DOCUMENT CONTROL PAGE

Title	**Title**: Guidelines for the Management of Neonatal and Paediatric Hyperammonaemia **Version**: 2 **Reference Number**: PCCN7
Supersedes	**Supersedes**: Version 1 **Description of Amendment(s)**: Incorporation of Neonatal transport teams into pathway Bolus dose of arginine Increased compatibilities of metabolic drugs with infusions Changes to ammonia sampling information
Minor Amendment	**Date**: **Notified To**: **Date**: **Summary of amendments**:
Author	**Originated By**: Rachael Barber **Designation**: NWTS Consultant and Consultant Paediatric Intensivist, RMCH **Co-Authors**: (1) Adam Nicholls; (2) Suzie Emsden; (3) Sharryn Gardner; (4) Adam Sutherland; (5) Beth Jameson ; (6) Simon Jones **Designation**: (1) Paediatric SpR, RMCH (2) PICU Grid Trainee, Alder Hey (3) Emergency Medicine Consultant, Southport & Ormskirk Hospitals NHS Trust (4) Metabolic Pharmacist, RMCH (5) Consultant in Metabolic Medicine, RMCH(6) Consultant in Metabolic Medicine, RMCH **Contributions to Version 2:** Co-Authors: Andrew Taylor (Paediatric Pharmacist, Alder Hey), Ian Dady (Consultant Neonatologist and Clinical Lead, GMNETS), Sarah McBride (Neonatal Pharmacist, St Mary's)
Ratification	**Ratified by:** 1. CMFT (Host Trust): - Paediatric Medicines Management Committee (MMC) on: 07/02/2018 - Divisional Children's Clinical Effectiveness Committee on: 01/03/2018 2. AHFT: - CDEG (Clinical Development & Evaluation Group) on: **TBC**
Application	Children only
Circulation	**Issue Date**: TBC **Circulated by**: Clinical Lead, North West & North Wales Paediatric Critical Care Network **Dissemination and Implementation**: NWTS & PCCN Network circulation lists
Review	**Review Date**: Feb 2021 **Responsibility of**: Clinical Lead, North West & North Wales Paediatric Transport Service (NWTS)

Date placed on the Intranet: **TBC**	**Please enter your EqIA Registration Number here**: **09/18**

1. Detail of Procedural Document

Guidelines for the Management of Neonatal and Paediatric Hyperammonaemia

2. Equality Impact Assessment

EqIA Registration Number: **09/18**

3. Consultation, Approval and Ratification Process

This guideline was developed with input from:
· North West and North Wales Paediatric Transport Service (NWTS).
· Representatives from the North West and North Wales Paediatric Critical Care Network (PCCN).
· Representatives from both Paediatric Intensive Care Units (Royal Manchester Children's Hospital and Alder Hey Children's Hospital).
· Representatives from the District General Hospitals within the PCCN.
Representatives from the North West Neonatal Network

These guidelines were circulated for comments as follows:

- Consultants from both Paediatric Intensive Care Units (Royal Manchester Children's Hospital and Alder Hey Children's Hospital), the Consultants from the North West and North Wales Paediatric Transport Service (NWTS), and the North West and North Wales Paediatric Critical Care Network - 14/7/2016
- North West Neonatal Operational Delivery Network - 19/4/17

All comments received have been reviewed and appropriate amendments incorporated.

For ratification process see appendix 1.

4. References and Bibliography

See guidelines.

5. Disclaimer

These clinical guidelines represent the views of the North West and North Wales Paediatric Critical Care Network and North West and North Wales Paediatric Transport Service, which were produced after careful consideration of available evidence in conjunction with clinical expertise and experience.

The guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient.

Clinical advice is always available from NWTS on a case by case basis. Please feel free to contact NWTS (01925 853 550) regarding these documents if there are any queries.

Guidelines for the Management of Neonatal and Paediatric Hyperammonaemia

Hyperammonaemia is a **medical emergency**. Prompt recognition, commencement of treatment and transfer of the child is vital for a good neurological outcome.

