2014

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 PD2013_043 Medication handling in NSW Public Health Facilities
- NSW Health Policy Directive PD2017_013 Infection Prevention & Control Policy
- NSW Health Policy Directive PD2017_032Clinical Procedure Safety

Prerequisites (if required)	N/A
Local Guideline note	This document reflects what is currently regarded as safe and appropriate practice. The guideline section does not replace the need for the application of clinical judgment in respect to each individual patient but the procedure/s **require mandatory compliance**. If staff believe that the procedure/s should not apply in a particular clinical situation they must seek advice from their unit manager/delegate and document the variance in the patients' health record.
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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/

RISK STATEMENT

This local guideline has been developed to provide guidance to clinical staff in NICU when nitric oxide is ordered for an infant in NICU. It ensures that the risks of harm to infants, staff and families during set-up and administration are identified and managed. *Any unplanned event resulting in, or with the potential for injury, damage or other loss to infants/ staff/ families as a result of this procedure must be reported through the Incident Information management System and managed in accordance with the Ministry of Health Policy Directive: Incident management PD2014_004. This would include unintended injury that results in disability, death or prolonged hospital stay.*
Risk Category*: Clinical Care & Patient Safety*

Outcomes

1	To deliver safe and effective inhaled nitric oxide (iNO) to the infant
2	Parents informed of therapy and infant's clinical progress
3	Staff to gain understanding of pathophysiology of persistent pulmonary hypertension and the potential benefits of iNO treatment

ABBREVIATIONS & GLOSSARY

Abbreviation/Word	**Definition**
CPAP	Continuous Positive Airway Pressure
INOmax DS_{IR} Plus	Delivery system for nitric oxide
ECMO	Extracorporeal membrane oxygenation
ETT	Endotracheal tube
FiO_2	Fractional concentration of inspired oxygen
FRC	Functional residual capacity
HFNC	High flow nasal cannula
HFOV	High-frequency oscillatory ventilation
IR	Infrared
IVH	intraventricular haemorrhage
Low Cal	Low-range calibration
MAP	Mean airway pressure

Met Hb	Methaemoglobin
MO	Medical Officer
NICU	Neonatal Intensive Care Unit
NO/iNO/NO_2	Nitric oxide/inhaled nitric oxide/ nitrogen dioxide
NOS	Nitric oxide synthase
OI	Oxygen Index
$PaCO_2$	Arterial partial pressure of carbon dioxide
PaO_2	Arterial partial pressure of oxygen
PAP	Pulmonary Arterial Pressure
PIP/PEEP	Peak inspiratory pressure/Positive End-Expiratory Pressure
PPE	Personal Protective Equipment
PPHN	Persistent pulmonary hypertension of the newborn
ppm	Parts per million
PPROM	Preterm premature rupture of membranes
psi	Pounds per square inch
RDS	Respiratory Distress Syndrome
SAP	Systemic Arterial Pressure
TA	Technical Assistant
WOW	Workstation on wheels

GUIDELINE

This Guideline does not replace the need for the application of clinical judgment in respect to each individual patient.

NITRIC OXIDE (iNO) THERAPY in NICU One **Page Summary and Checklist**

(Ctrl+Click on **Coloured** words to jump to that section) Pg

Section 1

Use of inhaled nitric oxide (iNO) for pulmonary hypertension

Top

Aims:

1. To provide guidance for appropriate use of iNO in the NICU

2. To optimise patient's clinical condition before starting iNO

3. To provide iNO in a manner that is safe, cost-effective & beneficial to patient outcomes

4. To establish suitable criteria to help assess patient responsiveness to iNO & it's weaning

Summary

In term or near-term infants with significant hypoxic respiratory failure defined as PaO_2 < 100 mmHg on FiO_2 > 0.8 and/or Oxygenation Index (OI) between 15 and 25, start iNO at 20 ppm.

Document respiratory, blood gas and cardiovascular parameters at start and after 15 to 30 minutes of iNO (use sticker).

	At start	After 15–30 minutes of iNO
Time		
Mean airway pressure		
FiO_2		
SpO_2 (post-ductal)		
Arterial PaO_2 (if available)		
OI (= MAP x FiO_2 / PaO_2)		
Systemic blood pressure		
Echo R-to-L shunt % (if available)		

***Positive response*:** Rise in post-ductal PaO_2 ≥ 20 mmHg or SpO_2 by ≥ 10% or able to drop FiO_2 by at least 0.2. On Echocardiograph echocardiography assessment, significant reduction in R-toL shunting and improved left ventricular filling.

***Partial response*:** Rise in post-ductal PaO_2 by 10–12 mmHg or SpO_2 by 5–10% or able to drop FiO_2 by 0.1–0.2 or reduction in R-to-L shunt on echocardiography.

***Negative response*:** Either no change or a rise in post-ductal PaO_2 of < 10 mmHg or SpO2 by < 5% or only able to drop FiO_2 by < 0.1, or no reduction in R-to-L shunt on echocardiography.

Continue iNO if responder or partial responder; stop if non-responder.

Initiate weaning when FiO_2 is less than 0.4 for 6–12 hours. Wean iNO 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.

Inhaled NO can be provided with any form of respiratory support (mechanical ventilation, CPAP, HFNC, nasal cannula).

In preterm infants with evidence of lung hypoplasia and pulmonary hypertension due to prolonged PPROM, start iNO 10-20 ppm early and monitor response.

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

Definitions

Persistent pulmonary hypertension of the newborn (PPHN): 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.

Pulmonary hypertension (PH): Increased pulmonary arterial pressure, where the mean pulmonary arterial pressure > ½ mean systemic arterial pressure. It is clinically significant when it produces hypoxia.

Pulmonary hypertension of the newborn, background

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, 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 (iNO).

Use of iNO for pulmonary hypertension

This guideline will focus on the use of inhaled nitric oxide (iNO) as pulmonary vasodilator therapy, but it is important to realise that additional steps are needed to control PH and optimise the efficacy of iNO.

Nitric oxide (NO) is an endogenous mediator of smooth muscle relaxation. NO is rapidly inactivated once it combines with haemoglobin in the blood stream. Due to this rapid inactivation, inhaled NO (iNO) can be administered exogenously as a selective pulmonary vasodilator. When NO reaches the capillary bed of the lungs, it is inactivated with minimal systemic haemodynamic effects.

iNO is approved for treatment for pulmonary hypertension and to support right ventricular function in newborn infants. Numerous, well-conducted, randomised, controlled trials have demonstrated benefits in term infants with hypoxic respiratory failure when ventilation and resuscitation measures alone were not enough. The use of iNO 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 iNO.

The routine use of iNO in preterm infants with hypoxaemic respiratory failure and infants with congenital diaphragmatic hernia (CDH) has not shown a reduction in mortality or morbidity. However, targeted use of iNO in certain pathophysiological situations can improve outcomes in these specific situations and will be discussed separately.

Treatment of pulmonary hypertension in the newborn, main pillars

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:

A. Optimise lung volumes

B. Lower pulmonary arterial pressure (PAP)

C. Support cardiovascular function

A. Optimise lung volumes

Before starting iNO, 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 can 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.

B. Lower pulmonary arterial pressure

There are various pharmacological preparations that can lower PAP. This guideline will primarily focus on the use of iNO to help lower pulmonary.

Starting iNO

The indication to start iNO is:

- Any infant ≥ 34 week gestation with severe respiratory failure
    - Defined as $PaO_2 < 100$ mmHg on $FiO_2 > 0.8$ and/or an Oxygenation Index (OI) between 15 and 25

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

Try not to make any ventilatory/FiO_2 changes or disconnect infant from ventilator for at least 30 minutes after iNO 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 might be appropriate to continue 'trial' of therapy to a maximum of 1 hour.

Assessing response

The iNO responsiveness must be assessed within 30 minutes of initiation. It is preferable to obtain another 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 0.2
- Significant reduction in R-to-L shunt and improved left ventricular filling on echocardiography

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 0.1–0.2
- Reduction in R-L shunt on echocardiography

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 < 0.1
- No reduction in R-L shunt On echocardiography

If there is a positive or partial response, continue iNO 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 iNO (negative response) then iNO therapy should be discontinued and details of lack of response documented. There is no need to wean iNO in this situation. It is important that during the trial period of iNO, no additional ventilator changes are made as it can make interpretation of 'response to iNO therapy' difficult. Be aware that, if the iNO 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 NO production. This should NOT be considered as an indication for restarting iNO therapy if there was a confirmed negative response.

Weaning iNO

After a sustained positive response is established and oxygenation improved, gradually but frequently wean FiO_2 to minimum required concentration (generally < 0.4). Once FiO_2 has been weaned to a clinically appropriate concentration, it is desirable to maintain iNO for a period of 6–12 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 iNO 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 > 0.2
- Pre-ductal saturation returns to > 10% higher than post-ductal

If weaning had to be discontinued, then increase iNO 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.

