Title:	**Guideline for Management of Generalised Convulsive Status Epilepticus in Children**
Version:	**2 PCCN1**
Supersedes:	Guidelines for Management of Generalised Convulsive Status Epilepticus in Children **Version 1** Ratified CMFT 6th June 2012 & AHCH 29th August 2012 **Reviewed by Authors September 2014. No changes made**
Application:	The guideline is intended for use by any hospital team caring for infants, children and young people under 16 years age across the Paediatric Critical Care Network in the North West & North Wales region.

Originated /Modified By: **Designation:**	**Guideline authors (version 1)** H. Northover, Consultant Paediatrician, Royal Bolton Hospital. T. Martland, Consultant Paediatric Neurologist, Royal Manchester Children's Hospital. R. Appleton, Consultant Paediatric Neurologist, Alder Hey Children's Hospital. J. Samuel, Consultant Paediatric Intensivist, Royal Manchester Children's Hospital **Modified By (version 2)** Kate Parkins, PICM Consultant, North West & North Wales Transport Service (NWTS) Constantinos Kanaris, PICM consultant, NWTS Gillian Rennie, Specialty Doctor in Anaesthetics, Royal Blackburn Hospital, Jeen Tan, Consultant Paediatric Neurologist, Royal Manchester Children's Hospital
Ratified by:	RMCH (Host Trust): - Paediatric Medicines Management Committee (MMC) - Paediatric Policies & Guidelines Committee
Date of Ratification:	09.03.2022 PMMC 10.06.2022 P&G committee
Ratified by:	AHFT:CDEG (Clinical Development & Evaluation Group)
Date of Ratification:	07.06.2022

Amendment	Use of levetiracetam bolus as first choice long acting anti-convulsant Dose banding included for midazolam and diazepam Aligned timings with APLS guideline 2022 Use of propofol for short-term sedation prior to decision re extubation at local hospital

Issue / Circulation Date:	**10.06.2022**
Circulated by:	**NWTS** **North West and North Wales Paediatric Critical Care Network**
Dissemination and Implementation:	NWTS & Paediatric Critical Care Network circulation lists
Date placed on NWTS website:	**10.06.2022**

Planned Review Date:	**3 years January 2025**
Responsibility of:	Clinical lead North West & North Wales Paediatric Critical Care Network & NWTS guideline leads (consultant & nurse)

EqIA Registration Number:	**258/11**

1. Detail of Procedural Document

Guideline for Management of Generalised Convulsive Status Epilepticus in Children

This guideline is for use by staff working in the District General Hospitals of the North West (England) and North Wales region and NWTS team to use when caring for any neonate, child or young person under 16 years age who has convulsive status epilepticus. It focuses on acute management and the potential differential diagnoses that need to be considered.

This does not replace an acute referral to NWTS team for advice on management, but is designed to help both NWTS and the referring team throughout the acute stabilisation period.

2. Equality Impact Assessment

EqIA Registration Number: **258/11**

3. Consultation, Approval and Ratification Process

This guideline was developed with input from:

- North West (England) and North Wales Paediatric Transport Service (NWTS) - medical & nursing
- Paediatric Neurology Consultants from Royal Manchester Children's Hospital and Alder Hey Children's Hospital
- Representatives from the District General Hospitals within the North West (England) & North Wales Paediatric Critical Care operational delivery network; includes medical, nursing and AHP (paediatrics, anaesthetics, and emergency medicine teams)
- Representatives from both Paediatric Critical Care Units (Royal Manchester Children's Hospital and Alder Hey Children's Hospital) - medical and nursing

These guidelines were circulated amongst the North West and North Wales Paediatric Critical Care Network for comments on 4.09.2020
All comments received have been reviewed and appropriate amendments incorporated.

These guidelines were signed off by the PCC Network Joint Clinical Leads
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 24/7 from NWTS on a case by case basis via the referral line: 08000 84 83 82

Please feel free to **contact NWTS (01925 853 550)** regarding these documents if there are any queries.

