Ashford and St. Peter's Hospitals
NHS Foundation Trust

Persistent Pulmonary Hypertension of the Newborn (PPHN)

Management in NICU

Date	Comment (s)	Approved by
2010	Author Dr Peter Lillitos	Neonatal clinical management group
2013	Reviewed, no changes needed	Chairman's action
2014	Prostin information updated	
January 2021	Guideline updated and formatting revised	Neonatal Guidelines Group

Author of revised edition: Dr Ranjith Kulappura, Specialty Registrar

Supervisor: Dr Tosin Otunla, Consultant Neonatologist and Paediatrician with Expertise in Cardiology

Contents

1. Introduction

Persistent pulmonary hypertension of the new born (PPHN) is characterized by sustained elevation of pulmonary vascular resistance (PVR) and is often associated with normal or low systemic vascular resistance (SVR). This leads to extra pulmonary shunting from right to left across persistent fetal channels (PDA and PFO) leading to labile hypoxemia.

PPHN is being increasingly recognised in neonatal practice with an estimated incidence of 2-6/1000 births

PPHN is usually secondary to an identifiable insult however it can be primary or idiopathic (10%).

Common pulmonary conditions are:

- Meconium Aspiration Syndrome (MAS)
- Sepsis
- Congenital Pneumonia
- Respiratory distress syndrome (RDS),
- Congenital Diaphragmatic Hernia (CDH)
- Pulmonary Hypoplasia e.g.: from CDH or renal abnormalities/ oligohydramnios
- Birth asphyxia

Rare causes of severe and intractable PPHN include:

- Alveolar capillary dysplasia
- Hyaline membrane disease caused by mutations in surfactant protein B (SP-B) gene
- Respiratory failure due to ATP binding cassette protein member A3 (ABCA3) deficiency
- Genetic association - With genetic variants in corticotropin-releasing hormone (cRh) receptor 1 and cRh-binding protein

Antenatal and perinatal risk factors

- Meconium stained amniotic fluid
- Perinatal acidosis and asphyxia
- Maternal risk factors for sepsis
- Exposure to nicotine and certain medications like SSRI's
- Maternal obesity and diabetes

2. When to suspect PPHN

- Clinical - Respiratory distress with cyanosis and hypoxaemia which is refractory to oxygen therapy, in the absence of congenital heart disease.

- Chest X Ray - May reveal features associated with secondary PPHN (such as a CDH or pneumonia), but hypoxemia disproportionate to the severity of parenchymal disease on CXR should suggest PPHN.

- Pre & Post-ductal oxygen saturations: Post ductal maybe 5-10% lower than pre-ductal, consistent with Right to Left shunting *(NB: PPHN not excluded if ≤ 5% difference).*

- Blood gas (arterial) : The blood gas (arterial) is likely to show severe hypoxemia with PaO2 <8kpa.

- Echocardiogram : Is essential in ruling out congenital cyanotic heart disease, supporting a diagnosis of PPHN and in estimation of pulmonary pressures. Evaluation of cardiac function and haemodynamic assessment will help in management of fluid therapy and choosing appropriate medications such as inotropes, lusitropes or vasopressors.

3. Management principles

Early recognition of PPHN and correction of factors that prevent decrease in PVR are important to the successful management.

Aims :

- Lower pulmonary vascular resistance.
- Maintain systemic blood pressure higher than pulmonary pressures
- Reverse right-to-left shunting
- Improve arteriolar oxygen saturation and oxygen delivery to the tissues
- Minimise Lung injury
- Ensure adequate sedation and pain relief

General measures :

- Maintain normothermia
- Correct metabolic abnormalities such as hypoglycaemia, hypocalcaemia, hypomagnesemia, acidosis and polycythaemia.
- Commence antibiotics (sepsis particularly GBS is difficult to exclude)
- Optimise nutrition and fluid balance.

