THAMES VALLEY & WESSEX NEONATAL OPERATIONAL DELIVERY NETWORK

THAMES VALLEY & WESSEX GUIDELINE FOR PATENT DUCTUS ARTERIOSUS (PDA) IN PRETERM INFANTS	
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Related documents and references	**Thames Valley and Wessex Neonatal Network Cardiac Care Pathway** https://neonatalnetworkssoutheast.nhs.uk/professionals/guidelines/tvw-guidelines/cardiac-care-pathway/ **Thames Valley and Wessex Neonatal Network Patent Ductus Arteriosus Ligation Referral Pathway (Appendix 2)** **References:** 1. Mitra S, de Boode WP, Weisz DE, Shah PS. Interventions for patent ductus arteriosus (PDA) in preterm infants: an overview of Cochrane Systematic Reviews Cochrane Database Syst Rev. 2023 Apr 11;4(4):CD013588 2. Jasani B, Mitra S, Shah PS. Paracetamol (acetaminophen) for patent ductus arteriosus in preterm or low birth weight infants. Cochrane Database Syst Rev. 2022 Dec 15;12:CD010061. Review. 3. Kluckow M, Jeffery M, Gill A, Evans N. A randomised placebo-controlled trial of early treatment of the Patent Ductus Arteriosus. Arch Dis Child Fetal Neonatal Ed. 2014 Mar; 99(2): F99-F104. 4. Rozé JC et al. Effect of Early Targeted Treatment of Ductus Arteriosus with Ibuprofen on Survival Without Cerebral Palsy at 2 Years in Infants with Extreme Prematurity: A Randomized Clinical Trial. J Pediatr. 2021 Jun;233: 33-42. 5. Schindler T, Smyth J, Bolisetty S, Michalowski J, Mallitt KA, Singla A, Lui K. Early PARacetamol (EPAR) Trial: A Randomized Controlled Trial of Early Paracetamol to Promote Closure of the Ductus Arteriosus in Preterm Infants. Neonatology. 2021;118(3):274-281.

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Implications of race, equality & other diversity duties for this document	**This guideline must be implemented fairly and without prejudice whether on the grounds of race, gender, sexual orientation or religion.**

Thames Valley Guideline for Patent Ductus Arteriosus (PDA) in Preterm Infants		
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1.0 Aim of Guideline

A guideline framework to support clinicians in the management of Patent Ductus Arteriosus (PDA) in neonates within neonatal services within TV & Wessex Neonatal ODN. Medical management is only indicated in the presence of one or more definite clinical symptoms **and** ECHO evidence of haemodynamically significant PDA.