Guidelines for management of generalised convulsive status epilepticus

Pre hospital setting
Seizure > 5mins

Diazepam rectal (max 10mg if <12yrs; 20mg if >12yrs)
or Midazolam buccal (max 10mg) see pg 4 for dose banding

Hospital setting

Assess & secure Airway / Breathing / Circulation / GCS + Pupils
Administer high flow oxygen 15 L/min
Obtain IV / IO access + bloods for appropriate investigations
Check blood glucose if < 3 mmol/L: IV 2mL/kg 10% glucose followed by maintenance
Confirm seizure clinically

5 MIN

After 1st benzodiazepine

Peripheral venous line (PVL) or intraosseous (IO)

YES

Lorazepam 0.1mg/kg (max 4mg) IV/IO over 1 minute
If lorazepam not available
Diazepam emulsion 0.3-0.4 mg/kg IV/IO (max 10mg)

NO

Midazolam buccal (max 10mg)
see pg4 for dose banding

Place an IO / PVL ASAP

SEIZURE CONTINUES after 10 minutes: CALL FOR SENIOR HELP

TOTAL 2 DOSES benzodiazepines given including pre-hospital?

NO

Lorazepam 0.1mg /kg IV or IO (max 4mg)
If not available
Diazepam emulsion 0.3-0.4 mg/kg IV or IO (max 10mg)

YES

Continuously re-assess Airway, Breathing, Circulation, GCS + Pupils during stabilisation

5 MIN

After 2nd benzodiazepine

1st choice: LEVETIRACETAM 40mg/kg (max 2.5 gram) IV or IO over 5 mins (except neonates)
Full loading dose to be given EVEN if the child is already taking background oral levetiracetam
NB dilute 1:1 with 0.9% sodium chloride (min volume 10 mL)
(reassess 10 mins post-levetiracetam)

2nd choice/alternative: if NOT on phenytoin, **PHENYTOIN** 20mg/kg (MAX dose 2 gram) IV / IO
Give over MIN 20 minutes **(infusion rate: 1mg/kg/minute not to exceed 50mg/min)**
See page 5 for information to help decision making between levetiracetam & phenytoin

For NEONATES (ie up to 44 weeks CGA) USE PHENOBARBITAL 20mg/kg (max 1 gram) IV or IO over 20 minutes or rate 1mg/kg/min (dilute to 20 mg/mL)

CONSIDER paraldehyde 0.8 mL/kg (MAX 20 mL) PR (prediluted preparation)

SEIZURE CONTINUES OR ENCEPHALOPATHIC OR REDUCED GCS ≤ 8/15

10 minutes

After levetiracetam infusion finished

REFRACTORY STATUS EPILEPTICUS – call anaesthetist / intensivist
Whilst preparing for intubation if seizure continues:
Consider giving either PHENYTOIN or LEVETIRACETAM or PHENOBARBITAL
Chose a drug that has NOT been given previously (doses as above)
MODIFIED RAPID SEQUENCE INDUCTION (see NWTS Intubation guideline)
1-2 mg/kg KETAMINE IV & 1-2 mg/kg ROCURONIUM IV +/- 1-2 microgram/kg Fentanyl IV
OR instead of Ketamine use either
1-3mg/kg PROPOFOL IV or 3-5 mg/kg THIOPENTONE IV
DISCUSS WITH NWTS

Guidelines for management of generalised convulsive status epilepticus in children

DIAZEPAM rectal dose 0.5 mg/kg max 20 mg	
Neonate (up to 44 weeks CGA)	0.5 mg/kg
1 month—1 year	5 mg
2—11 years	5-10 mg
12-17 years	10-20 mg

MIDAZOLAM buccal dose 0.3 mg/kg max 10 mg	
Neonate (up to 44 weeks CGA)	0.3 mg/kg
Infant 1-2 months	0.3 mg/kg
Infant 3-11 months	2.5 mg
1-4 years	5 mg
5-9 years	7.5 mg
10-17 years	10 mg

DEFINITION: any seizure lasting more than 5 minutes or recurrent seizure episodes within 5 minutes without re-turning to pre-convulsive neurological baseline. NB Most seizures stop within five mins.