Be aware that some infants may still develop a transient hypoxaemia once iNO therapy is discontinued. This is due to suppression of endogenous NO by exogenous therapy. The hypoxaemia is usually moderate (needing increase in FiO_2 by 0.2) and short-lasting (up to an hour). This should not be a reason to restart iNO therapy but should be treated by increasing FiO_2.

Monitoring during treatment with iNO

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 iNO at ≤ 20 ppm. If Met Hb level is ≥ 3%, then medical team should be notified and weaning of iNO should be considered. Subsequent levels should be checked every 24 hours. A Met Hb level ≥ 5% should prompt discontinuation of iNO.

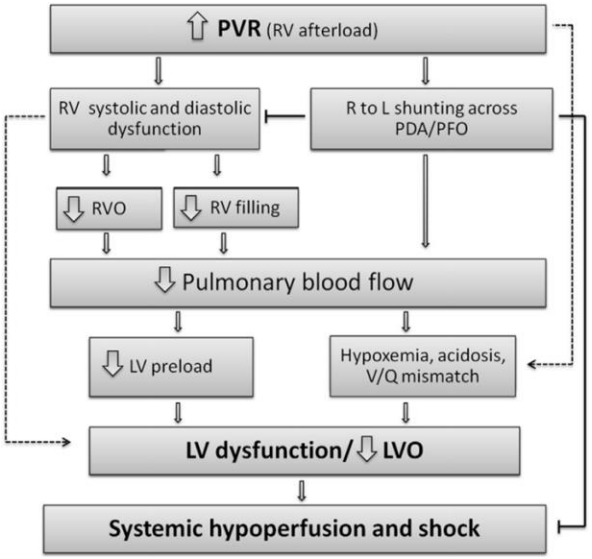
In any infant with hypoxaemic respiratory failure, the possibility of structural heart defect should be strongly considered if one or more of the following occurs in addition to iNO non-responsiveness:

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

C. Supporting cardiovascular function

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.



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 iNO treatment should be guided by the systemic arterial blood pressure (SAP), estimates of pulmonary arterial pressure and the PAP:SAP ratio.

Significant systemic hypotension should be corrected before iNO 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
Volume	Improves cardiac input		Low preload, collapsed systemic veins
Dopamine	Pressor	Increases afterload Increases PAP:SAP ratio	Systemic hypotension, normal blood flow
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

Noradrenaline (norepinephrine)	Pressor, improves contractility	Increases afterload Decreases PAP:SAP ratio	Low contractility, systemic hypotension, PH
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	Neurohormone, increases peripheral vascular resistance	May decrease PAP:SAP ratio	Systemic hypotension, PH
Alprostadil	Prostaglandin E2, 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

Specific clinical situations and other considerations for iNO use

Preterm infants with hypoxic respiratory failure

Trials of prophylactic or early (within first 2 postnatal days) rescue use of iNO 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 iNO. 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, iNO exposure must be kept to lowest duration possible as there are unresolved concerns of possible adverse long-term effects associated with use of iNO in preterm infants.

Inhaled NO 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 iNO 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 iNO without documenting significant pulmonary hypertension on echocardiography.

In preterm infants with severe CLD and associated significant PH documented on echocardiogram, iNO may be appropriate when clear clinical goals are defined prior to initiation of iNO 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 NO treatment in infants with CHD did not improve morbidity or mortality nor reduce the need for ECMO. However, iNO 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 NO should be used cautiously in infants with CDH and it is recommend to start only after echocardiography has documented a reasonable LV size, acceptable LV function and the presence of significant pulmonary hypertension or right ventricular dysfunction.

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Section 2

INOmax DS_{IR} Plus setup and testing Top

The INOmax DS_{IR} Plus system is currently used to deliver iNO to the infant. It delivers nitric oxide gas into the inspiratory limb of the patient breathing circuit in a way that provides a constant concentration of NO, as set by the user, to the patient throughout the inspired breath whilst tracking the ventilator waveform via the injector module.

The INOmax DS_{IR} Plus also includes an INOblender. The INOblender is used independently of the INOmax DS_{IR} Plus. It allows NO delivery via the Neopuff or Laerdel bag.

Before you begin—Some points to be aware of:

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 NO to the infant until an alternate INOmax DS_{IR} Plus can be provided.

The INOmax DS_{IR} Plus relies on infrared (IR) technology to detect the presence of the nitric oxide (INOmax) cylinder. The infrared detection device can be affected by bright lights and anything that covers the top of the cylinder dial.

DO NOT COVER THE CYLINDER DIAL and keep it away from BRIGHT LIGHTS

REMEMBER
NITRIC OXIDE IS VERY EXPENSIVE!!
PLEASE ENSURE CYLINDERS ARE TURNED OFF WHEN NOT IN USE

- Keep plugged in and connected to power at all times
- Determine when the last 'pre-use' procedure check was completed. It must be performed 12th hourly.
- The injector module must have the arrow pointing in the direction of the gas flow from the ventilator (or CPAP circuit) towards the patient.
- Touch screen wizard technology assists with the pre-use procedure
- Low calibration will occur automatically when in use. The system delivers the set parts per million (ppm) of NO; however, during calibration the values will read as 0.
- **The injector module must be placed between the ventilator inspiratory gas outlet and the HFOV tubing**

ALERT

If the backup system is switched on whilst the INOmax DS_{IR} Plus is running, it will deliver250 mL/minute of NO in addition to the prescribed dose of NO.

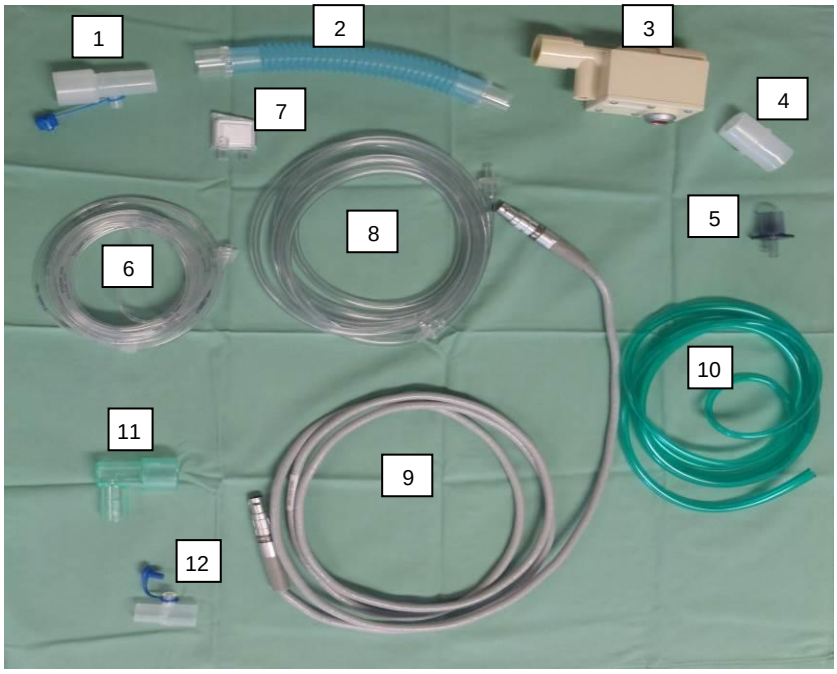
A high priority alarm will be present

INOmax DS_{IR} Plus setup

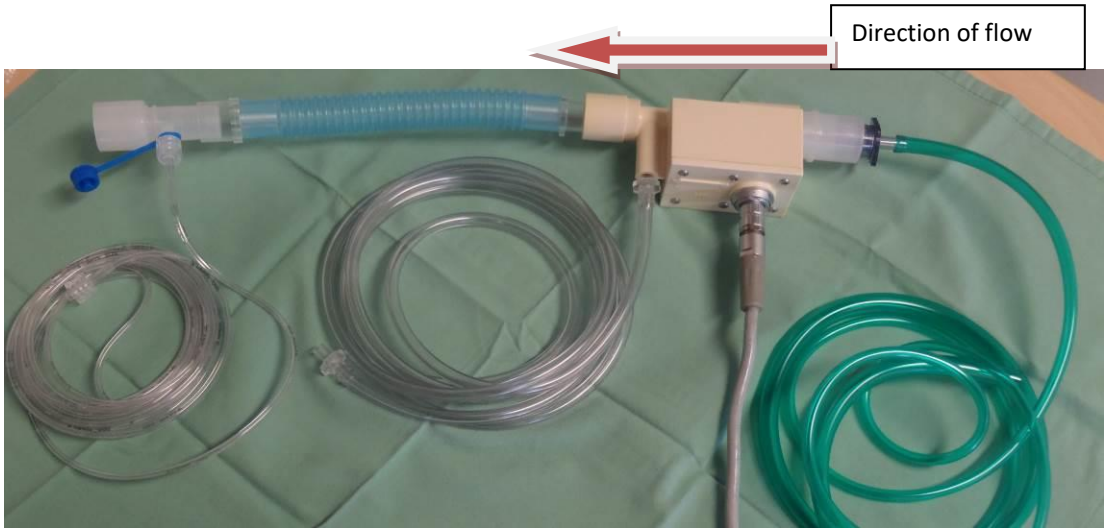
Setting up of the INOmax DS_{IR} Plus is a staged process with which all staff should be familiar.