2.0 Scope of Guideline

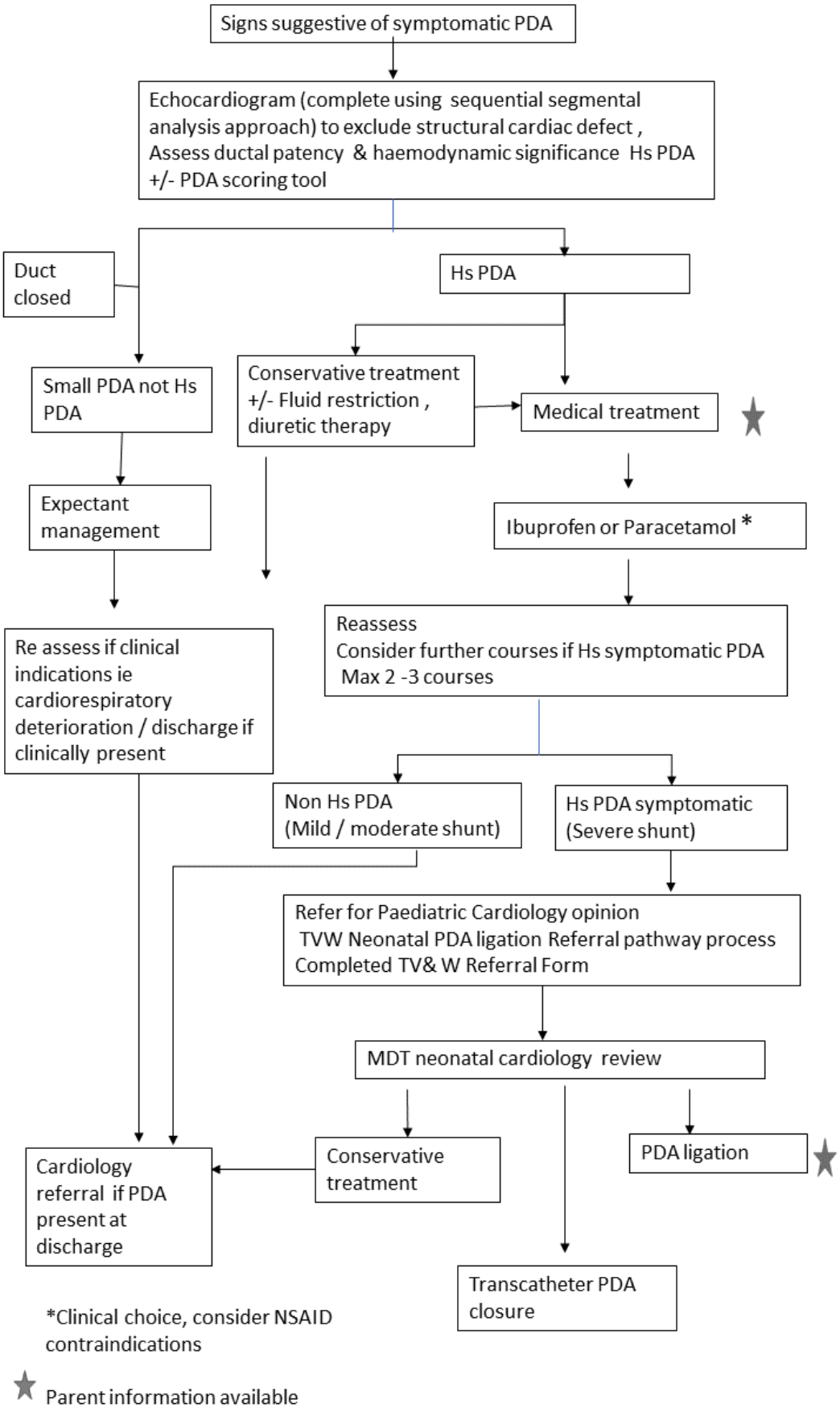
This guideline applies to all neonatal Units within the TV & Wessex Neonatal ODN. This includes the following hospitals.

Thames Valley		
TRUST	**Hospital**	**Designation**
Oxford University Hospitals NHS Foundation Trust	- John Radcliffe Hospital, Oxford	NICU
Buckinghamshire Healthcare NHS Trust	- Stoke Mandeville Hospital, Aylesbury	LNU
Frimley Health NHS Foundation Trust	- Wexham Park Hospital, Slough	LNU
Milton Keynes University Hospital NHS Foundation Trust	- Milton Keynes General Hospital	LNU
Royal Berkshire NHS Foundation Trust	- Reading	LNU

Wessex		
TRUST	**Hospital**	**Designation**
University Hospital Southampton NHS Foundation Trust	- Princess Anne Hospital	NICU
Portsmouth Hospitals University NHS Trust	- Queen Alexandra Hospital	NICU
University Hospitals Dorset NHS Foundation Trust	- Poole Hospital	LNU
Salisbury NHS Foundation Trust	- Salisbury District Hospital	LNU
Hampshire Hospitals NHS Foundation Trust	- Basingstoke and North Hampshire Hospital	SCU (Temporary designation)
Hampshire Hospitals NHS Foundation Trust	- Royal Hampshire County Hospital, Winchester	SCU (Temporary designation)
Dorset County Hospital NHS Foundation Trust	- Dorset County Hospital, Dorchester	SCU
Isle of Wight NHS Trust	- St Mary's Hospital	SCU
University Hospitals Sussex NHS Foundation Trust	- St Richard's Hospital, Chichester	SCU

3.0 Guideline

Summary PDA Management Flow Chart



Background, treatment options and definition of 'symptomatic' treatment

There is a wide variation in the rate of spontaneous ductal closure in preterm babies. A persistently patent duct with a large ductal shunt can lead to increased pulmonary perfusion, as well as decreased systemic blood flow (and/or end-organ perfusion); and has been associated with increased mortality and numerous preterm morbidities (fluctuations in BP and resultant IVH, pulmonary haemorrhage, ventilator dependence, CLD and NEC).