- **Duration:** Longer seizures are more difficult to treat. Status epilepticus is life-threatening, and may cause serious neurological sequelae (neuronal death), especially if seizures > 30 minutes
- **Refractory status** occurs in up to 30% patients and is associated with high morbidity and mortality.

CONSIDER TREATABLE CAUSES

- Hypoglycaemia: treat glucose less than 3 mmol/L with bolus 2 mL/kg 10% glucose and start maintenance fluids with glucose
- Electrolyte disturbances eg treat hyponatraemia (Na <130): give 3-5 mL/kg hypertonic sodium chloride (2.7-3%) **OR** 3 mL/kg 5% hypertonic sodium chloride
- Meningitis / Encephalitis: follow local guidelines, but consider ceftriaxone, aciclovir & clarithromycin
- Known epilepsy: check anti-convulsant drug levels as non-compliance with medication is relatively common
- Febrile seizure: maintain normothermia
- Hypertensive emergency: d/w paediatric renal consultant at tertiary centre
- Toxins: consult TOXBASE if specific substance known to guide management.
- Intracranial bleed or Blocked VP shunt follow trauma pathway ie time critical transfer by local team
- Inborn error of metabolism: see NWTS guideline for management of hyperammonaemia: www.nwts.nhs.uk

BASELINE INVESTIGATIONS: all children with seizures lasting >30 minutes:

- Blood gas including lactate and glucose
- FBC, Clotting, U&Es, CRP, Liver function tests, Amylase, Calcium, Magnesium, Phosphate
- If evidence AKI check creatinine kinase levels (ie for evidence of rhabdomyolysis)
- Ammonia +/- blood and urine samples for inborn error metabolism if history or examination findings suggestive (lethargy, coma, metabolic acidosis or alkalosis) or where initial evaluation reveals no clear cause.
- Toxicology testing when no apparent aetiology is immediately identified. Send urine for toxicology ASAP
  If specific substance suspected from history, send specific serum toxicology level (not just urine toxicology)
  Ensure any drugs that may have been given in hospital or are reported to be available in the household are documented in the notes and on the test request (e.g. antibiotics or ketamine and fentanyl for RSI) to avoid any confusion with results. NB it is advisable to send a chain of custody form with urine or serum toxicology samples if there are any safeguarding concerns.
- Check Phenytoin concentrations (if used) ideally 1 to 1.5 hours after the loading dose has completed
  Blood level less than 10 microgram/mL, consider further loading dose 5 mg/kg over 20 minutes

Febrile/query infection:

- Blood, urine, viral cultures
- Bacterial/viral PCR (ie meningococcal, pneumococcal, HSV & COVID-19)

NEVER lumbar puncture immediately after prolonged seizure as high risk raised intracranial pressure and coning NB normal CT scan does NOT mean that there is no evidence of raised intra-cranial pressure

NEURO-IMAGING STUDIES CT/MRI IMAGING +/- CONTRAST:

- Only consider neuroimaging once the child is stable and seizure activity controlled
- Always intubate and ventilate prior to scan if GCS ≤ 8/15 or variable level of consciousness
  NB your patient is at risk of aspiration in this situation as they are unable to protect their own airway
- Consider neuro-imaging if:
  - New prolonged seizure
  - Suspected raised ICP
  - Suspected space occupying lesion, haemorrhage or blocked VP shunt
  - Atypical or unilateral / focal seizures
  - Suspicion meningoencephalitis
  - Cause unknown
  - Trauma or NAI: always discuss with trauma team leader at appropriate tertiary paediatric centre pre-scan
- Remember to request a contrast enhanced scan if suspicion of venous sinus thrombosis or abscess