- Ensure adequate sedation and pain relief. Paralysis may be considered after discussing with Consultant.
- Minimal handling, nurse in quiet environment
- Systemic blood pressure should be maintained at normal values for gestational age
- Surfactant may be beneficial in MAS or Sepsis
- If perfusion is poor, consider fluid bolus (10 mL/kg of 0.9% sodium chloride or if coagulopathy, fresh frozen plasma)

Specific measures:

(a) Respiratory:

The two most potent natural pulmonary vasodilators are oxygen and good lung inflation.

(1) Oxygenation & Ventilation

(a) Saturations :

Aim for saturations >95% in term babies, aim for 91-95% in preterm babies with minimal difference between pre-and post-ductal saturations. ** Talk about PO_2 on arterial gases**

Hypoxia increases PVR . Hyperoxia does not further decrease PVR , instead results in free radical injury

(b) Ventilation:

Optimal lung expansion is essential for adequate oxygenation as well as the effective delivery of iNO. Keeping babies in high level of FiO2 >45-50% and on Non invasive support can potentiate hypoxia and increase the risk of development and exacerbation of PPHN.

Consider intubation and ventilation, if oxygen requirement is >45-50% . Early ventilation can lead to optimisation of oxygenation, CO2, pH and prevention of severe PPHN.

Aim for normocapnia, avoid hypocapnia

Gentle ventilation strategies with optimal PEEP, relatively low PIP and some permissive hypercapnia are now being recommended to ensure adequate lung expansion without causing lung injury. Optimal lung recruitment (8 – 9 posterior rib expansion on an inspiratory chest radiograph) with the use of PEEP/MAP decreases PVR

HFOV in combination with iNO can improve oxygenation in newborns who has severe PPHN complicated by diffuse parenchymal lung disease (RDS, MAS)

(2) Pulmonary Vasodilators:

(a) Inhaled Nitric Oxide :

Inhaled nitric oxide (iNO) is the preferred first choice pulmonary vasodilator therapy. It acts via cGMP pathway causing pulmonary vasodilation and improved V/Q matching.

Criteria to commence iNO include :
- Difference in pre & post-ductal saturations ≥ 5%
- Oxygen index (OI) >15
- Evidence of PPHN on Echocardiography.

Start iNO at 20 ppm.
iNO can be adjusted in the range between 5-20ppm
Monitor Methaemoglobin on blood gas and keep <5%

(b) Sildenafil (Oral /IV) :

Acts by inhibition of the cGMP degrading phosphodiesterase (PDE5) .
Consider add on Sildenafil in severe PPHN
IV sildenafil loading dose can cause systemic hypotension .
Sildenafil may reduce the rebound pulmonary hypertension noted during iNO weaning

Recommended dosing regimen for IV sildenafil**: loading dose of 0.4 mg/kg delivered over 3 hours, followed by a maintenance infusion at 1.6 mg/kg/day** .

(c) Milrinone :

Acts as a selective PDE-3 inhibitor in cardiac myocytes as well as in the vascular smooth muscle. . Milrinone may be the pulmonary vasodilator of choice in the presence of PPHN with left ventricular dysfunction

Dose 30 – 45 µg /kg/ min or 0.5 – 0.75 µg /kg/ min via Central line
Note : In emergency , can be given via large peripheral vein , but monitor for extravasation injury *.
Milrinone can cause hypotension, and should only be used after discussion with consultant

(d) Other medications:

Magnesium Sulphate:

On Cochrane review (2007), there was lack of evidence for the use of magnesium in the treatment of PPHN. Maintain magnesium > 1.0 as it may cause secondary PPHN

Vasopressin:

Case series publications have suggested that vasopressin use was associated with improvement in systemic BP, reduction in OI, steady reduction in iNO use and enabled weaning of other inotropes. However, these were not controlled and vasopressin was not the only intervention.