Note: The technical assistants prepare the INOmax DS_{IR} Plus setup to be ready for bedside use. However, it is the nurse who is responsible for ensuring that the equipment is in correct and working order.

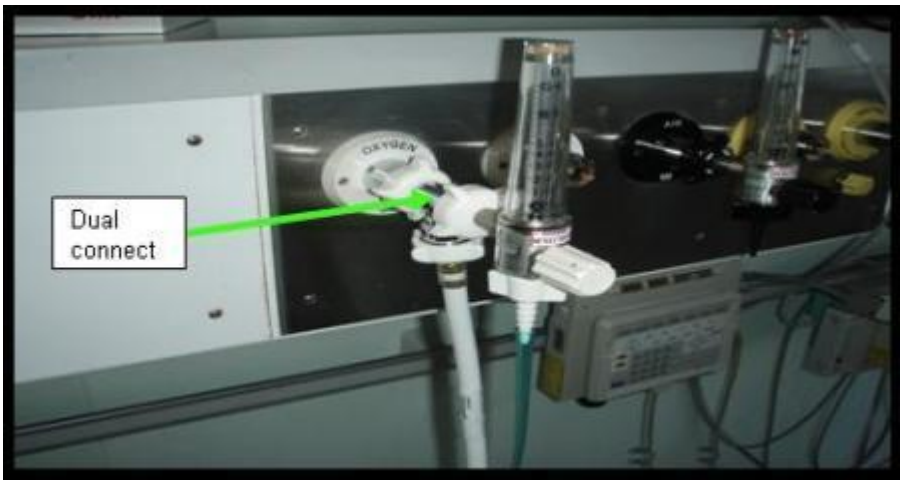
If the INOmax DS_{IR} Plus is not set up ready for testing, the following description takes you through the process.



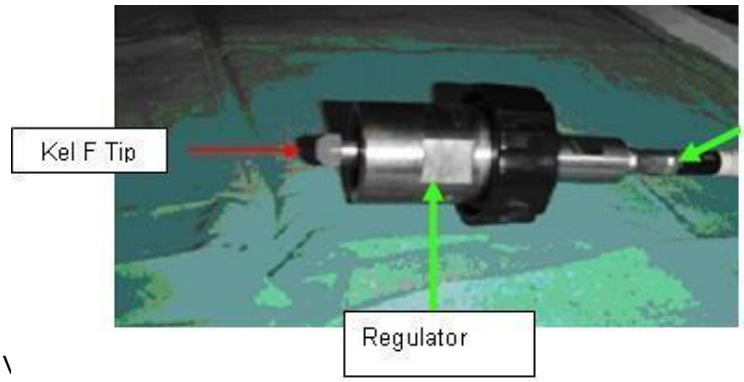
1. Sample T-piece
2. Blue corrugated hose
3. Injector module (note direction of arrow towards sample T-piece)
4. White straight connector
5. Grey adaptor
6. Patient gas sample line
7. Water filter cartridge
8. Clear injection tubing
9. Grey electrical cable (ensure red dots are aligned)
10. Green oxygen tubing
11. Inspiratory limb elbow (ventilator attachment-may be grey or green)
12. Sample T-piece connector to attach to inspiratory limb the ventilator at patient end.



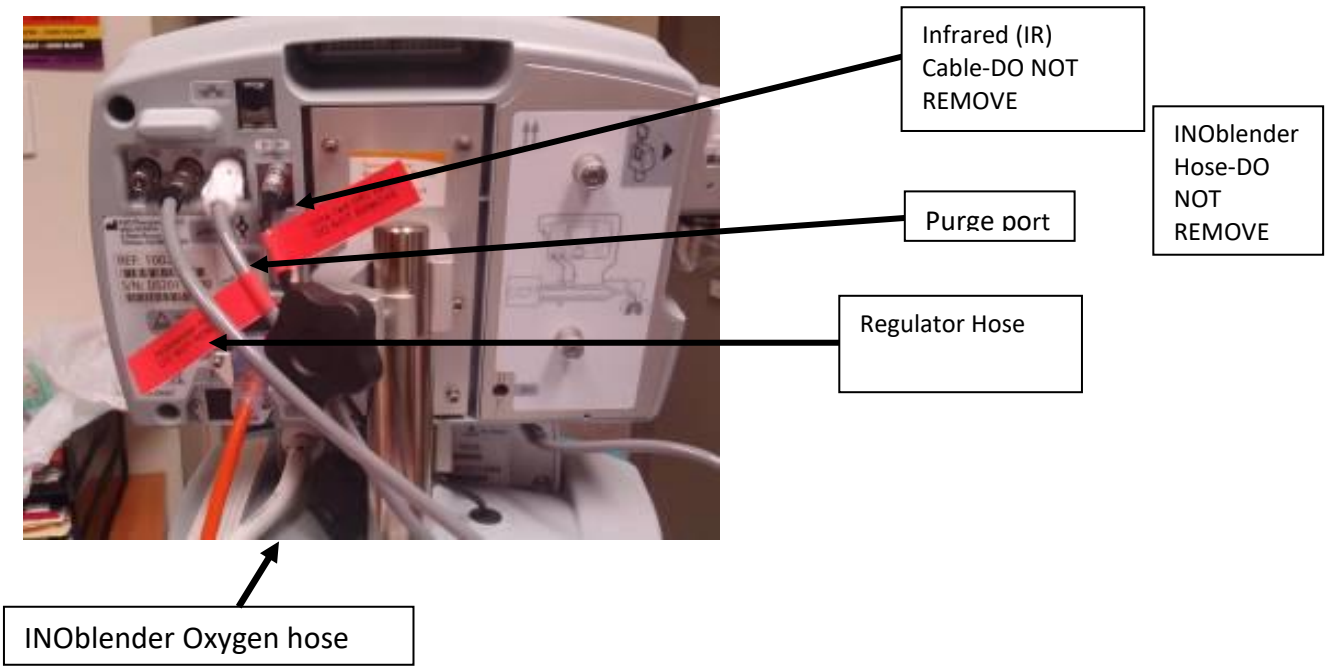
Dual Wall Oxygen Outlet



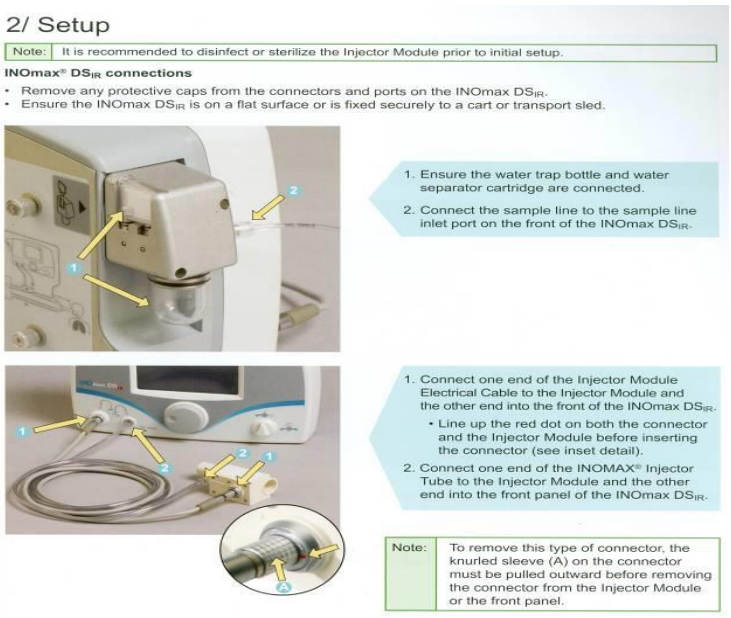
- Plug in power cord and verify green AC power light is ON
- Attach the **DUAL** oxygen outlet to the wall oxygen
- Attach the free end of the green oxygen tubing to the dual oxygen wall outlet
- Check date and dose of gas cylinder to be used. The cylinders contain 800 parts per million (ppm) nitric oxide gas
- Remove INOMAX regulator and pressure gauge from back of cart and verify that the white **Kel-F** tip is in place and not damaged. (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