- NB When transferring to/from CT or MRI always do a risk assessment (see STOPP document on NWTS website www.nwts.nhs.uk) & make sure that the patient is transferred by a team with appropriate competencies and with appropriate resuscitation equipment / drugs

INTUBATION: (see NWTS intubation guideline: www.nwts.nhs.uk)

INDUCTION AGENTS: Ketamine +/- fentanyl + rocuronium are the preferred induction agents especially in context sepsis or lactic acidosis

Alternatives: propofol or thiopentone consider using lower doses due to their hypotensive effects if there are any concerns re sepsis

Ketamine, propofol and thiopentone all have anti-convulsant properties at doses used for induction anaesthesia

AVOID suxamethonium if evidence of hyperkalaemia, myopathy or acute kidney injury

ON-GOING SEDATION:

FOR urgent CT scan consider using **propofol** infusion (range 1-4 mg/kg/hr) or boluses short-term (ie max 12 hours) to avoid propofol infusion syndrome. NB only use in the cardiovascularly stable patient

Why use propofol: it is a rapid acting, potent anaesthetic agent with anti-convulsant effects. Termination of it's effects is faster than other anaesthetic agents, allowing more rapid assessment of neurology post sedation hold prior to extubation

Avoid propofol if suspected inborn error of metabolism eg LCAD

Only consider using morphine and midazolam infusions after discussion with NWTS (see www.crashcall.net)

NEUROMUSCULAR RELAXANTS: only used during intubation or during transport.

- Discontinuation NMR agents allows monitoring of ongoing seizure activity.
- Ongoing seizure activity should be managed with escalating doses of anticonvulsant therapy, **not** paralysis.

RISK SEIZURE RECURRENCE: often within 4-6 hours, especially if only treated with short-acting benzodiazepines

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CHOICE OF LONG-ACTING ANTICONVULSANT

BETWEEN LEVETIRACETAM OR PHENYTOIN: Two studies have not shown any superiority of Levetiracetam over Phenytoin (or vice versa) in terminating status epilepticus.

1st choice LEVETIRACETAM: preferred as easy to draw up, and administration **over 5 mins**

It is compatible with usual IV maintenance fluids, has a low risk of extravasation injury and has a wide safety margin. ALWAYS wait for 10 minutes post-levetiracetam infusion before re-assessing whether seizure is controlled.

2nd choice PHENYTOIN: time intensive during drug preparation AND must be administered over **MIN 20 mins**

It is very irritant to veins (always give via large vein), and high risk of extravasation injury or injection site necrosis.

Adverse effects (more likely if administration too fast): arrhythmias (atrial or ventricular conduction depression; VF; cardiac arrest) which may be very difficult to treat; respiratory arrest; liver damage or Steven-Johnson Syndrome

SEIZURES DUE TO TOXINS OR DRUG OVERDOSE: Levetiracetam is the **anticonvulsant of choice**

Phenytoin should <u>not</u> be used due to its own sodium channel blockade effect and inappropriate mode of action

PHENOBARBITAL: 1st line in neonates (ie up to post-gestational age 44 weeks) or those with specific rescue plan

PARALDEHYDE only used at consultant discretion or if part of specific rescue plan. ALWAYS give long acting anti-convulsant ie levetiracetam/phenytoin/phenobarbital even if seizure terminates with paraldehyde.