Symptomatic (Lethargy, coma, metabolic acidosis or alkalosis)

Measure ammonia
Investigate and treat for sepsis
Broad spectrum antibiotics and aciclovir
Treat ABC and check blood glucose

STOP FEEDS and start IV Fluids containing 10% Glucose

Ammonia >150 µmol/L

Urgent repeat sample
2nd IV access

Send FBC,U&E, LFT, clotting, lactate, glucose, acylcarnitines, urine organic acids, plasma amino acids, blood gas

If ammonia > 200 µmol/L escalate management without waiting for second sample

Ammonia >200µmol/L

Ammonia <200µmol/L

Contact NWTS – 08000 84 83 82 who will conference in metabolic consultant

Discuss with metabolic team & inform NWTS if clinically necessary

Commence infusions within 30 minutes **after** discussion with Metabolic consultant:
Sodium Phenylbutyrate, L-Arginine, Sodium Benzoate, L-Carnitine (for doses see page 6)

Contact anaesthetic team/NICU consultant

Intubate and ventilate

Give carglumic acid (NWTS carry this)

Repeat ammonia level to be sent pre-departure and telephone to accepting centre

NWTS team to transfer to PICU. Do NOT delay transfer. If NWTS unavailable, conference in Connect NW on 0300 330 9299 asap

Additional information available on BIMDG website www.bimdg.org.uk including drug calculator. Link available from NWTS website.

Guidelines for the Management of Neonatal and Paediatric Hyperammonaemia

Hyperammonaemia is a **medical emergency**. Prompt recognition, commencement of treatment and transfer of the child is vital for a good neurological outcome. Hyperammonaemia leads to direct neurological damage and outcome seems to be related to duration of hyperammonaemia and peak ammonia levels.

The goal of treatment should be to get the infant or neonate with raised ammonia >400µmol/L that is resistant to pharmacological treatment onto haemofiltration within **6 hours** of identification.

Symptoms and Signs of Hyperammonaemia

These can be subtle and varied. Suspect and check ammonia levels in the following:

Neonate	Child and adolescent
Vomiting Lethargy Poor feeding Encephalopathy Irritability Pulmonary haemorrhage Seizures Abnormal movements Temperature instability Low blood sugar Previous sudden death in family Unexplained metabolic acidosis Unexplained metabolic alkalosis	Vomiting Lethargy Encephalopathy Altered behaviour Signs of intoxication Previous sudden death in family Unexplained metabolic acidosis

Investigations

- **Send urgent ammonia. Samples can be analysed if received within 20 minutes and should ideally be sent on ice.** Ensure lab are aware that sample is being sent.
- NB. Samples analysed after 20 minutes or not on ice at room temperature will give a falsely elevated result. A normal result will therefore exclude hyperammonaemia.
- Samples for ammonia should be **free flowing venous samples** – capillary samples can give spuriously high results.
- **If ammonia >150µmol/L, repeat sample**
- **If ammonia >200µmol/L, repeat sample BUT DO NOT DELAY STARTING TREATMENT**
- **Second IV access.** Send bloods for FBC,U&E, LFT, clotting, lactate, glucose, acylcarnitines, plasma amino acids, blood gas
- Collect urine sample for organic acids including orotoic acid if possible (to be transferred with NWTS team to RMCH). Insertion of a urinary catheter will allow rapid collection of a sample in a critically ill patient.