Pharmacologic treatment with COX-inhibitors, cyclo-oxygenase inhibitors (ie indomethacin, ibuprofen) and paracetamol) can be prophylactic, 'pre-symptomatic' (before the evolution of symptoms of ductal shunt) or 'symptomatic' (treatment is delayed until the presence of clinical symptoms). Prophylactic treatment with indomethacin or ibuprofen hasn't been associated with increased survival or better long-term outcome. There is not enough evidence at present to recommend prophylactic paracetamol administration. Recent results from RCTs comparing echo screening and early pharmacologic treatment in asymptomatic babies versus delaying treatment until well-defined clinical symptoms of high-volume ductal shunt were met demonstrated no benefit (or very little benefit (TRIOCAPI)) of echo screening.

In view of these results, routine echo screening and pharmacologic treatment in preterm infants without clinical symptoms are not indicated. Preterm and IUGR infants below 32 weeks with clinical symptoms (as below) should undergo diagnostic echocardiography and receive treatment if needed. Scoring systems for clinical symptoms and echo findings of haemodynamic significance have been introduced recently to aid decision-making. An example is shown in Appendix 1.

Clinical symptoms suggestive of high-volume ductal shunt:

Pulmonary symptoms suggestive of high-volume ductal shunt **in ventilated babies**	• persistent ventilator dependence
	• deteriorating respiratory status without other obvious explanation
	  ○ infants ≥ 27^{+0} weeks gestational age: FiO_2 > 40%, Mean airway Pressure > 12 cmH_2O
	  ○ infants ≤ 26^{+6} weeks gestational age: FiO_2 > 30%, Mean airway Pressure > 10 cmH_2O
	• pulmonary haemorrhage
	• radiological features of pulmonary oedema

Pulmonary symptoms suggestive of high-volume ductal shunt in babies **on nasal high-flow therapy or nCPAP**	• increasing FiO_2 requirement (especially with radiological features of pulmonary oedema) • increasing work of breathing without other explanation
Symptoms of **ductal steal from systemic circulation**	• hypotension without any other aetiology • unable to wean from inotropes • persistent metabolic acidosis

Table 1. Symptoms of high-volume ductal shunt

Echo features of haemodynamic significance. Initial assessment should include establishment of normal structure (complete sequential segmental analysis). If baby doesn't tolerate study, please measure PDA size, flow pattern, LA:Ao, LPA end-diastolic flow velocity and flow pattern in descending aorta.

Feature	Small shunt	Moderate shunt	Large shunt
Size of PDA			
• Diameter	< 1.5 mm	1.5 mm – 2 mm	> 2 mm
• PDA:LPA ratio	< 0.5	0.5 – 1	> 1
• Diameter to weight	< 1.4 mm/kg		>1.4 mm/kg
Flow through PDA			
• Vmax	> 2 m/s	1.5 – 2.0	< 1.5
• Vmax : Vmin	< 2	2 – 4	> 4
Pulmonary overcirculation **(Choose one parameter for each category)**			
• **Left-sided overload**			
○ LA/Ao	< 1.5	1.5 – 2.0	> 2.0
○ LVEDD			
• **Pressure increase in LA**			
○ Mitral wave E:A	< 1	1	> 1
○ IVRT (TDI or PW)	> 40 ms	30 – 40 ms	< 30 ms
• **Pulmonary overflow**			
○ LPA end-diastolic flow velocity	< 0.2 m/s	0.2 – 0.5 m/s	> 0.5 m/s
○ Pulmonary vein d wave velocity	< 0.3 m/s	0.3 – 0.5 m/s	> 0.5 m/s
○ LVO	< 200 ml/kg/min	200 – 300 ml/kg/min	> 300 ml/kg/min
Systemic blood flow / End-organ perfusion			
• Desc Ao diastolic flow	Forward	Absent	Reversed
• Sup Mes or Celiac art diastolic flow	Forward	Forward	Absent/Reversed
• Mid Cerebral art diastolic flow	Forward	Absent	Reversed
LPA Left pulmonary artery, LA Left atrium, Ao aortic root, LVEDD left ventricular end-diastolic diameter, LA left atrium, E early diastolic flow, A atrial contraction flow, IVRT isovolumic relaxation time, LVO left ventricular output, TDI Tissue			

Table 2. Echo assessment of haemodynamic significance. Adapted from Van Laere et al., 2018.