Dosage:
The recommended dose used of vasopressin in PPHN: 0.0001-0.001 U/kg/min[12]

Infusion preparation: [0.15 X wt. in kg] units of drug in 25ml of 5% Dextrose or Normal saline, will give 1ml/hr =0.0001 U/kg/minute (Argipressin – 20units/ml)

(b) Circulation:

- UAC/UVC placement
- Early invasive blood pressure monitoring
- Echocardiography: To rule out Congenital Heart Disease, to assess pulmonary artery pressures & assess right to left shunting across the PFO and PDA
- Fluid bolus and volume management may be required if hypovolaemia is suspected

(c) Inotropes : (Please refer to hypotension guidelines as well)

Aim to keep the mean arterial pressures above 60mm Hg in term infants or higher if RV pressure calculated to be greater than this

Does the baby need Prostin? There may be undiagnosed congenital heart disease and prostin is unlikely to make this worse and may be helpful (prostin is a pulmonary vasodilator). If there is no/poor response to Nitric Oxide, echocardiography is unavailable to rule out duct dependant CHD, or if in doubt, commence Prostin therapy.

1. ***Dopamine*** - Start at 5mcg/Kg/min, can be increased to 20mcg/Kg/min

   - Dose range of 4-10 mcg/Kg/min – inotropic and chronotropic effect
   - Dose range of 11-20 mcg/Kg/min – vasopressor, increased systemic and pulmonary vascular resistance

2. ***Dobutamine*** - Works well as inotrope and useful if poor cardiac function suspected, but also reduces SVR so may be less beneficial at maintaining BP

   - Dose range of 5-20 mcg/Kg/min – inotrope, reduced SVR and increases cardiac output

3. ***Noradrenaline*** - Can be useful to increase SVR, reduce PVR and increase BP, however if SVR is too high , then the ability of myocardium to pump against the resistance may become compromised

   - Dose (as base) 50- 500 nanograms/kg/min via Central line– vasopressor and significantly increases SVR

4. ***Adrenaline*** - Has dose dependent effects and is useful in neonates with vasodilatory shock +/- myocardial dysfunction

   - Dose range of 0.03 -0.1 mcg/Kg/min – inotropic effect and reduced SVR
   - Dose range of 0.1-1.0 mcg/Kg/min.- vasopressor and increased SVR

5. ***Hydrocortisone*** - It may be helpful to start hydrocortisone when second line inotropes are commenced as it may take 2-3 hours to have an effect.

(d) Neurological :

- Ensure adequate sedation +/- muscle relaxant/paralysis
- Minimise handling, PPHN babies can be very susceptible to significant desaturations on handling
- Cranial ultrasound to rule out IVH (ECMO may be contraindicated in the presence of IVH)
- Consider CFM if difficult to assess for seizures (e.g. In a sedated/muscle relaxed patient)

4. Ongoing Management

- Monitor transcutaneous CO_2
- Until stable, calculate OI hourly using the formula (see below)
- Hourly blood gases until stable
- Monitor Methaemoglobin 12 hourly while on iNO (< 2.5% normal; reduce NO if ≥4%; give Methylene blue if >7%)

$$\text{Oxygenation Index} = \frac{\text{Mean airway pressure} \times \text{FiO2 (\%)}}{\text{Post} - \text{ductal PO2 (kPa)} \times 7.6}$$

5. Weaning Nitric Oxide

- Wean Oxygen first maintaining saturations >95% .
- Nitric Oxide weaning should be done under direct observation.
- Nitric Oxide weaning may be initiated as early as 4-6hrs after starting treatment.
- Haemodynamic stability & oxygenation should be monitored for 30-60mins after each weaning step.
- Increase Nitric Oxide to previous level if Oxygen drops & wait at least 4-6hrs before attempting weaning again.

