NeoLEV3 Phase III — Nurse Quick Reference

Three treatment tracks by pre-treatment electrographic seizure burden

LEV = Levetiracetam
PHB = Phenobarbitone

1. Screening and study entry

Check eligibility — start EEG, give parent flyer, notify the neurology team for:

- HIE stage 2 or 3
- Any therapeutic hypothermia
- Other encephalopathy, including meningitis
- Suspected seizure, including unexplained apnoea or severe hypoglycaemia
- Moderate to severe metabolic acidosis (pH <7.0, base excess >12 mmol/L) and at risk of encephalopathy — discuss with SMO if EEG appropriate

The parent flyer is in the research page (www.nepios.net).

Follow the unit EEG guideline (ensure temporal leads are placed).

Facilitate consent

- Once parents have read the flyer, ask if they would be prepared to speak with a neurologist.
- Provide the Parent Information Sheet and Consent Form (PISC) which can be printed from the research page (www.nepios.net).
- Facilitate the neurology consult using the parent's phone or the charge nurse phone.
- A health professional must sign as witness, collect the parent's signature, and note the time the parent writes on the consent form (store at the bedside for Kelly Roczniak).
- Neurologists taking consent remotely will sign a virtual consent form (Cia, Sue or Hannah).

NeoLEV3 phone: 09 631 6128

Baseline bloods — pre-dose

- Ensure FBC, Cr, LFTs have been done within the last 24 hours; otherwise send before the first LEV dose.

2. Get LEV ready at bedside while neurologist reviews EEG

- Pre-made LEV syringes are stored in the NICU drug fridge.
- Pharmacy delivers 6 syringes to NICU every second Thursday afternoon.

The neurologist reviews the EEG and makes a rapid estimate of pre-treatment electrographic seizure burden — this determines the track:

- Less than 8 minutes per hour → **Track A (similar to Phase I and II NEOLEV3)**
- 8 to 20 minutes per hour → **Track B rapid treatment with LEV is imperative**
- Greater than 20 minutes per hour (not eligible for LEV randomisation) → **Track C rapid treatment with PHB is imperative**

Levetiracetam first dose (Tracks A and B only)

- LEV1 60 mg/kg IV over 5 minutes.
- Use pre-filled syringes from the drug fridge; if unavailable, prepare to unit guideline dilution.
- Record HR, RR, SpO_2 and BP in BadgerNet before and after the infusion.

3. Three-track quick reference

Use the table below to navigate the dose-escalation phase. Track C exits the study to standard PHB care.

Seizure burden	Track A: <8 min/h	Track B: 8–20 min/h	Track C: >20 min/h
First action	LEV1 60 mg/kg IV over 5 min Document obs after LEV #1	LEV1 60 mg/kg IV over 5 min Document obs after LEV #1 IV PHB to be prepared in case it is needed	Not eligible for LEV randomisation Give PHB 20 mg/kg IV over 15–20 min (standard of care, study exit)
Wait before next dose?	Yes — wait 15 min after LEV #1 before next treatment Randomisation if seizures ongoing at 15 min	No — randomisation during the 5-min infusion If seizures persist/recur after LEV #1, do not wait	N/A — transition to PHB standard of care
2nd treatment (randomised)	LEV #2 60 mg/kg over 5 min OR PHB 20 mg/kg over 15 min Obs + EDTA PK sample first (only if <1–2 min delay)	LEV #2 60 mg/kg over 5 min OR PHB 20 mg/kg over 15 min Obs + EDTA PK sample first (only if <1–2 min delay)	—
Wait before LEV3?	Yes — wait 15 min after LEV #2 if seizures still <8 min/hr	No — if seizures persist/recur after LEV #2, give LEV #3 without delay	—
LEV3	LEV #3 60 mg/kg IV over 5 min Obs before infusion	LEV #3 60 mg/kg IV over 5 min Obs before infusion	—
After LEV3 if seizures continue	If burden remains <8 min/h: WAIT 1 h before transitioning to PHB	If burden remains <20 min/h: WAIT 30 min before transitioning to PHB	—
Escalation trigger	If burden rises to >20 min/h at any stage → transition to PHB (standard of care)	If burden rises to >20 min/h at any stage → transition to PHB (standard of care)	Already on PHB standard of care

4. Track A — Seizures <8 minutes per hour

Step 1 — LEV #1

- LEV #1 60 mg/kg IV over 5 minutes.
- Document a set of observations after LEV #1.
- Wait 15 minutes after LEV #1 before any further treatment for ongoing or recurring seizures.

Step 2 — Randomise if seizures continue at 15 minutes

- Collect a micro EDTA sample for the PK trough level — only if it will not cause a delay of more than 1–2 minutes.
- Start the 2nd randomised treatment: LEV #2 60 mg/kg over 5 min OR PHB 20 mg/kg over 15 minutes.