Conservative management:

Fluid restriction Consider fluid restriction (not below 120 ml/kg/day) and diuretic therapy. Chlorothiazide and spironolactone are preferred over furosemide if enteral intake is more than 50% of total intake. Once full enteral feeding has been established, fluid intake can be increased in order to reach adequate energy and protein intake with the concurrent administration of diuretics.
PEEP Consider increasing PEEP by 1-2 cm H2O if ventilated or on nCPAP. No data on nHFT.
Correct anaemia Keep Hb > 12 g/L in ventilated preterm infants with significant PDA. Transfuse with co-administration of diuretics ie Furosemide

Pharmacological treatment:

Pharmacological treatment is only indicated in babies with PDA-related clinical symptoms and echo-confirmed haemodynamically significant PDA. Use of COX-inhibitor in asymptomatic babies is not indicated, unless very significant echo findings. Scoring systems for clinical and echo findings can aid decision-making. An example is shown in Appendix 1.

Ibuprofen or Paracetamol

Recent meta-analyses suggest that the efficacy of Paracetamol and Ibuprofen is very similar, but Paracetamol has a more favourable side effect profile (less NEC, GI bleeding and renal impairment).

Most studies included very preterm babies (GA < 32 weeks) and there is a relative paucity of data regarding the more preterm population (GA < 28 weeks). Well-designed studies in babies GA < 28 weeks are pending. It is difficult to make firm recommendation at present which drug should be used as routine first-line.
High-dose Ibuprofen (beyond day 7) has been reported to be more effective than standard dose. Oral administration is more effective for both drugs.

Use **standard dose Ibuprofen** 3 day course: 10mg/kg/OD on day 1 followed by 5mg/kg/OD on days 2 and 3 at 24 hourly intervals **or Paracetamol** (15 mg/kg, QDS, for 3 days) as routine pharmacological treatment.

Use **oral preparations** (rather than IV) if baby is receiving >100 ml/kg enteral feeds; the use of oral preparations can be considered with smaller enteral volumes (senior clinician choice) Re-assess the ductus arteriosus and ductal shunt after 3 days;

A second course or course extension to 6 days of **high dose Ibuprofen** (3 day course: 10mg/kg/OD on day 1 followed by 5mg/kg/OD on days 2 and 3) or **same dose Paracetamol** can be considered, if necessary. A third course of the alternate drug might be considered, but literature data about the efficacy of a third course is scarce.

Contraindications
Ibuprofen Life-threatening infection; active bleeding; thrombocytopenia (platelets <50); coagulation defects; significant renal impairment; known/suspected NEC; pulmonary hypertension; duct-dependent circulation, recent IVH (within 24 hours).
Side effects GI perforation (consider Ibuprofen carefully in IUGR and after hydrocortisone administration due to pressor-resistant hypotension); increased serum creatinine; hyponatraemia; oliguria; fluid retention; acute renal failure, platelet dysfunction and thrombocytopenia; neutropenia; haematuria; pulmonary haemorrhage; IVH; PVL. Less common: GI haemorrhage; hypoxaemia.
Monitor/Caution Watch for signs of bleeding; may mask symptoms of infection; monitor renal function. Ibuprofen may decrease clearance of aminoglycosides so strict surveillance of serum levels is recommended. In cases of oliguria or rising creatinine, doses of aminoglycosides should be held until levels are available. Ibuprofen interferes with bilirubin-albumin binding increasing unbound bilirubin and should not be used in infants with hyperbilirubinaemia approaching exchange transfusion levels.
Paracetamol Use Paracetamol if there are contraindications to Ibuprofen. Overdose can cause liver toxicity. Check liver function before each course and at least once during the course.

Ligation:
PDA ligation should not be the primary treatment of choice and should be preceded by pharmacological treatment where possible. Ligation is generally not recommended in the first 3 weeks of life. If multiple courses of medical treatment have failed to close or restrict a haemodynamically significant duct and echo assessment confirms a high-volume shunt in a symptomatic patient refer for a paediatric cardiology opinion. If respiratory problems are predominant consideration of steroids and diuretics should be given prior to PDA ligation.