Weaning steps:

- Firstly, wean FiO_2 slowly until <40%
- If stable, start weaning iNO in steps of 2ppm 2-4 hourly until at level of 5ppm
- Once at 5ppm, if stable, wean by 1ppm 1-2 hourly
- Once iNO has been stopped, Sildenafil weaning may then commence (If on Sildenafil)

Note: Rebound PPHN may occur if iNO is stopped suddenly
Note: Sildenafil aims to reduce fluctuations in Oxygen thus aiding iNO weaning

Weaning Sildenafil

Wean Sildenafil once NO has been successfully weaned and stopped.
- Reduce by 0.5mg/kg every 12-24hrs

6. Escalating to ECMO

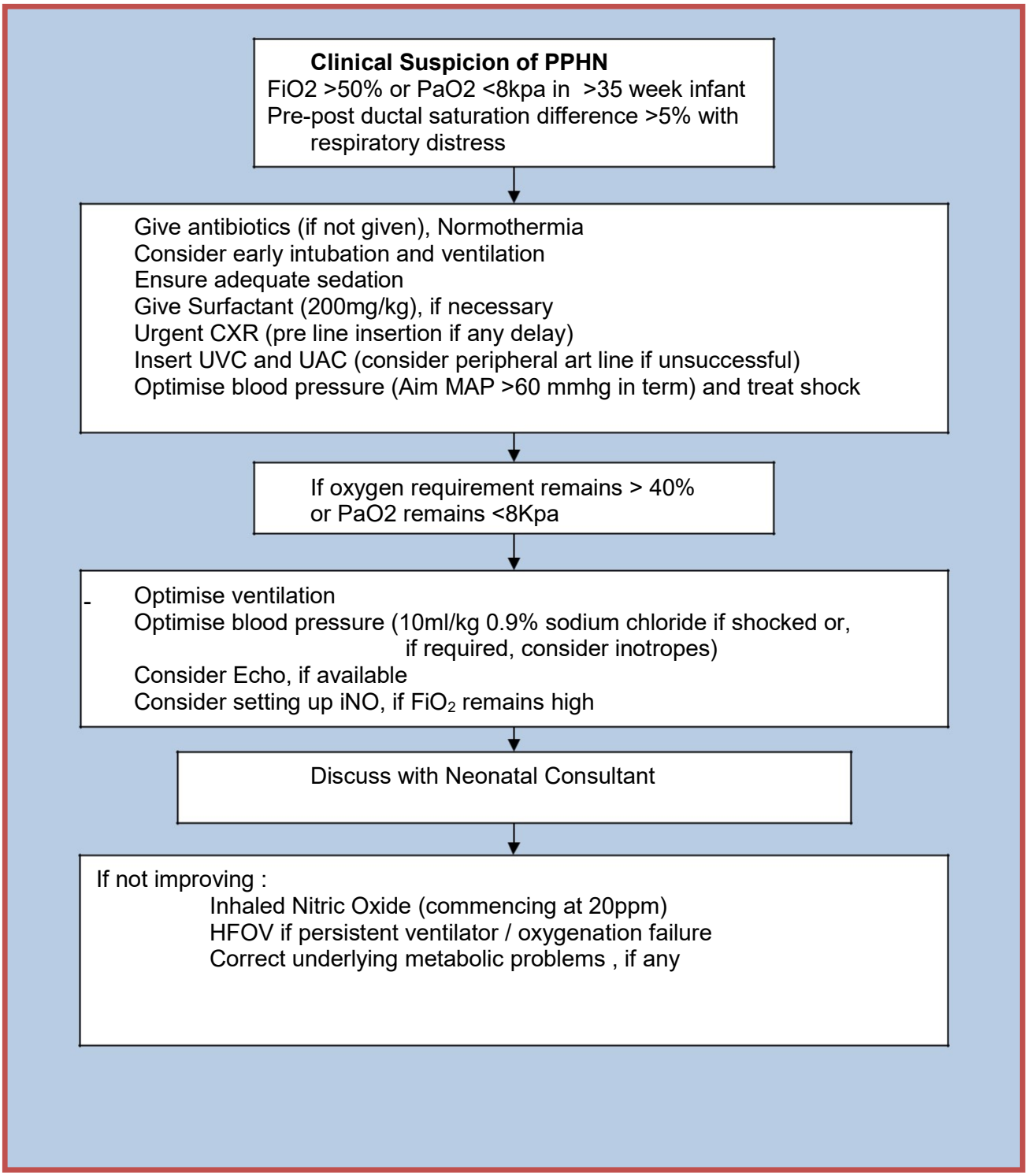
The decision to refer for ECMO should always involve the consultant on-call.
6 national paediatric centres offer ECMO in the UK: GOSH (London), Glenfield (Leicester), York hill (Glasgow), Freeman (Newcastle), Alder Hey (Liverpool), Birmingham Children's Hospital.
Our referral centre is GOSH but referrals are made via CATS: 0800 0850003