Acute Management

- **Stop feeds and commence fluids containing 10% glucose. Ideally this should be 0.9% saline with 10% glucose or 0.45% saline with 10% glucose if this is unavailable.** This reduces the patient's nitrogen load and also prevents hypoglycaemia. Instructions on making intravenous fluids for metabolic patients available on BIMDG website. *http://www.bimdg.org.uk/store/guidelines/intravenous_fluidsrev4_864191_09092016.pdf*
- **Start broad spectrum antibiotics and aciclovir.** Sepsis and disseminated HSV can cause raised ammonia levels as can low cardiac output states.
- **Contact the NWTS team on 08000 848382. NWTS will conference in the metabolic consultant at RMCH. If NWTS transport team is unavailable NWTS should conference in the neonatal transfer team (Connect NW) on 0300 330 9299 as early as possible.**
- **Commence infusions as directed by metabolic team (Doses and infusions in appendix).** Metabolic infusions should be commenced within 30 minutes once agreed by the metabolic consultant on call. **Ammonia can rise precipitously in a decompensated metabolic disorder and delays of more than 30 minutes are not acceptable.** Transferring drugs from RMCH or Alder Hey has been found to add a considerable delay to commencement of these drugs. All hospitals must have small supplies of *intravenous* sodium phenylbutyrate, sodium benzoate, L-arginine (arginine hydrochloride) and L-carnitine.
- **Contact local anaesthetic team/neonatal team.** Patient will require intubation and ventilation for transfer. This is to reduce the metabolic demands on the baby and hence reduce ammonia production. Ensure endotracheal tube is well secured. Target normal saturations and CO_2.

Pre Transfer Management

- Transport team to administer **carglumic acid (Carbaglu®)** on arrival at referring hospital. This is not stocked by many DGHs so will be carried by the transport team. It is given as a single enteral dose.
- **Send a repeat ammonia sample pre-departure from DGH.** This result will determine the need for haemofiltration.

Transfer

- **Patient to be transferred to PICU at RMCH if at all possible for easier access to metabolic team**.
- If NWTS are unable to undertake the transfer, the neonatal team Connect NW should be contacted
- If neither transport team is available, the transfer should not be delayed and the local hospital will have to undertake the transfer as the priority is for the patient to receive definitive treatment (haemofiltration) within 6 hours of identification of hyperammonaemia.

References:

- British Inherited Metabolic Disease Group: Undiagnosed hyperammonaemia. Diagnosis and immediate management, 2008. www.bimdg.org.uk
- British Inherited Metabolic Disease Group: Medicines used for the treatment of hyperammonaemia, 2008
- Leonard JV, Morris AAM, Diagnosis and early management of inborn errors of metabolism presenting around the time of birth, Acta Paediatrica, 2006; 95: 6-14
- Saudubray J-M, Sedel F, Walter JH. Clinical Approach to treatable inborn metabolic diseases: An introduction. J Inherit Metab Dis, 2006; 29: 261-274
- Schutze GE, Edwards MS, Adham BL, Belmont JW. Hyperammonaemia and neonatal herpes simplex infection. Paediatr Infect Dis J, 1990; 9; 749-5

MEDICATIONS FOR METABOLIC DECOMPENSATION

For infusions in children over 10kg please see next page

Sodium Benzoate	Loading Dose:	**250mg/kg over 90minutes**
	Maintenance Dose:	**250mg/kg/day by continuous infusion**
PREPARATION:	**Use the 1g in 5ml preparation.**	**Dilute 2.5g (12.5ml) to 50ml with 10% glucose**
ADMINISTRATION:	Loading Dose:	**5ml/kg over 90minutes**
	Maintenance Dose:	**0.2ml/kg/hr**
Sodium Phenylbutyrate	Loading Dose:	**250mg/kg over 90minutes**
	Maintenance Dose:	**250mg/kg/day by continuous infusion**
PREPARATION:	**Use the 1g in 5ml preparation.**	**Dilute 2.5g (12.5ml) to 50ml with 10% glucose**
ADMINISTRATION:	Loading Dose:	**5ml/kg over 90minutes**
	Maintenance Dose:	**0.2ml/kg/hr**
L-Arginine	Loading Dose:	**150mg/kg over 90 minutes**
(in certain cases 300mg/kg may be required as per metabolic consultant advice)		
	Maintenance Dose:	**150-300mg/kg/day by continuous infusion**
PREPARATION:	Add 25ml arginine 10% pre-mixed solution to 25ml 10% dextrose to make 50mg/ml solution which is maximum concentration peripherally	
	Maintenance Dose:	**0.12-0.26ml/kg/hr**
Other solutions are available—if used check calculations carefully		
Carglumic Acid	**NWTS WILL BRING CARBAGLU® WITH THEM**	
	Loading Dose:	**250mg/kg as a single ENTERAL dose**
Mix 200 mg tablet in 2.5mL of water to give 80 mg/mL. Shake gently. Draw up appropriate volume and administer immediately down NGT. Flush NGT with additional water to clear.		
L-Carnitine	Usual dose:	**25mg/kg FOUR times a day**
Should not be used if suspected LCFA disorder—discuss with Metabolic consultant first		
PREPARATION:	**Dilute dose as required with 0.9% sodium chloride or glucose 10%**	
ADMINISTRATION:	**Give as a bolus over 2-3 minutes. Occasionally the metabolic team will request for this to be run as an infusion. The dose for this is on *www.bimdg.org.uk* website**	