Ligation is only indicated when a) the PDA echo score is high (haemodynamically significant duct on echo) and b) there is no other explanation for persistent clinical symptoms such as:

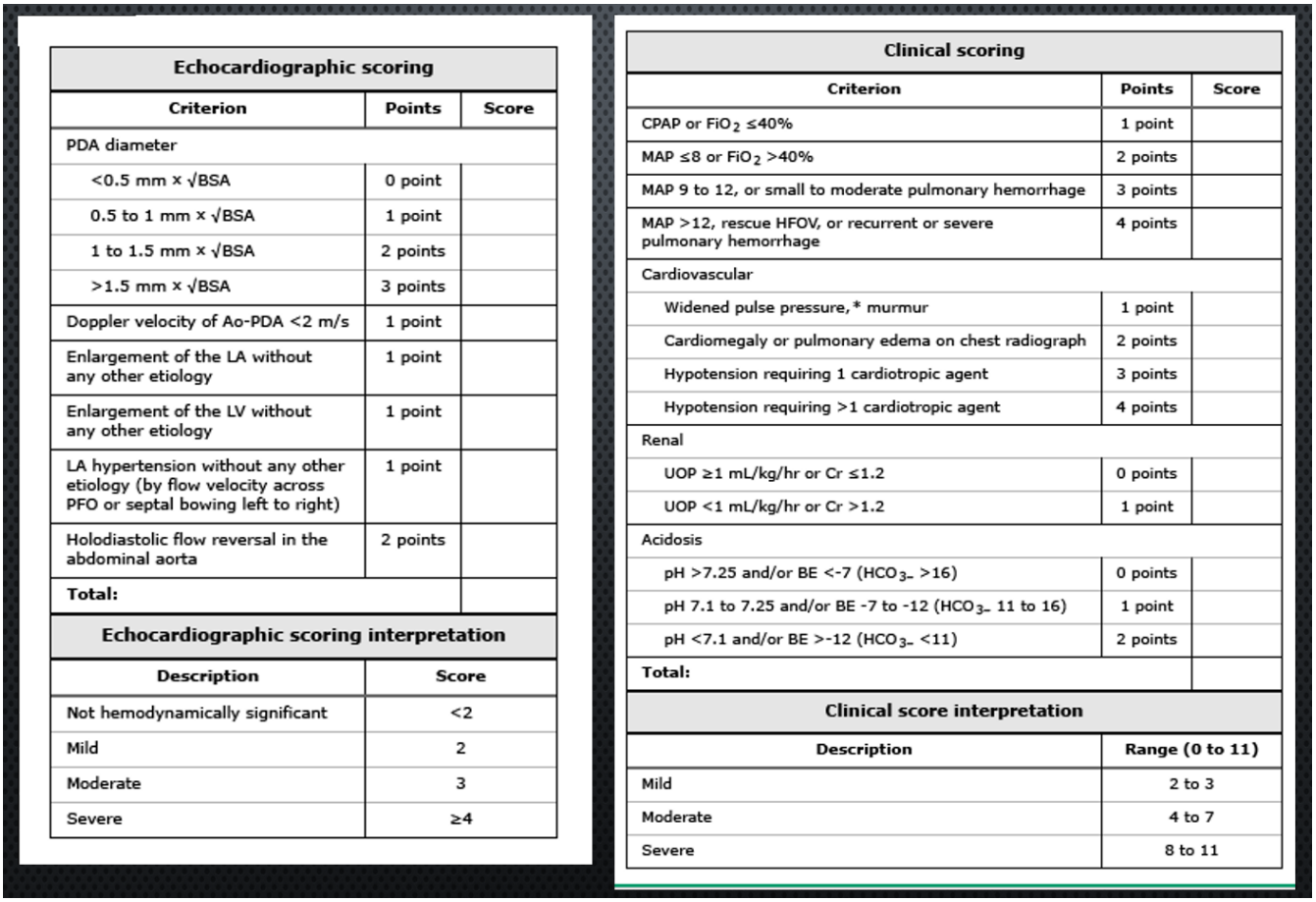
- Increasing ventilatory requirement over several days (FiO_2 > 40-50%, MAP >12-13 cmH_2O) with signs of pulmonary hyperaemia on the CXR or ventilator dependence and unable to extubate.
- Hypotension requiring inotropic support.
- Oliguria/renal failure.