Criteria for referral:
- Failure to respond to maximal conventional treatment
- Reversible disease
- < 14 days of high pressure ventilation
- Weight > 2Kg
- >34 weeks gestation
- Oxygenation Index >25
- No CI to systemic anticoagulation (such as IVH)
- No lethal congenital abnormalities
- No irreversible organ dysfunction
- No major immunodeficiency

For full referral details, information required, survival to discharge and risk figures, see the CATS ECMO Clinical guideline:

http://site.cats.nhs.uk/wp-content/uploads/guideline-ecmo.pdf

Summary


Clinical Suspicion of PPHN
FiO2 >50% or PaO2 <8kpa in >35 week infant
Pre-post ductal saturation difference >5% with respiratory distress
Give antibiotics (if not given), Normothermia
Consider early intubation and ventilation
Ensure adequate sedation
Give Surfactant (200mg/kg), if necessary
Urgent CXR (pre line insertion if any delay)
Insert UVC and UAC (consider peripheral art line if unsuccessful)
Optimise blood pressure (Aim MAP >60 mmhg in term) and treat shock
If oxygen requirement remains > 40%
or PaO2 remains <8Kpa
Optimise ventilation
Optimise blood pressure (10ml/kg 0.9% sodium chloride if shocked or, if required, consider inotropes)
Consider Echo, if available
Consider setting up iNO, if FiO2 remains high
Discuss with Neonatal Consultant
If not improving :
Inhaled Nitric Oxide (commencing at 20ppm)
HFOV if persistent ventilator / oxygenation failure
Correct underlying metabolic problems , if any

References:

1. CATS PPHN Clinical Guideline – January 2020

2. CATS Extracorporeal Membrane Oxygenation (ECMO) Referrals Clinical Guideline – January 2020

3. Patwardhan K. Inotropes in neonates. Infant 2009; 5(1): 12-17

4. Qasim A, Jain SK. Milrinone Use in Persistent Pulmonary Hypertension of the Newborn. Neoreviews. 2020;21(3):e165-e178. doi:10.1542/neo.21-3-e165

5. Kelly LE, Ohlsson A, Shah PS. Sildenafil for pulmonary hypertension in neonates. Cochrane Database of Systematic Reviews 2017, Issue 8. Art. No.: CD005494. DOI: 10.1002/14651858.CD005494.pub4

6. Ho JJ, Rasa G. Magnesium sulfate for persistent pulmonary hypertension of the newborn. Cochrane Database of Systematic Reviews 2007, Issue 3. Art. No.: CD005588. DOI: 10.1002/14651858.CD005588.pub2

7. Keszler M, Lakshminrusimha S. Persistent Pulmonary Hypertension of the Newborn: NeoReviews Dec 2015, 16 (12) e680-e692; DOI: 10.1542/neo.16-12-e680

8. Nair J, Lakshminrusimha S. Update on PPHN: mechanisms and treatment. Semin Perinatol. 2014;38(2):78-91. doi:10.1053/j.semperi.2013.11.004

9. Storme L, Aubry E, Rakza T, Houeijeh A, Debarge V, Tourneux P, et al. Pathophysiology of persistent pulmonary hypertension of the newborn: impact of the perinatal environment. Arch Cardiovasc Dis. 2013;106:169–77

10. Kinsella JP, Abman SH. High-frequency oscillatory ventilation augments the response to inhaled nitric oxide in persistent pulmonary hypertension of the newborn: Nitric Oxide Study Group. Chest. 1998;114:100S.