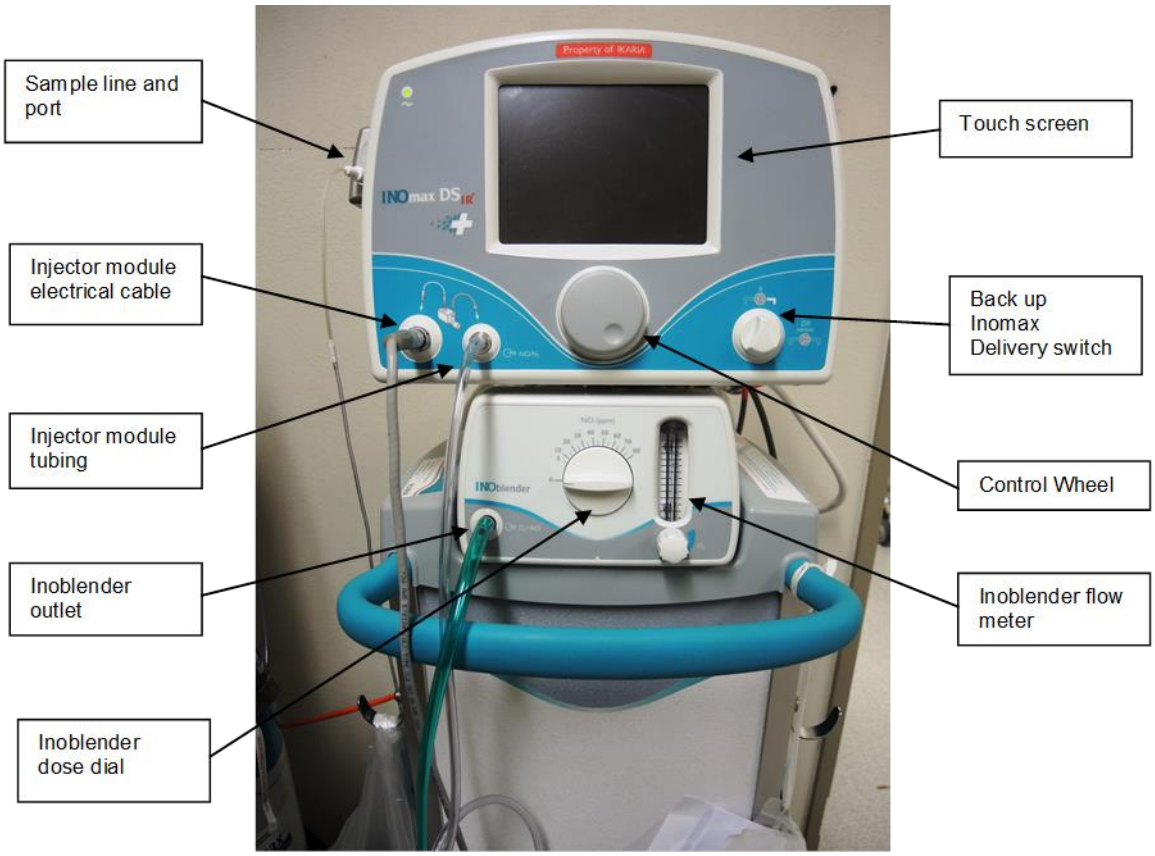
Back of INOmax DS_{IR} Plus—showing infrared cable (IR), INOblender hose, regulator hose, INOblender O_2 hose and purge port; all of which are labelled in red.



- Connect regulator hose to the inlet on the back of the device
- Note that 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 as shown above
- Ensure the patient gas sample line is connected to the port above the water trap bottle
- Ensure the injector module cable and electrical cable are in place as shown below
- Ensure the backup switch is OFF. (Dial set at 0 when in the off position)



Front of machine

- Ensure INOblender dose setting dial is OFF. (Dial set at 0 when in the off position)
- Turn the INOmax DS_{IR} Plus delivery system **ON** (on/off switch located at the back of the machine)—a splash screen will appear followed by an Ikaria test screen which may take a minute or so. The speaker will sound followed by the main screen.
- Press the patient-head icon on the screen and type in 'Training', this is important as the NICU doesn't get charged for nitric oxide used for training purposes.
- Low calibration will automatically begin and complete when the system is turned on.

INOmax DS_{IR} Plus Pre-use tests

Step 1

High-pressure leak test

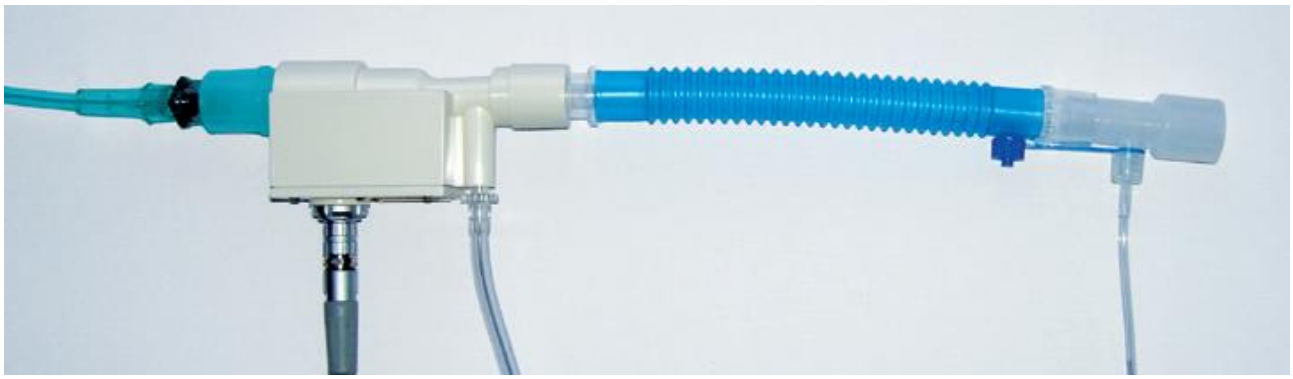
- Make sure INOMAX cylinder icon is present
- Open/close INOMAX cylinder valve (verify cylinder is >500 psi)
- Wait 30 seconds and ensure there is no pressure drop
- If no pressure decrease observed, the high pressure leak test is complete

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 shows how to do this.

Complete pre-use procedure setup



- Press CANCEL to exit pre-use wizard
- Ensure INOMAX cylinder valve is closed
- Connect green oxygen tubing to wall oxygen
- Set O_2 flow meter to 10 L/min
- Set the INOMAX dose to 40 ppm ('Cylinder Valve Closed' alarm will occur and cylinder pressure should drop to 0)
- 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 wall oxygen to 10 litres/minute
- Turn integrated backup on (250 mL/minute)
- Verify backup alarm occurs
- Allow values to stabilise NO_2 < 1.0 ppm, NO 14–26 ppm
- Backup delivery test complete; turn backup off

Step 4

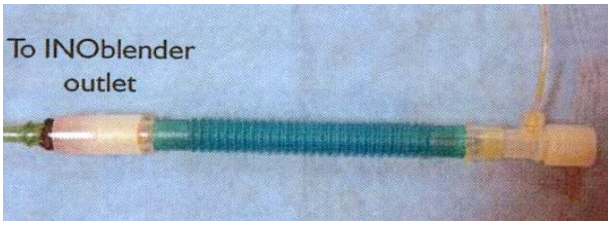
Performance test

- Verify oxygen flow set at 10 litres/minute
- Press next button to automatically set dose to 40 ppm
- Verify monitor values
- NO_2 <1.5 ppm, NO 35–45 ppm and O_2 92–98%
- Performance test complete

Step 5

INOblender test

- Turn O_2 flow meter off and remove green oxygen tubing from flow meter and attach to front of INOblender
- Remove injector module from pre-use setup and re-connect connectors



- Set INOblender to 40 ppm of NO and O_2 to 10 litres/minute
- Allow values to stabilise with NO 32–48 ppm
- Turn NO dose and flow to off
- INOblender test is complete

If the NO isn't 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

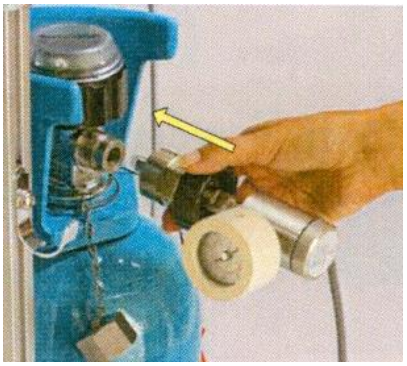
General information

- Patient information can be filled in at any time and is useful for data collection; the system requires rebooting to remove patient data
- 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.
- Sample error may occur; the most common reason is an issue with the water filter which needs to be replaced. Be aware that the NO 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. Be aware that the NO dose will read zero, however the set dose is still being delivered while the water trap is disconnected. Empty the water trap contents in to a kidney dish and clean dish after use
- The monitor and delivery system of the INOmax DSIR Plus are separate, therefore, if the monitor powers out, NO will continue to be delivered even though it is not indicating so on the monitor screen.
- Backup is independent of power. There is a 30-minute alarm.
- Flow sensor calculates the dilution of 800 ppm to be delivered based on the flow from the ventilator
- NO is directed to the ventilator at 250 mL/minute (800 ppm cylinder) when backup switch turned on. When the ventilator flow is 10 litres/minute, the baby will be receiving 20 ppm of NO. If there is a pressure leak and low pressure, check INOblender or backup switch are not turned on
- Yellow is a low-priority alarm
- Red is a high-priority alarm
- If the low-pressure alarm warning is signalling you really have no gas! Always change when at 500 psi
- Alarm help key available to direct you through steps to fix a problem
- Only one regulator hose can be plugged in at any time as two can cause a leak of NO
- 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)
- 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
- A diagram is available within the setup menu to facilitate the correct setup of the equipment
- Time can be changed via the settings button