Exact dose will vary with different metabolic disorders —and a final decision on doses will be made by the Metabolic consultant on call

Infusions can be administered PERIPHERALLY

Infusions are COMPATIBLE WITH EACH OTHER ON THE SAME LINE and with GLUCOSE and ELECTROLYTE-CONTAINING MAINTENANCE FLUIDS

CHILDREN OVER 10KG

Occasionally these drugs will be required in children >10kg. The doses are unchanged but for ease of administration, the following method of making up the infusions is advised.

Sodium Benzoate and Sodium phenylbutyrate

Add 12.5g of sodium benzoate and 12.5g of sodium phenylbutyrate to a SINGLE 500ml bag of 10% glucose.

Run at 6.67ml/kg/hr for first 90 minutes to give loading dose of 250mg/kg (10ml/kg) of both and then maintenance rate of 0.42ml/kg/hr

L-Arginine

As per infants under 10 kg

Advice to Pharmacy Departments:

- These medications are time critical.

NWTS recommends that ALL sites have access to the following products WITHIN **30 minutes** OF REQUEST:

1. Sodium benzoate 1g in 5ml ampoules (20 ampoules)
2. Sodium phenylbutyrate 1g in 5ml ampoules (20 ampoules)
3. L-Arginine 10% 200ml vials (2 vials). Other strengths are acceptable.
4. L-Carnitine 1g in 5ml ampoules (5 ampoules)

Advice to Transport Teams:

1. DGHs are not required to stock carglumic acid (Carbaglu®) but this can have a dramatic effect at reducing ammonia levels in some patients.
2. All transport teams should stock a small amount of carglumic acid so that when they reach the patient a dose can be given if advised by the metabolic team.