DURING LEVETIRACETAM, PHENOBARBITONE OR PHENYTOIN INFUSION MONITOR: BP, ECG & HR, RR & SpO_2

Slow or stop Infusion if hypotension, impaired respiratory effort, ectopics or bradycardia during administration

<u>MANAGEMENT OF REFRACTORY SEIZURES POST INTUBATION AND VENTILATION: D/W PAEDIATRIC NEUROLOGY</u>

- Consider loading with phenytoin or levetiracetam or phenobarbitone whichever has not been previously used
- Consider midazolam infusion: 100 microgram/kg bolus and start infusion at 120 microgram/kg/hr wait 10 mins
  Increase rate midazolam infusion every 10 –15 minutes (max 360 microgram/kg/hr) until seizures controlled
  Caution: hypotension may develop and fluid bolus +/- vasopressors may be required
- Consider thiopentone infusion after discussion with NWTS and paediatric neurology.
  Caution: hypotension may develop and vasopressors may be required.
- **IF UNDER 18 MONTHS** and idiopathic status epilepticus: consider pyridoxine 100 mg IV if not had previously, **but be aware** of possibility of apnoea after administration. Always discuss with paediatric neurology before use.

<u>POTENTIAL SEQUELAE OF CONVULSIVE STATUS EPILEPTICUS</u>

- Blood glucose changes: initial hyperglycaemia, later hypoglycaemia.
- Hyperkalaemia
- Acute Kidney Injury or renal failure: secondary to rhabdomyolysis (check Creatinine Kinase levels if evidence AKI)
- Disseminated intravascular coagulopathy
- Cerebral oedema or raised ICP: ventilate to normal pH, avoid hypercarbia, keep well oxygenated, and maintain BP within normal limits
  Prevent hyponatraemia: maintenance fluids ideally should be balanced crystalloid eg Plasmalyte 148 or Hartmann's solution (if not available use 0.9% sodium chloride) with glucose as required
  Avoid fluid overload: restrict fluids to 70% normal requirements
  Consider bolus 3-5 mL/kg hypertonic sodium chloride (preferred option is 2.7% sodium chloride 5 mL/kg if available; if not available use 3 mL/kg for 3-5% sodium chloride) OR 0.25-1 g/kg mannitol over 30 minutes if any features of raised ICP eg hypertension, bradycardia, fixed and dilated pupils
  NB caution with mannitol: it does cause diuresis watch for subsequent hypotension, and / or urinary retention (which will cause a spike in ICP)
- Pulmonary oedema: usually managed with intubation & ventilation, and high PEEP (not usually with furosemide)
- Chronic epilepsy
- Irreversible brain damage and death (rarely)

EXTUBATION OF CHILD / ADOLESCENT INTUBATED FOR STATUS EPILEPTICUS

Early extubation in uncomplicated CSE is recommended as it reduces the risks associated with transfer and prolonged ventilation, and reduces the impact of hospitalisation on the child and family. Repeat NWTS audit data shows that children and adolescents are appropriately and successfully extubated by local teams without the need for transfer to PICU.

TRIAL OF EXTUBATION SHOULD ONLY OCCUR IF CLINICAL SUPPORT IS AVAILABLE TO RE-INTUBATE IF NECESSARY

CONSIDER THE REASON FOR INTUBATION

Apnoea/respiratory depression due to anticonvulsant
Probable febrile convulsion
Usual seizure type
LIKELY to be successful extubated locally

Previous episodes CSE requiring PICU
Epilepsy syndromes e.g. Dravet Syndrome
Intractable or refractory CSE
UNLIKELY to be extubated locally: D/W NWTS

POST intubation & ventilation
Seizures controlled with long-acting anticonvulsant?

YES

Normal (or no change from previous) CT or MRI
Normal U&E's, glucose, LFTs & ammonia
Normal observations: especially no persistent ↑HR
Normal pupil reactions

YES

Good respiratory drive
End tidal CO_2 normal + SpO_2 > 94% in FiO_2 ≤ 0.4
Min. settings on ventilator & normal blood gas & lactate

SEDATION HOLD

Neurological status unchanged from pre-morbid state
GCS ≥ 10/15
No flexor or extensor posturing
Intact airway protective reflexes
No concerns about difficult airway or OSA

YES

TRIAL EXTUBATION

Successful?