Step 3 — LEV #3

- If seizures remain <8 min per hours, wait 15 minutes after LEV #2 before giving LEV #3.
- Obs before LEV #3. LEV #3 60 mg/kg IV over 5 minutes.

Step 4 — After LEV #3

- If seizures persist/recur but burden remains <8 min per hour: WAIT 1 hour before transitioning to PHB standard of care.
- If burden rises >20 minutes per hour at any stage → transition to PHB standard of care.

5. Track B — Seizures 8 to 20 minutes per hour

Step 1 — LEV #1

- LEV #1 60 mg/kg IV over 5 minutes.
- PHB to be prepared in case it is needed while LEV1 infuses.
- Randomisation during the 5-minute infusion so the next treatment is known.

Step 2 — If seizures persist or recur after the end of the LEV #1 infusion, do NOT wait

- Ask for a set of observations and a micro/ EDTA PK sample (only if it will not delay by more than 1–2 minutes).
- Start the 2nd randomised treatment: LEV #2 60 mg/kg over 5 min OR PHB 20 mg/kg over 15 minutes.

Step 3 — If seizures persist or recur after LEV #2, do NOT wait

- Document a set of Obs, then give LEV #3 60 mg/kg IV over 5 minutes.

Step 4 — After LEV #3

- If seizures persist/recur but burden remains <20 min per hours: WAIT 30 min before transitioning to PHB standard of care.
- If burden rises >20 min per hour at any stage → transition to PHB standard of care.

6. Track C — Seizures >20 minutes per hour

- Infant is NOT eligible for levetiracetam randomisation under NeoLEV3.
- Neurologist will advise phenobarbitone 20 mg/kg IV over 15–20 minutes (standard of care).
- Continue neurological monitoring; follow standard-of-care pathway from this point.
- If at any earlier stage in Tracks A or B the seizure burden rises >20 minutes per hour, transition to this pathway.

7. Post-randomisation care

Neurological monitoring

- Neurologist continues to monitor the EEG over the next hour and advises next steps as per protocol.

Maintenance doses

- LEV maintenance is continued for 5 days (IV or oral depending on feeding).
- If still seizing → LEV maintenance + PHB load, and in some cases PHB maintenance

ECG rhythm strips

- Obtain a baseline strip from the monitor at any time point before the 2nd dose escalation drug.
- Obtain a strip from the monitor after the 2nd dose-escalation drug (LEV or PHB).
- Obtain a strip from the monitor after LEV #3.
- Annotate each with date, time and dose; store with clinical notes.
- Note: ECGs may be printed retrospectively the next day if needed.

8. PK levels (higher-dose LEV arm)

Collected at Auckland and Middlemore for babies randomised to higher-dose LEV.

Check that parents have consented to PK samples.

- Micro-EDTA purple-top tube, on ice, with the special lab form (download from the research page – ask Neurologist for study ID)
- Stick a patient label on the tube.
- Time the 4th and 5th doses for daytime hours.

Planned PK levels

- 1. Trough pre-LEV #2
- 2. Peak 1-hour post-LEV #2 (may not occur if LEV #3 given before the hour)
- 3. Peak 1-hour post-LEV #3
- 4. Trough before the 3rd, 4th or 5th maintenance dose
- 5. Trough before the 12th, 13th or 14th maintenance dose

9. Safety bloods

For babies randomised to higher-dose LEV OR to PHB.

Timepoints — baseline, 24 hours, and day 4–5

- FBC, U&Es, calcium, gas, glucose, ALT, creatinine.
- If randomised to LEV, collect trough PK levels 4 and 5 at the same time.

After maintenance dosing completed (day 5)

- FBC, ALT, LFTs and a full blood gas with creatinine.

10. Ready-to-use LEV syringes

Ready-to-use levetiracetam IV syringes are compounded by Slade Health for the NeoLEV3 Trial.

- Each 12.5 mL syringe contains 500 mg of levetiracetam (40 mg/mL)
- Kept in the fridge (expiry 14 days)
- Do not dilute, 60 mg/kg = 1.5 ml/kg
- Administer IV over 5 min with a filter
- Record observations before and after infusion

Ready-to-use levetiracetam IV syringes should only be used for infants enrolled in the NeoLEV3 Trial.

PRESCRIPTION ONLY MEDICINE
KEEP OUT OF REACH OF CHILDREN

LEVETIRACETAM 500MG
IN 0.9% SODIUM CHLORIDE
IN SYRINGE (TERUMO)
FOR INTRAVENOUS USE

Volume: 12.5mL

Store REFRIGERATED (2-8C)

Expires DD/MM/YYYY | Protect From Light
HH:MM

Test PATIENT
URN DOB (Participant Number)

Test Pharmacy **SH BATCH NUMBER**
Use in one patient on one occasion only

Study Name/Protocol Number
For Clinical Trial Use Only