Section 3

Changing the NO cylinder



Step 1

- Change the INOMAX cylinder when the pressure gauge shows a pressure of **200 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 pressure hose which has been in use on the old cylinder from the back of the INOmax DS_{IR} Plus
- **Inform the TAs that the cylinder is empty and label as empty**
- Remove cylinder from bedside using gas trolley
- Replace with new cylinder if and when possible

Section 4

Management

Top

Management of an infant receiving iNO

Infants receiving INO are extremely fragile and require skilled nursing and medical management/care to support their cardio-respiratory system. Please refer to:

- Assisted Ventilation of the newborn 5-5.1.4(a)
- High Frequency Oscillatory Ventilation (HFOV) 5-5.1.4(b)
- Hypotension and poor circulation in neonates JHCH_NICU_13.04
- Endotracheal Tube (ETT) Suction in NICU 5-5.1.9
- Transcutaneous Oxygen /carbon dioxide Monitoring JHCH_NICU 12.05_
- Assessment and Management of Pain in the Neonate JHCH_NICU 03.04_

Monitoring and precautions when using iNO therapy

- Infants requiring increasing iNO are very sensitive to changes in iNO delivery
- The half-life of NO is 5 seconds; abrupt disconnections or interruptions to the circuit should be avoided as it may lead to increased pulmonary vascular resistance and worsening oxygenation
- ***Minimal handling***, as these babies are often hemodynamically unstable; they may require pacing through cares and cares may be required 8 to 12th hourly
- Adapt the environment for the baby; provide a noise and light-reduced setting as these infants are also highly sensitive to noxious stimuli
- NO 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
- Arterial blood gas analysis is performed PRN and requires consultation between nurse and medical team
- Methaemoglobin levels are dose dependent and should be maintained at < 3%; levels of 3–5% are rare at doses ≤ 20 ppm; however, if 5%, neonatologist must be informed and nitric oxide treatment ceased[3, 4].
- FiO_2 is monitored from the INOmax DS_{IR} Plus, not the ventilator
- Oxygen index calculation
- Transcutaneous carbon dioxide monitoring and hourly documentation
- Pre- and post-ductal saturation monitoring and hourly documentation
- Continuous heart rate and arterial blood pressure monitoring and hourly documentation
- Check with in-charge MO what is an acceptable systolic and mean arterial pressure for the baby
- Ventilation and humidity settings and hourly documentation
- Cardiac ECHO is recommended prior to commencing iNO 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

- Ensure that ventilator trigger setting is accurate as the commencement of NO can affect trigger sensitivity
- Inhaled NO must be prescribed in ppm on the stat medication chart, signed by two staff and recharted daily
- Document iNO and NO_2 levels hourly on the nursing flow chart
- The INOblender should be set at 10 litres/min when in use
- Match INOblender dose to treatment dose
- Check PIP and PEEP of the Neopuff are at desired levels prior to attachment to baby
- Prior to use, purge NO_2 from the Neopuff circuit by running system for 10 seconds prior to connection to baby
- Empty water trap into yellow kidney dish when water observed in the trap. Empty at the bedside as the NO concentration can be affected during this procedure **(PPE must be worn)**
- Inhaled NO should be weaned gradually once the desired effect has been achieved; see weaning in section 1. When iNO ceased, and not re-used within 10 minutes, remove from the ventilator circuit and depressurise
- Keep parents informed of their infants condition

Appendices

Appendix 1 Connections and setup for iNO via Fabian Ventilator

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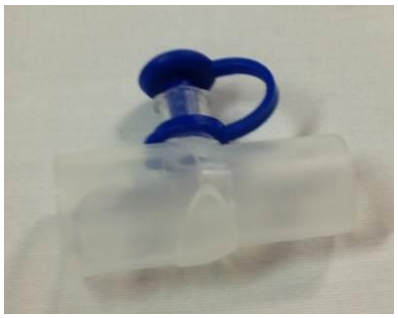
Two connectors—an inspiratory limb sampling port and an inspiratory limb elbow—are required to attach the INOmax DS_{IR} Plus to the Fabian; these are kept with the INOmax DS_{IR} Plus