Admit to PHDU
Monitor PEWS including GCS
GCS min 10/15 & improving
Check blood gas post extubation

NO

D/W NWTS + neurology
Consider adding 2nd long-acting anticonvulsant

YES

Seizures controlled after 2nd long-acting anticonvulsant

NO

D/W NWTS & neurology
Transfer to PICU

NB reintubate if respiratory concerns, seizure recurs, if encephalopathic or reduced GCS ≤ 8/15
Discuss with NWTS

Resources

NWTS website: www.nwts.nhs.uk

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

Selected References:

Roland D, Davis T. ConSEPT and EcLiPSE - Levetiracetam versus Phenytoin for Status Epilepticus, Don't Forget the Bubbles, 2019.

Dalziel SR, Borland ML, Furyk J, Bonisch M, Neutze, J, Donath S et al Levetiracetam versus phenytoin for second-line treatment of convulsive status epilepticus in children (ConSEPT): an open-label, multicentre, randomised controlled trial Lancet 2019; 393(10186): 2135-2145

Lyttle MD, Rainford NEA, Gamble C, Messahel S, Humphreys A, Hickey H et al Levetiracetam versus phenytoin for second-line treatment of paediatric convulsive status epilepticus (EcLiPSE): a multicentre, open-label, randomised trial Lancet 2019; 393(10186):2125-2134

Appleton et al. Lorazepam v diazepam in the acute treatment of epileptic seizures and status epilepticus. Dev Med & Child Neurology 37 683-8

Appleton R et al. The treatment of convulsive status epilepticus in children. The Status Epilepticus Working Party. Archives of Disease in Childhood 2000.83(5):415-419

Mitchell WG, Crawford TO. Lorazepam is the treatment of choice for status epilepticus. J Epilepsy 3 7-10

McIntyre et al. Safety and efficacy of buccal midazolam versus rectal diazepam for emergency treatment of seizures in children: a randomised controlled trial. Lancet. 2005 Jul 16-22;366(9481):205-10

Advanced Paediatric Life Support Manual 6th Edition December 2018 & updated algorithm 2022