11. Adel Mohamed, Nehad Nasef, Vibhuti Shah, Patrick J. McNamara. Vasopressin as a Rescue Therapy for Refractory Pulmonary Hypertension in Neonates. Retrospective Case Series: Pediatr Crit Care Med. 2014;15(2):148-154

12. Sick kids Neonatal Formulary 2015 ; Lexicomp Pediatric & Neonatal Dosage Handbook 25th Edition

Appendix : Echocardiographic assessment of Pulmonary Hypertension:

1. Tricuspid regurgitation:

- Right Ventricular pressure can be calculated from TR jet (4 X V^2 + estimated right atrial pressure)
- Ensure the Doppler envelope is complete
- Interpret in the context of systemic BP

2. Atrial shunting and other shunts:

- Some degree of right-to-left atrial shunting through the patent foramen ovale is common, although it is rare for this to be purely right-to-left (Pure right-to-left flow indicates total anomalous pulmonary venous connection (TAPVC) until proved otherwise).
- Bowing of the interatrial septum to the left is commonly seen.
- Right-to-left atrial shunting reflects right atrial filling (diastolic) pressure
- If a VSD is present, bidirectional shunting may be noted.

3. Ductal flow:

The direction and velocity of ductal blood flow can gives useful information on PAP.

- Pure right-to-left flow indicates Pulmonary arterial pressure is higher than the aortic pressure throughout the cardiac cycle.
- Bidirectional flow occurs when the aortic and pulmonary arterial pressures are approximately equal. Flow is left-to-right during diastole and right-to –left, in systole (as the pulmonary arterial pressure wave reaches the duct before the aortic pressure wave).

- Bidirectional flow is common in healthy babies in the first 12 hours but changes to pure left-to-right when aortic pressures become higher than pulmonary pressures.

4. Cardiac function

- There may be enlargement of Right atrium, Right ventricle and main pulmonary artery.
- There may be flattening (RV: LV pressure >0.5) and or even bowing (RV: LV pressure ≥1.0) of interventricular septum to the left as RV pressure rises.
- Quantitative assessment of cardiac function may assist with decisions and assessments of the roles of inotropes and inhaled nitric oxide.
- If the LA and LV appear under-filled, it is critical to exclude TAPVD. Demonstration of left to right shunt at atrial level essentially excludes TAPVD.

7. Guideline Governance

a. Scope

This guideline is relevant to all staff caring for babies across neonatal intensive care, transitional care and maternity.

b. Purpose

This guidelines aims to facilitate a common approach to the management of babies admitted under neonatal care. At times deviation from the guideline may be necessary, this should be documented and is the responsibility of the attending consultant.

This guideline is subject to regular review to ensure ongoing evidence based practice.

c. Duties and responsibilities

All healthcare professionals responsible for the care of neonates should be aware of practice according to this guideline.

d. Approval and Ratification

This guideline will be approved and ratified by the Neonatal Guidelines Group.

e. Dissemination and Implementation

i. This guideline will be uploaded to the trust intranet 'Neonatal Guidelines' page and thus available for common use.
ii. This guideline will be shared as part of ongoing education within the Neonatal Unit for both medical and nursing staff.
iii. All members of staff are invited to attend and give comments on the guideline as part of the ratification process.

f. Review and Revision Arrangements

i. This policy will be reviewed on a 3 yearly basis.
ii. If new information comes to light prior to the review date, an earlier review will be prompted.
iii. Amendments to the document shall be clearly marked on the document control sheet and the updated version uploaded to the intranet. Minor amendments will be ratified through the Neonatal

Guidelines Group. A minor amendment would consist of no major change in process, and includes but is not limited to, amendments to documents within the appendices.