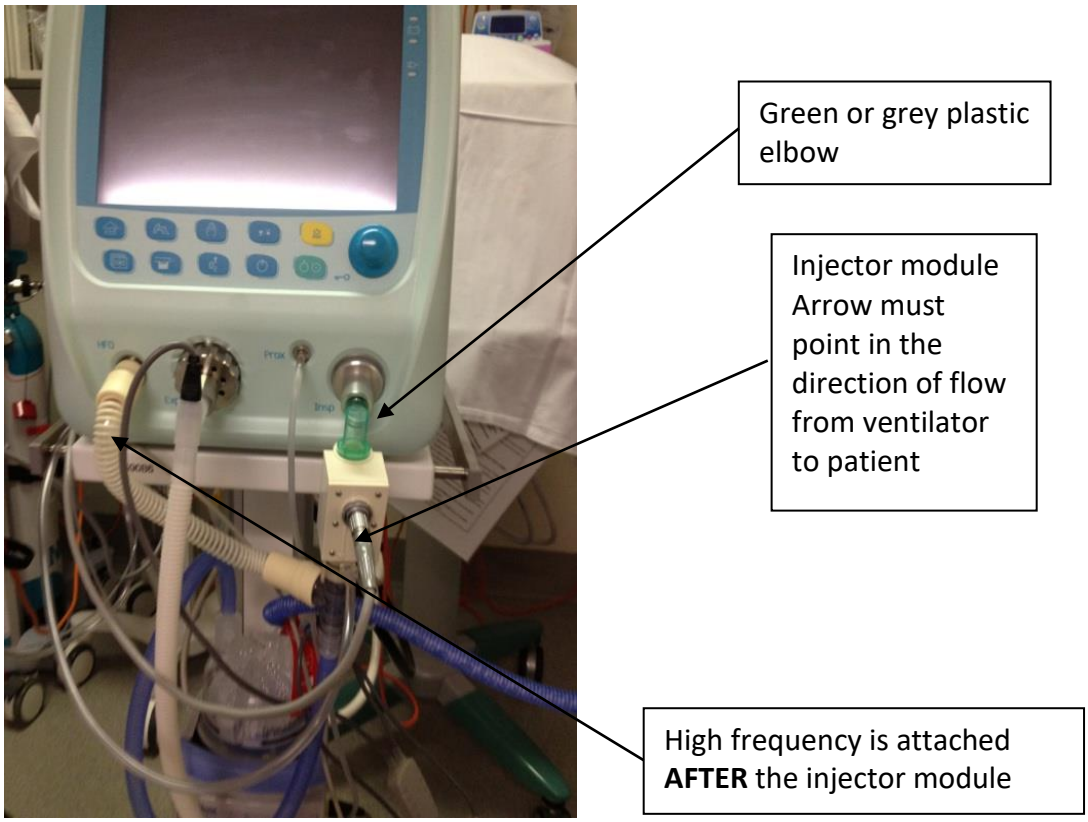
Inspiratory limb sampling port

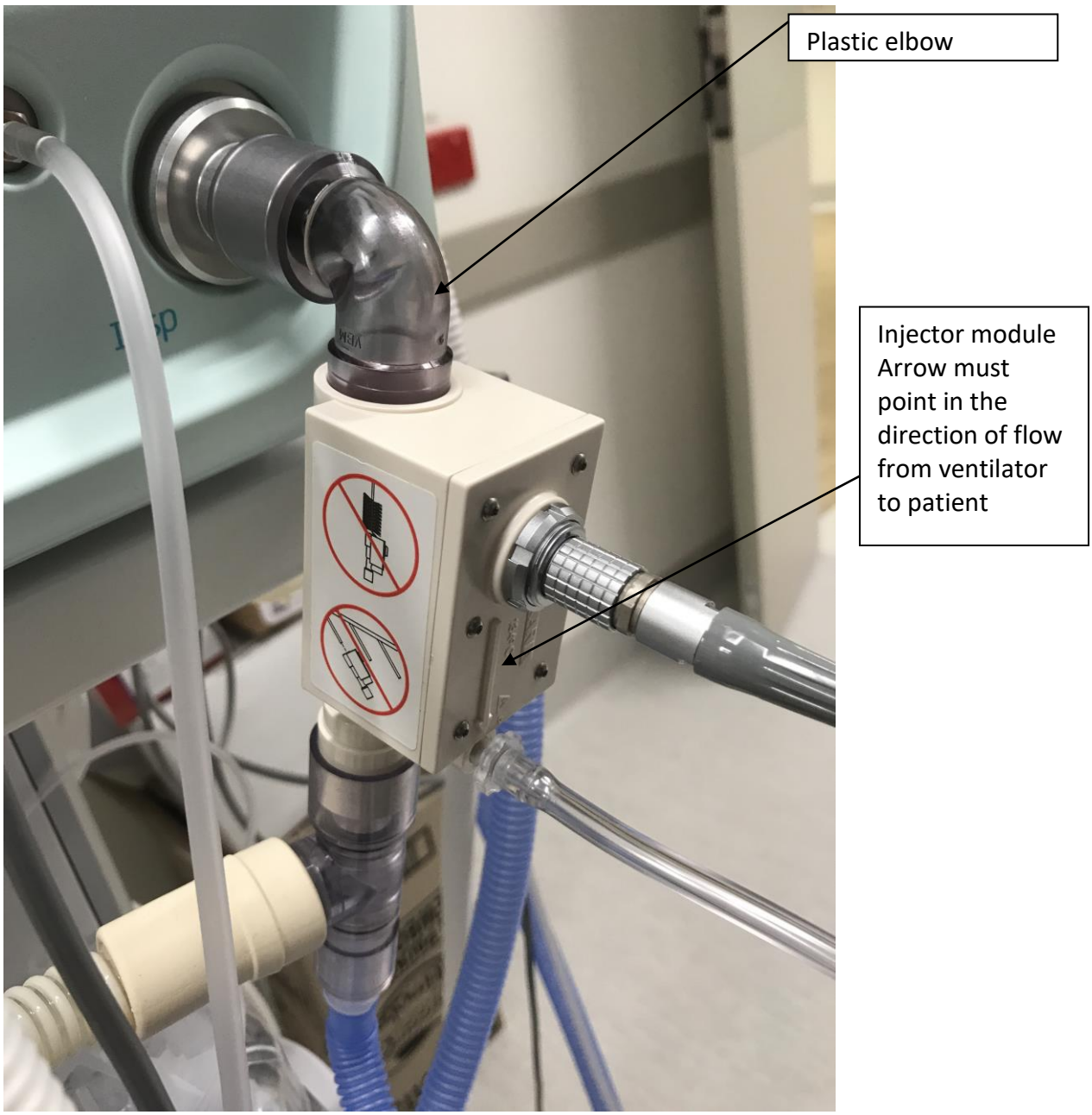
Elbow

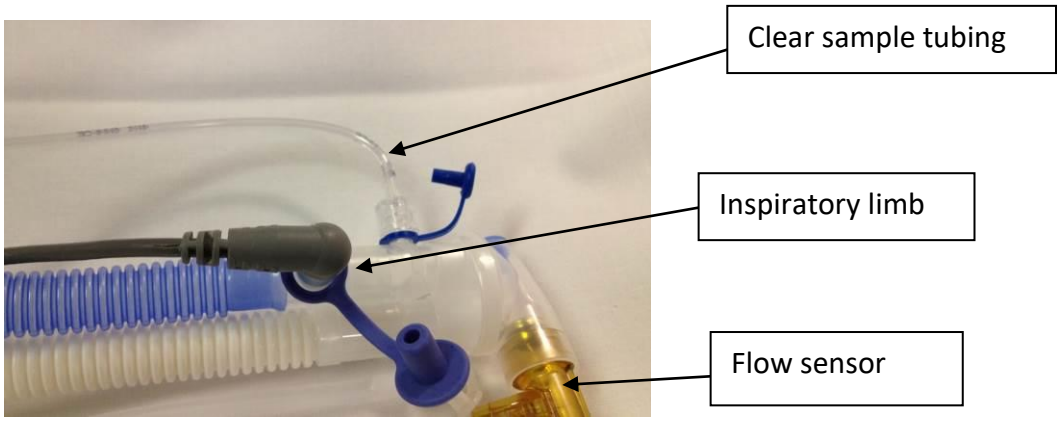
- Remove clear sample T-**tubing** from the plastic sample T-piece connector (which is next to the blue corrugated tubing)
- Attach clear sample tubing to inspiratory limb sampling port
- The plastic sample T-piece connector and blue corrugated tubing are no longer required
- Attach green or clear elbow to injector module

If the system has previously been depressurised, turn the cylinder on now

Attaching the INOmax DS_{IR} Plus to the Fabian ventilator







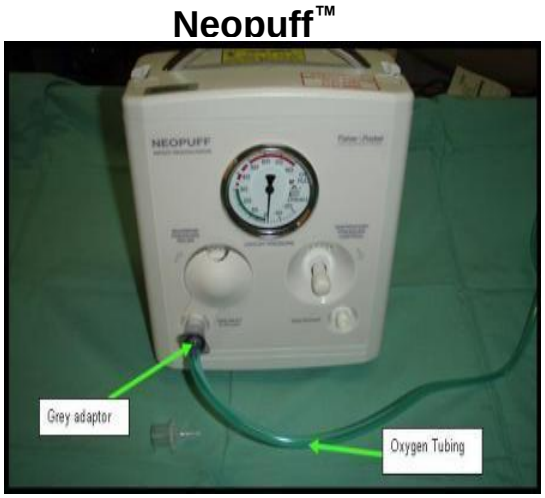
Sample T-tubing must face upwards once attached to the circuit to prevent water collection.

SET iNO dose as per medical officer. Press touchscreen dial, set dose with control wheel and press the control wheel to confirm.

Appendix 2 Attachment to T-piece flow driver (Neopuff™)

Top

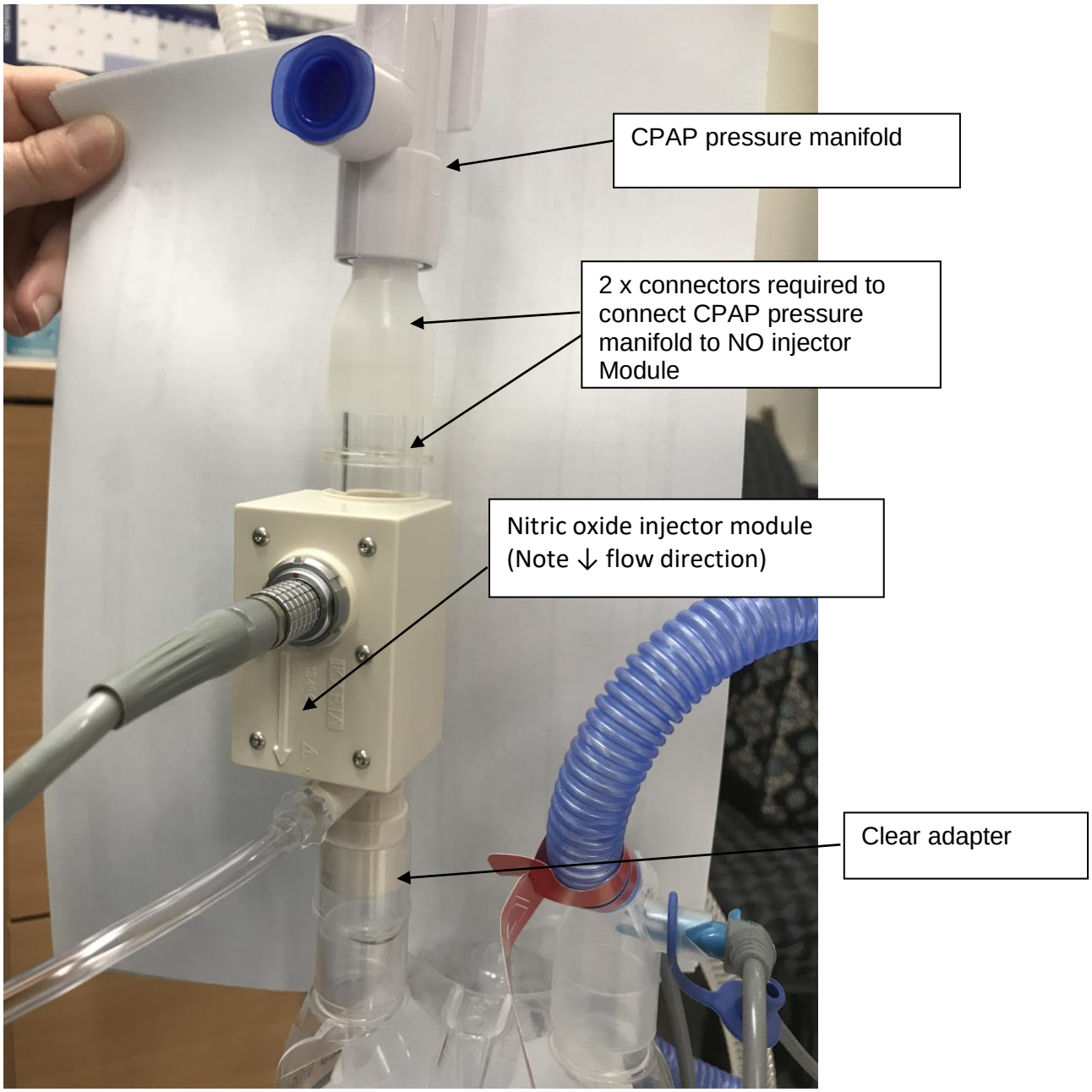
Attach grey adapter and oxygen tubing to the Neopuff, as shown