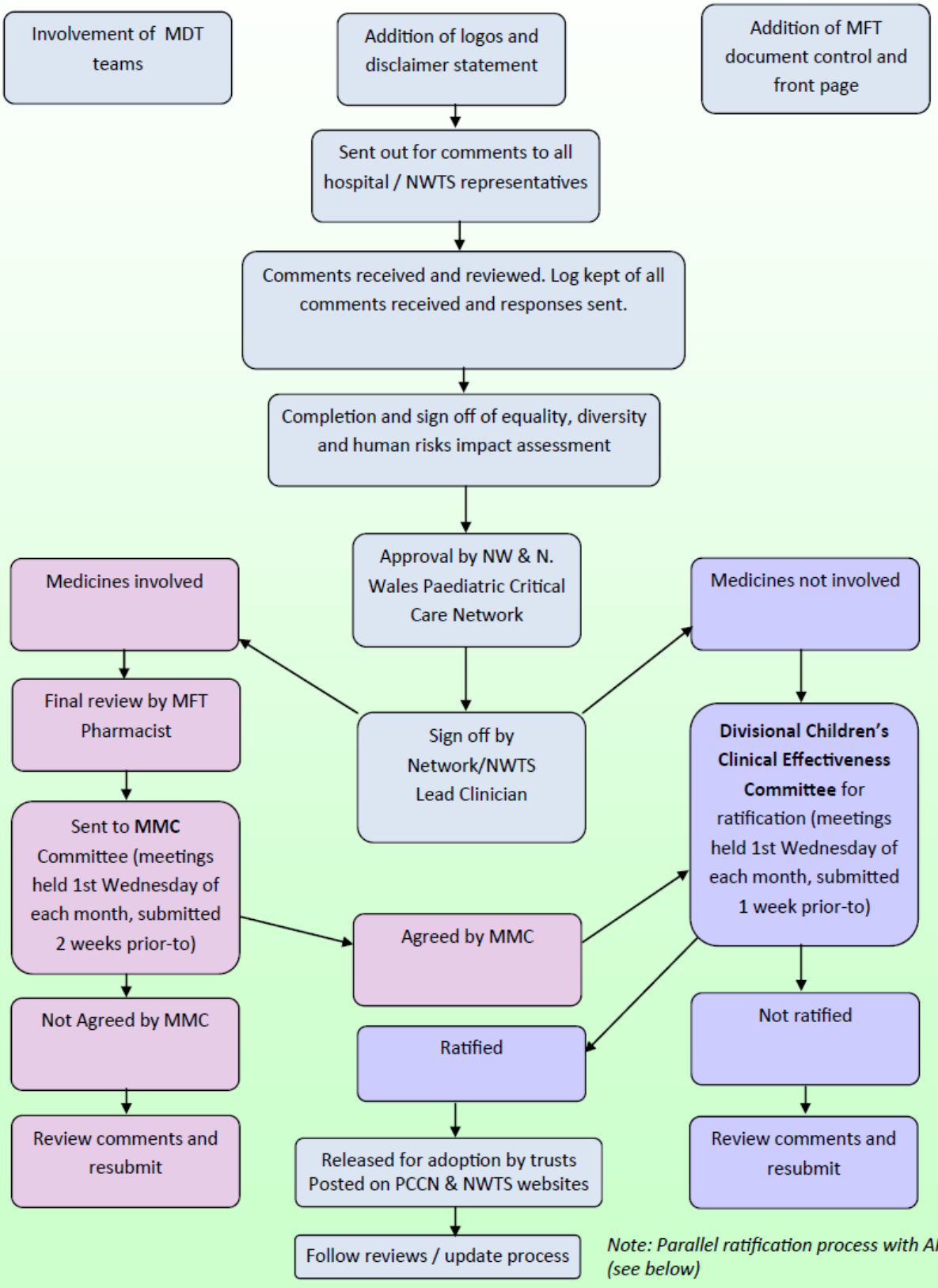
Appendix 1

Alder Hey Children's NHS Foundation Trust

North West & North Wales Paediatric Critical Care Network

Manchester University NHS Foundation Trust

Ratification of Guidelines with Host Organisation (MFT)