g. Monitoring compliance with this Policy

Measurable Policy Objective	Monitoring/ Audit method	Frequency of monitoring	Responsibility for performing the monitoring	Monitoring reported to which groups/ committees, inc responsibility for reviewing action plans
e.g. All policies will be reviewed by their authors at least annually to ensure that they remain valid and in date	Compliance audit of sample of policies (including Review History)	Annual	Associate Director of Quality	Management Executive

APPENDIX 1: EQUALITY IMPACT ASSESSMENT

Equality Impact Assessment Summary

Name and title: Management of PPHN in the Newborn

Background • Who was involved in the Equality Impact Assessment
Neonatal guidelines group
Methodology • A brief account of how the likely effects of the policy was assessed (to include race and ethnic origin, disability, gender, culture, religion or belief, sexual orientation, age) • The data sources and any other information used • The consultation that was carried out (who, why and how?)
All groups of staff and patients were taken into account
Key Findings • Describe the results of the assessment • Identify if there is adverse or a potentially adverse impacts for any equalities groups
No evidence of discrimination
Conclusion • Provide a summary of the overall conclusions
No evidence of discrimination to any group
Recommendations • State recommended changes to the proposed policy as a result of the impact assessment • Where it has not been possible to amend the policy, provide the detail of any actions that have been identified • Describe the plans for reviewing the assessment
Guideline appropriate for use

APPENDIX 2: CHECKLIST FOR THE REVIEW AND APPROVAL OF DOCUMENTS

To be completed (electronically) and attached to any document which guides practice when submitted to the appropriate committee for approval or ratification.

Title of the document: PPHN Guidelines
Policy (document) Author: Dr R Kulappura
Executive Director:

		Yes/No/ Unsure/ NA	Comments
1.	**Title**		
	Is the title clear and unambiguous?	**Y**	
	Is it clear whether the document is a guideline, policy, protocol or standard?	**Y**	
2.	**Scope/Purpose**	**Y**	
	Is the target population clear and unambiguous?	**Y**	
	Is the purpose of the document clear?	**Y**	
	Are the intended outcomes described?	**Y**	
	Are the statements clear and unambiguous?	**Y**	
3.	**Development Process**		
	Is there evidence of engagement with stakeholders and users?	**Y**	
	Who was engaged in a review of the document (list committees/ individuals)?	**Y**	Neonatal guidelines group (MDT)
	Has the policy template been followed (i.e. is the format correct)?	**Y**	
4.	**Evidence Base**		
	Is the type of evidence to support the document identified explicitly?	**Y**	
	Are local/organisational supporting documents referenced?	**Y**	
5.	**Approval**		
	Does the document identify which committee/group will approve/ratify it?	**Y**	
	If appropriate, have the joint human resources/staff side committee (or equivalent) approved the document?	**Na**	
6.	**Dissemination and Implementation**		
	Is there an outline/plan to identify how this will be done?	**Y**	
	Does the plan include the necessary training/support to ensure compliance?	**Y**	
7.	**Process for Monitoring Compliance**		

		Yes/No/ Unsure/ NA	Comments
	Are there measurable standards or KPIs to support monitoring compliance of the document?	**N**	
8.	**Review Date**		
	Is the review date identified and is this acceptable?	**Y**	
9.	**Overall Responsibility for the Document**		
	Is it clear who will be responsible for coordinating the dissemination, implementation and review of the documentation?	**Y**	
10.	**Equality Impact Assessment (EIA)**		
	Has a suitable EIA been completed?	Y	

Committee Approval (Neonatal Guidelines Committee)			
If the committee is happy to approve this document, please complete the section below, date it and return it to the Policy (document) Owner			
Name of Chair	**Dr M. S. Edwards**	**Date**	**17/2/21**
Ratification by Management Executive (if appropriate)			
If the Management Executive is happy to ratify this document, please complete the date of ratification below and advise the Policy (document) Owner			
Date: n/a			