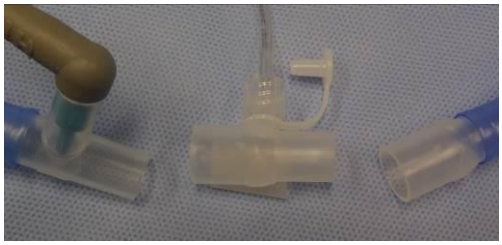


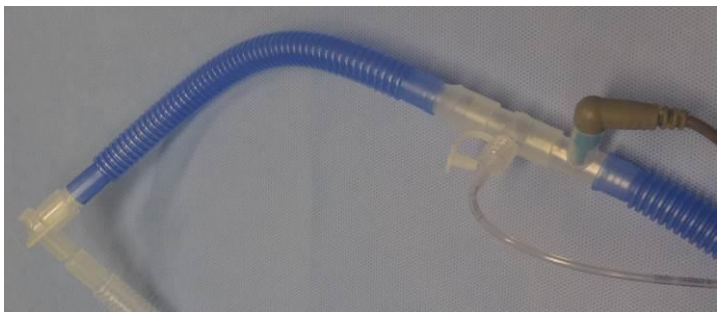
- To test the Neopuff™, set INOblender dose to 20 ppm and flow to 10 litres/minute
- Set Neopuff pressures as per infant's condition
- Turn INOblender dose and flow off
- If Neopuff™ is required, match INOblender dose to treatment dose and purge the system by running a flow of 10 litres/minute for 10 seconds prior to connection to the baby

Appendix 3 Connections & setup for iNO via HP circuit

Top







Nitric oxide sampling port attached to T-piece and placed in blue inspiratory tubing as shown

Appendix 4.

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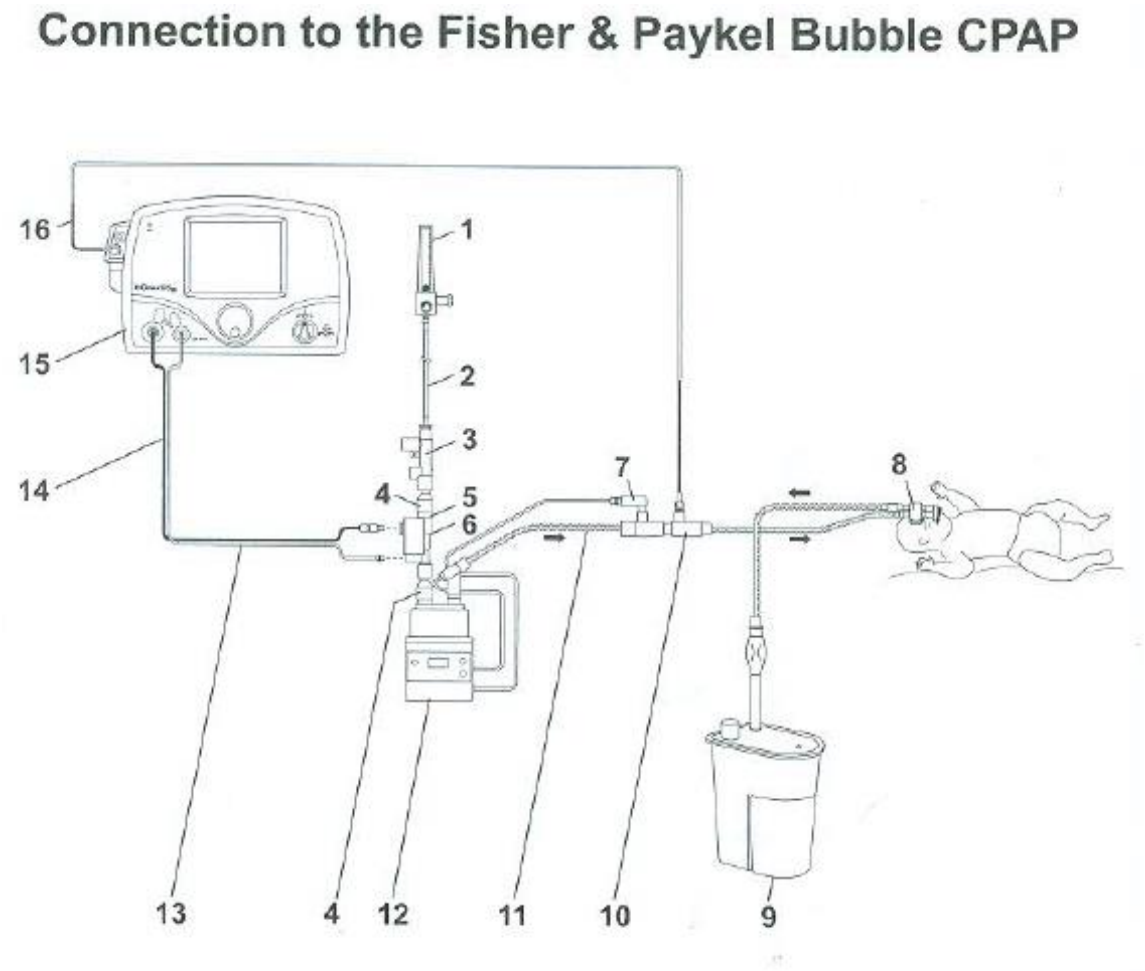

1. Oxygen source	10.Inspiratory limb sampling port
2. Oxygen tubing	11.Breathing circuit
3. Bubble CPAP pressure manifold	12. Humidifier
4 & 5. Green adapter	13. NO/N_2 injector tube
6. Injector module	14. Injector module electrical cable
7. Temperature probe	15. INOmax DS_{IR} Plus
8. Nasal prong infant interface	16.Patient gas sampling line
9. Bubble CPAP generator	

from INOmax DS_{IR} ® Plus Pocket Guide (2012)

Appendix 5

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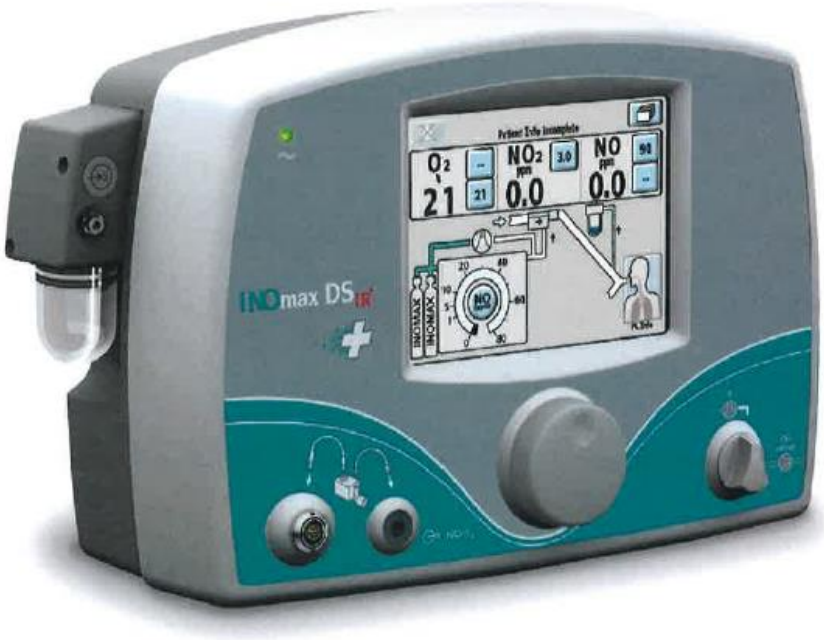
Manual pre-use checkout

Mallinckrodt Pharmaceuticals

INOmax DS$_{IR}$® Plus



9/ Appendix

Appendix

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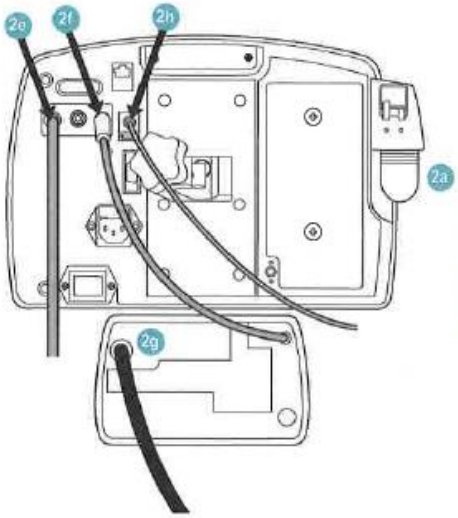
2015-07

9/ Appendix

Manual Pre-Use Checkout

The following instructions are provided for when the on-screen pre-use wizard is not used.