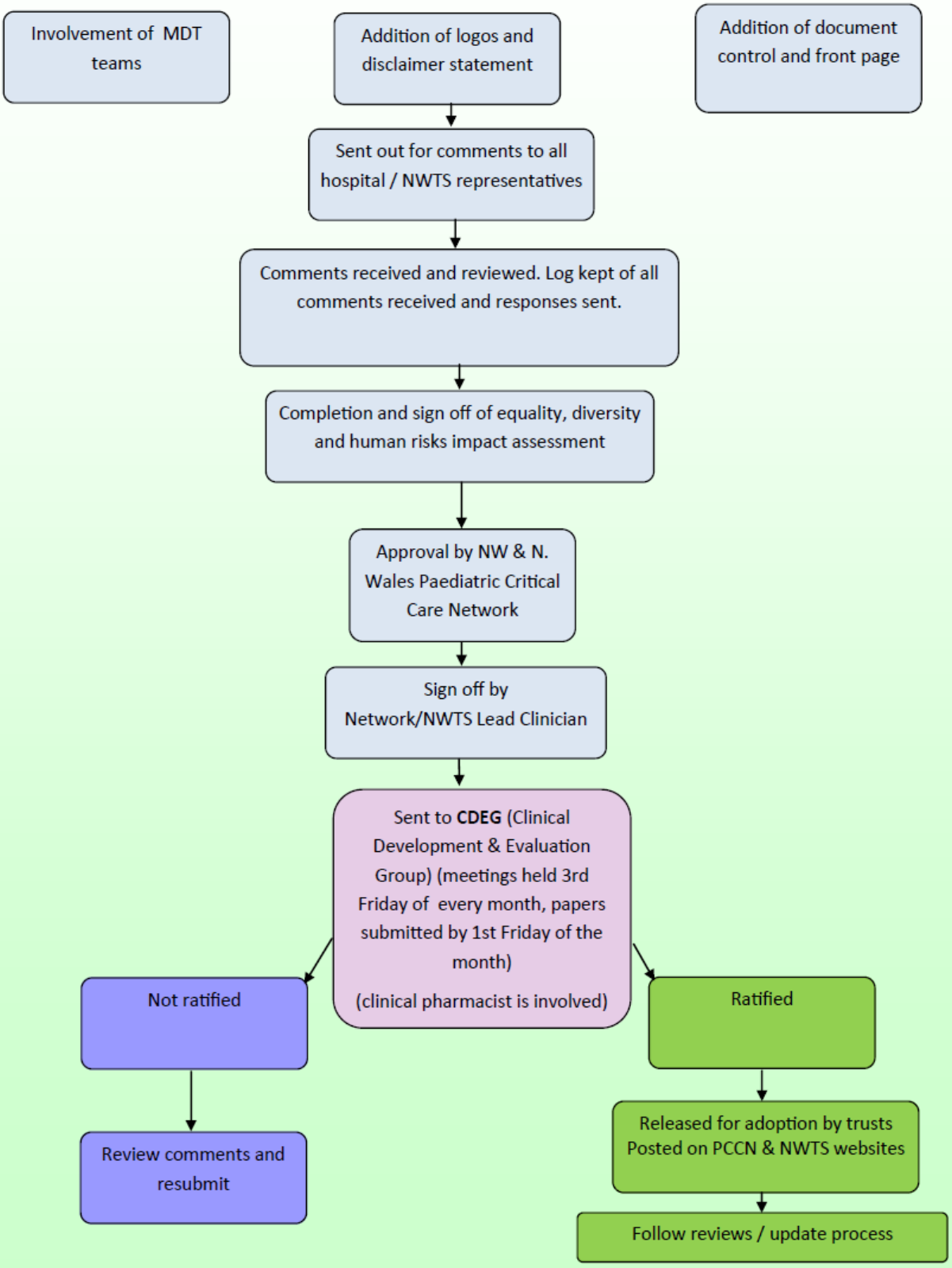
Appendix 1 continued

Alder Hey Children's NHS Foundation Trust

North West & North Wales Paediatric Critical Care Network

Manchester University NHS Foundation Trust

Ratification of Guidelines with Alder Hey



Resources

www.crashcall.net - for intubation drugs / sedation regime

Contact numbers:
Regional Paediatric Intensive Care Unit Alder Hey Childrens Hospital 0151 252 5241
Regional Paediatric Intensive Care Unit Royal Manchester Childrens Hospital 0161 701 8000
NWTS (North West & North Wales Paediatric Transport Service) 01925 853 550

Guideline authors:
Authors:
Rachael Barber, NWTS Consultant and Consultant Paediatric Intensivist , RMCH
Adam Nicholls, Paediatric SpR, RMCH
Suzie Emsden, PICU Grid Trainee, Alder Hey
Sharryn Gardner, Emergency Medicine Consultant, Southport & Ormskirk Hospitals NHS Trust
Adam Sutherland, Metabolic pharmacist, RMCH
Beth Jameson , Consultant in Metabolic Medicine, RMCH
Simon Jones, Consultant in Metabolic Medicine, RMCH

Consulted parties:
North West & North Wales Paediatric Transport Service (NWTS)
North West and North Wales Paediatric Critical Care Network
PICU, Royal Manchester Children's Hospital
PICU, Alder Hey Children's Hospital
North West Neonatal Transport Network

Next Review Due: June 2020

Guideline contact point: Rachael.Barber@mft.nhs.uk

Please visit our website for the most up to date version of this guideline:
www.nwts.nhs.uk
or
www.networks.nhs.uk/nhs-networks/north-west-north-wales-paediatric-critical-care

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