British National Formulary for Children (BNFc) online edition 2021

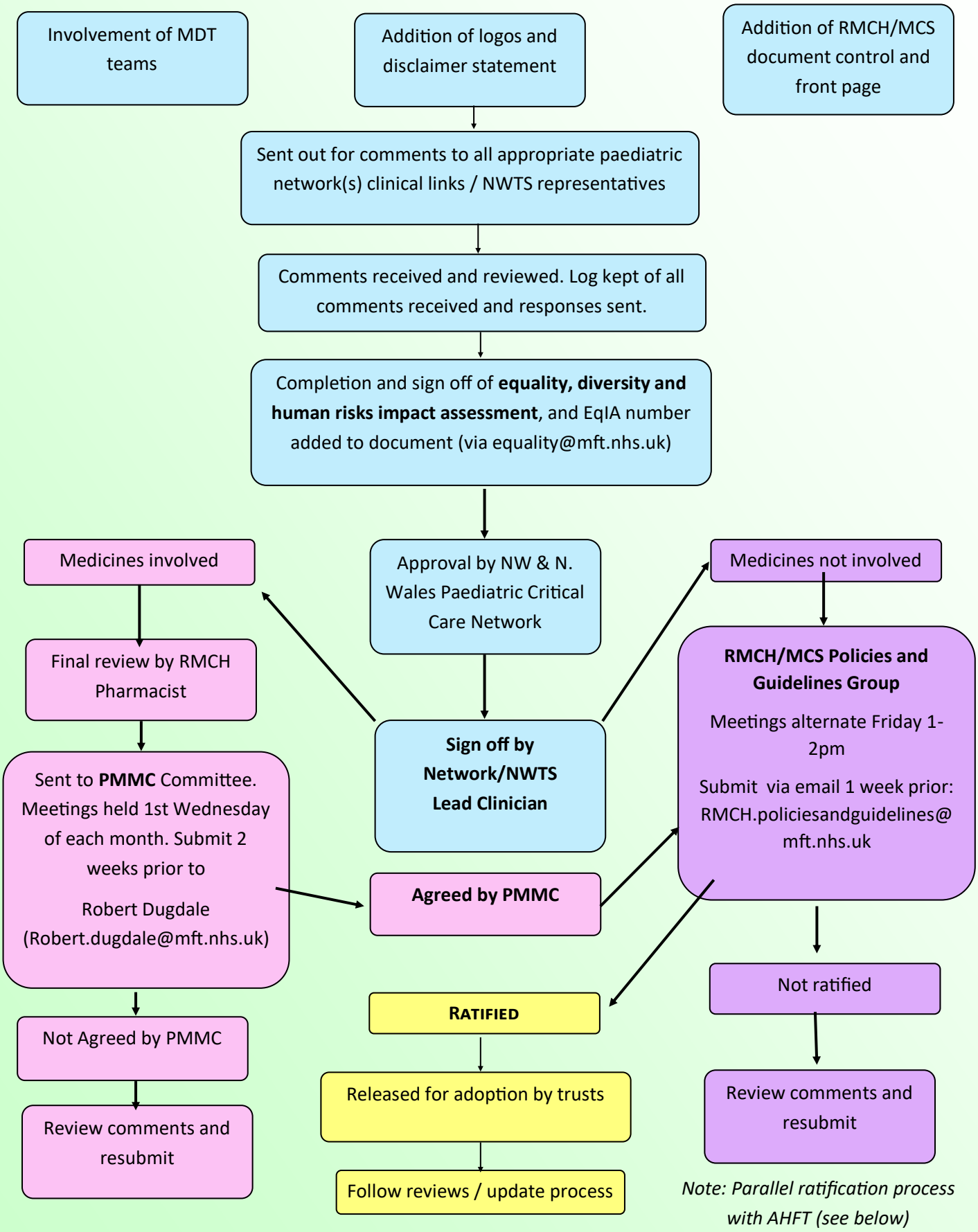
Paediatric Anaesthesia (Oxford Specialist Handbooks in Anaesthesia) Edited by Steve Roberts 2nd edition 2020

Guidelines consulted:

North West and North Wales Paediatric Transport Service - 2014 Status Epilepticus guidelines version 1
NICE: Protocols for treating convulsive status epilepticus in adults and children CG137 last updated: 22 September 2020
Clinical Practice guidelines consulted