1. Turn device ON, low calibration will begin and complete (Continue with steps 2-4 while calibration completes)
2. **Initial Connections:**

   Confirm attachment of the following:

   a. Water separator cartridge, water bottle, and patient gas sample line in place
   b. Injector module cable and tubing are connected
   c. Plug in power cord and verify AC power light is ON
   d. Regulator to INOMAX cylinder
   e. Regulator hose to INOmax DS_{IR} inlet
   f. INOblender hose connected and white lock in place
   g. Oxygen source (50 psig) to back of INOblender
   h. IR cable in place
3. Assemble pre-use set-up connectors (see Figure 9-1). Do Not turn on O_2 flowmeter yet.
4. **High Pressure Leak Test:**

   Open/close INOMAX cylinder valve

   a. Verify, at least 34.5 bar (500 psig) cylinder pressure
   b. Verify, no decrease in cylinder pressure for 30 seconds

6b

6c

5. **Manual Purge/Alarm Verification:**
   a. Press CANCEL to exit pre-use wizard (low calibration should be complete to continue).
   b. Verify INOMAX cylinder valve is closed.
   c. Set O_2 flowmeter to 10 L/min
   d. Purge INOmax DS_{IR}
   - Set the INOMAX dose based on cylinder concentration:

Cylinder Concentration (ppm)	800	400
Set Dose (ppm)	40	20

   - "Cylinder Valve Closed" alarm will occur.
   - Continue until cylinder gauge pressure drops to 0 psig.
   - Measured NO_2 will increase and then decrease as NO_2 is purged from the system.
   - "Low Cylinder Pressure" alarm will occur.

   e. Turn INOMAX dose to zero.
   f. Open INOMAX cylinder valve.

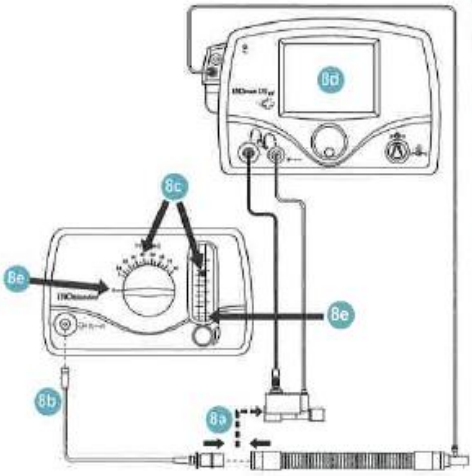
6. **Integrated Pneumatic Backup Test:**
   a. Verify pre-use assembly flowmeter set to 10 L/min
   b. Turn INOmax DS_{IR} backup switch ON
   c. Allow monitored values to stabilize
   d. Verify measured values based on cylinder concentration

Cylinder Concentration (ppm)	800	400
NO (ppm)	14 - 26	7 - 13
NO_2 (ppm)	≤ 1.0	≤ 1.0

   e. Turn backup switch OFF

9-2

Part No. 20573 Rev-03
2015-07



7. **Performance Test:**
   a. Verify O_2 flowmeter is set to 10 L/min
   b. Set INOMAX dose based on cylinder concentration:

Cylinder Concentration (ppm)	800	400
Set Dose (ppm)	40	20

   c. Verify monitored values

Cylinder Concentration (ppm)	800 ppm	400 ppm
Set Dose (ppm)	40	20
Acceptable NO Value (ppm)	35 - 45	17 - 23
Acceptable NO_2 Value (ppm)	< 1.5	< 1
Acceptable FiO_2 (%)	95 ± 3	95 ± 3

   d. Set INOMAX dose to 0 ppm
   - "Set Dose is Zero, Please Close Cylinder Valve" reminder will appear- DO NOT close cylinder valve at this time, dismiss reminder.

   e. Turn oxygen flowmeter OFF

8. **INOblender Test:**
   a. Remove injector module from pre-use assembly and reconnect tubing
   b. Remove O_2 tubing from flowmeter and attach to INOblender outlet
   c. Set INOblender flow to 10 L/min, INOMAX dose to:

Cylinder Concentration (ppm)	800	400
Set Dose (ppm)	40	20

   d. Verify monitored values on the INOmax DS_{IR} Plus

Cylinder Concentration (ppm)	800	400
Acceptable NO Value (ppm)	32 - 48	16 - 24

   e. Set INOblender dose and flow to 0

Appendix 6 Handover Circuit Check List

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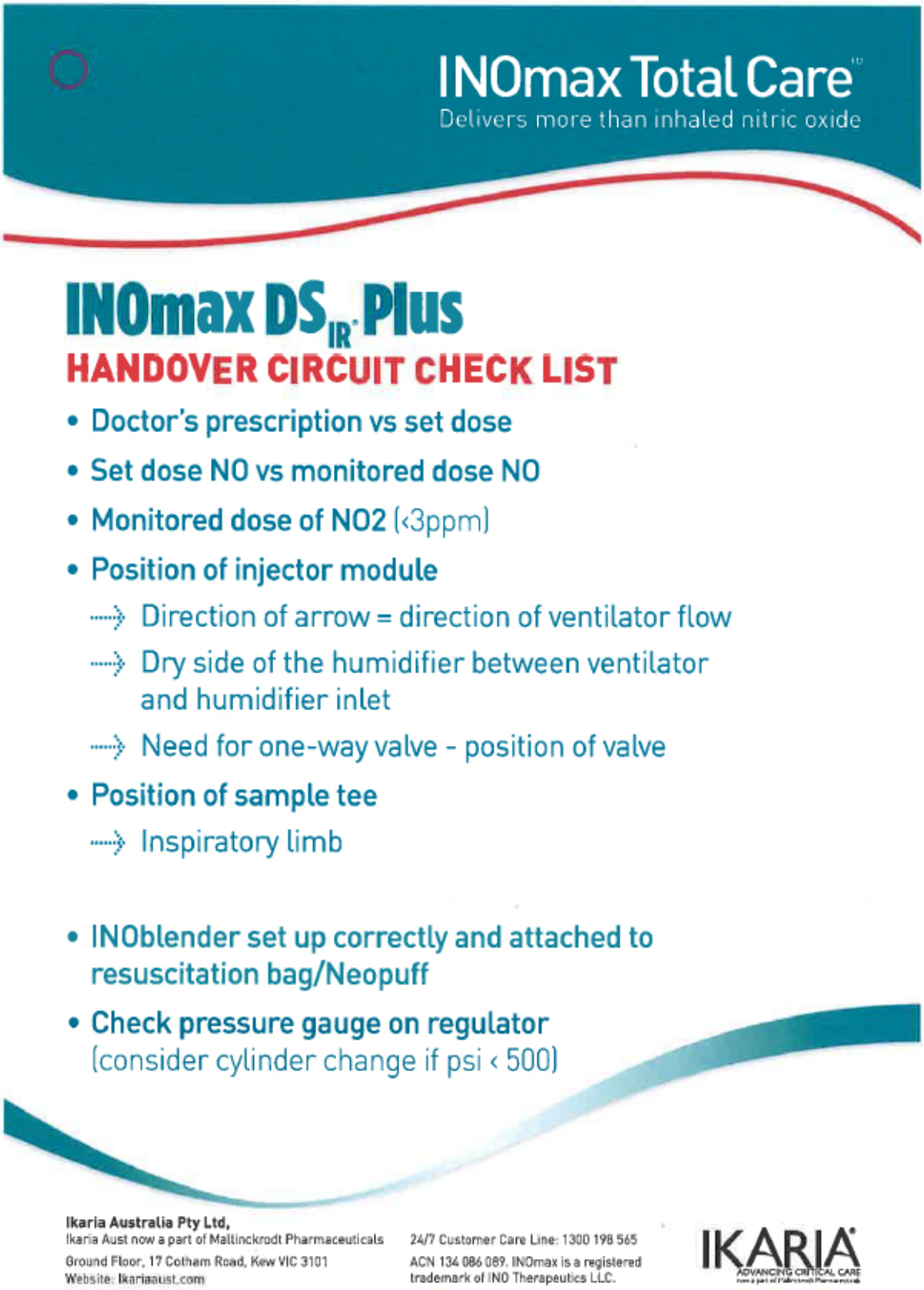

References

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10. Fabian. Neonatal and Infant Operating Manual, 2013 Acutronic Medical Systems AG, Switzerland

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