Transcatheter PDA closure

Although transcatheter closure of PDA is common practice in older infants and children, it is still a relatively new approach in preterm infants. In this method, a device is used to plug the PDA via a transcatheter approach through the femoral vein. The data although limited is encouraging. However more studies are needed for analysing long term and short-term outcomes compared to surgical ligation.

In selected cases of preterm infants of reasonable size (body weight approximately 2 kg and more), this option for PDA closure could be considered with the cardiology team. This should include a clear plan around transport to the theatres, temperature management and support in the theatre and the logistics of the post-operative recovery period.

Appendix 1. Echocardiographic and clinical scoring (adapted from Brigham's Neonatal Unit, Boston, MA guideline)



Echocardiographic scoring

Criterion	Points	Score
PDA diameter		
<0.5 mm × √BSA	0 point	
0.5 to 1 mm × √BSA	1 point	
1 to 1.5 mm × √BSA	2 points	
>1.5 mm × √BSA	3 points	
Doppler velocity of Ao-PDA <2 m/s	1 point	
Enlargement of the LA without any other etiology	1 point	
Enlargement of the LV without any other etiology	1 point	
LA hypertension without any other etiology (by flow velocity across PFO or septal bowing left to right)	1 point	
Holodiastolic flow reversal in the abdominal aorta	2 points	
Total:		

Echocardiographic scoring interpretation

Description	Score
Not hemodynamically significant	<2
Mild	2
Moderate	3
Severe	≥4

Clinical scoring

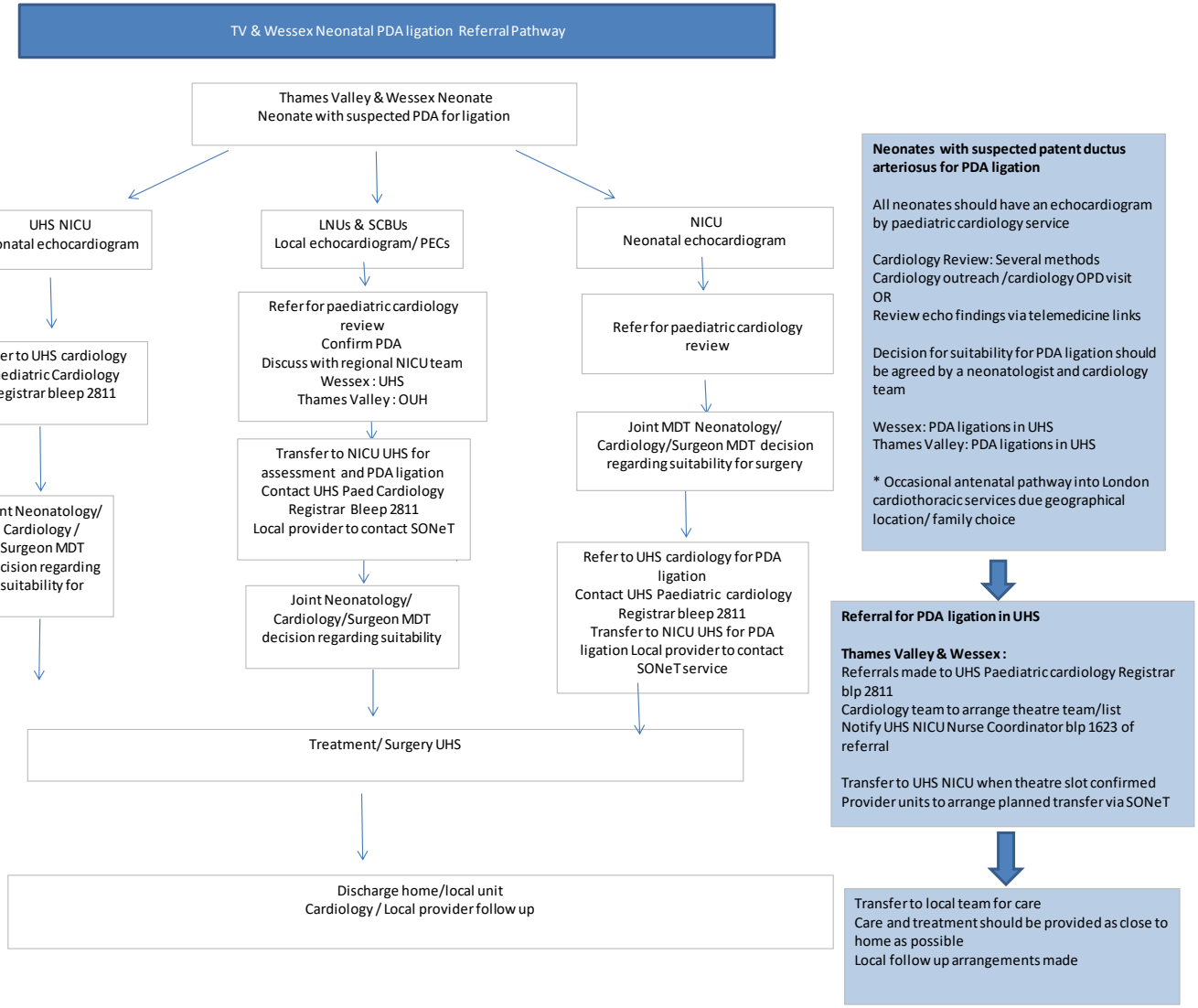
Criterion	Points	Score
CPAP or FiO_2 ≤40%	1 point	
MAP ≤8 or FiO_2 >40%	2 points	
MAP 9 to 12, or small to moderate pulmonary hemorrhage	3 points	
MAP >12, rescue HFOV, or recurrent or severe pulmonary hemorrhage	4 points	
Cardiovascular		
Widened pulse pressure,* murmur	1 point	
Cardiomegaly or pulmonary edema on chest radiograph	2 points	
Hypotension requiring 1 cardiotropic agent	3 points	
Hypotension requiring >1 cardiotropic agent	4 points	
Renal		
UOP ≥1 mL/kg/hr or Cr ≤1.2	0 points	
UOP <1 mL/kg/hr or Cr >1.2	1 point	
Acidosis		
pH >7.25 and/or BE <-7 (HCO_{3-} >16)	0 points	
pH 7.1 to 7.25 and/or BE -7 to -12 (HCO_{3-} 11 to 16)	1 point	
pH <7.1 and/or BE >-12 (HCO_{3-} <11)	2 points	
Total:		