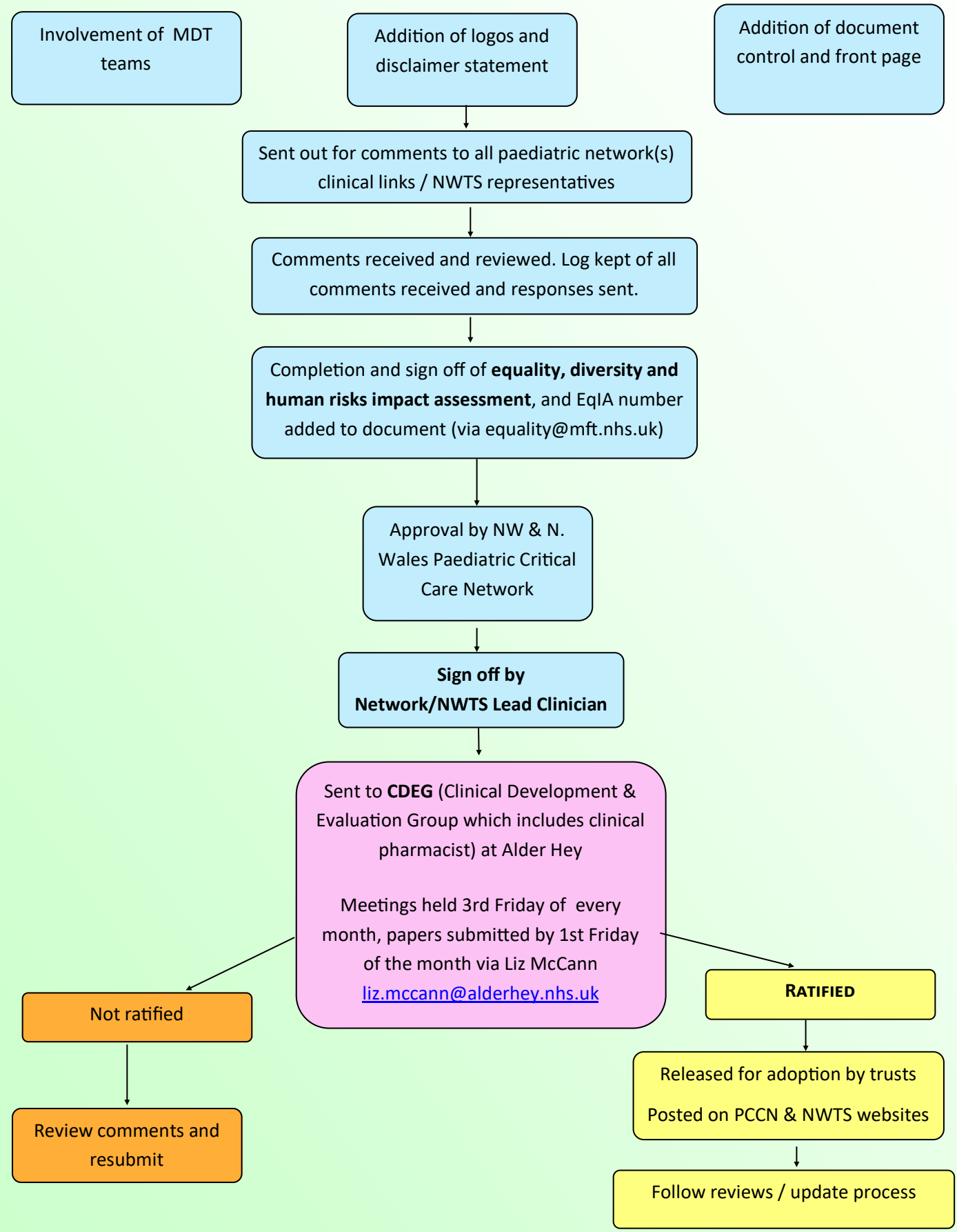
- Perth Children's Hospital, Australia, June 2020
- Royal Children's Hospital, Melbourne, Australia, August 2020
- Starship Hospital, Aukland, New Zealand, May 2019
- Southampton & Oxford Retrieval and Transport (SORT) service guidelines, November 2020
- Children's acute transport service (CATS) guidelines version 5 January 2020
- South Thames Retrieval Service (STRS) version 3 2021
- Wales & West Acute Transport for Children (WATCh) version 3 October 2020
- Kids Intensive Care Decision Support (KIDS) - version 1.2 Nov 2019

Ratification of Guidelines with Host Organisation (MFT)



Appendix 1 continued

Ratification of Guidelines with Alder Hey



Resources

NWTS website: www.nwts.nhs.uk

www.Crashcall.net - for intubation drugs / sedation regime
UK Paediatric Antibiotic Stewardship—website: http://www.uk-pas.co.uk/

Contact numbers:

North West (England) & North Wales Paediatric Transport Service (NWTS)

- NWTS REFERRAL LINE: 08000 84 83 82
- NWTS Office: 01925 853 550

Regional Paediatric Intensive Care Unit Alder Hey Children's Hospital : 0151 252 5241

Regional Paediatric Intensive Care Unit Royal Manchester Children's Hospital : 0161 701 8000

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Next Review Due: January 2025

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