Clinical score interpretation

Description	Range (0 to 11)
Mild	2 to 3
Moderate	4 to 7
Severe	8 to 11

Please click on the link below to calculate the PDA score on the adapted PDA SCAMP tool
https://neogrow.shinyapps.io/pdascamp/

Appendix 2: PDA Ligation Referral Pathway (from TVW Neonatal ODN Cardiac Care Pathway v1.3)



** No Network Neonatal NICU or PICU bed available UHS SONeT / local team to arrange referral & transfer out of network
PECs : Paediatrician with Expertise in Cardiology

Appendix 3:
PDA Ligation Referral Pathway – Guidance Notes

TVW PDA Ligation Referral Pathway Nc

Appendix 4:
PDA Ligation Referral Form

TVW Neonatal PDA Ligation Referral Fo

Appendix 5:
PDA Parent Information Leaflet

PDA PIL v1.3 updated.pdf

Appendix 6:
Paracetamol administration details, PDA closure, monitoring and further information

PARACETAMOL.pdf

Appendix 7:
Ibuprofen administration details, monitoring, further information and repeated course

IBUPROFEN.pdf

Version Control:

Version	Date	Details	Author(s)	Comments
Final v1	14 Sep '15	OUH Guideline for Thames Valley Network	Dr Zoltan Molnar	Approved by Neonatal Consultants and Paediatric Cardiologists
Version 2	23 Feb '16	TV Neonatal ODN Format	Dr Zoltan Molnar	Approved by TV&W Neonatal ODN Governance Group 28 April 2016 subject to agreed amendments
	May 2016	Amendments completed		
Version 3 3.1 4	January 2023 April 2023	TV & Wessex Guidance Update and revision of guidance	TV & W PDA working group (ZM, RB, HH, VP, HW)	
Version 5	Feb 2024	PDA Task and Finish group revision of guidance with UHS cardiology and Suzannah Hibberd (Pharmacy) . Circulated to TV& W Paed Cardiac Network	TV & W PDA working group as above and SH	Comments from TB, UHS Cardiology Lead T Richens Intervention Cardiac Lead AC , SA TV & W Paed Cardiac Network. Ratified March 2024
Review Date:	**March 2027**			