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Real-time seizure detection in paediatric intensive care patients: the RESET child brain protocol

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ABSTRACT:

Introduction Approximately 20%–40% of comatose children with risk factors in intensive care have electrographic-only seizures; these go unrecognised due to the absence of continuous electroencephalography (EEG) monitoring (cEEG). Utility of cEEG with high-quality assessment is currently limited due to high-resource requirements. New software analysis tools are available to facilitate bedside cEEG assessment using quantitative EEG (QEEG) trends. The primary aim of this study is to describe accuracy of interpretation of QEEG trends by paediatric intensive care unit (PICU) nurses compared with cEEG assessment by neurologist (standard clinical care) in children at risk of seizures and status epilepticus utilising diagnostic test statistics. The secondary aims are to determine time to seizure detection for QEEG users compared with standard clinical care and describe impact of confounders on accuracy of seizure detection.

Methods and analysis This will be a single-centre, prospective observational cohort study evaluating a paediatric QEEG programme utilising the full 19 electrode set. The setting will be a 36-bed quaternary PICU with medical, cardiac and general surgical cases. cEEG studies in PICU patients identified as 'at risk of seizures' will be analysed. Trained bedside clinical nurses will interpret the QEEG. Seizure events will be marked as seizures if >3 QEEG criteria occur. Post-hoc dedicated neurologists, who remain blinded to the QEEG analysis, will interpret the cEEG. Determination of standard test characteristics will assess the primary hypothesis. To calculate 95% (CIs) around the sensitivity and specificity estimates with a CI width of 10%, the sample size needed for sensitivity is 80 patients assuming each EEG will have approximately 9 to 18 1-hour epochs.

Ethics and dissemination The study has received approval by the Children's Health Queensland Human Research Ethics Committee (HREC/19/QCHQ/58145). Results will be made available to the funders, critical care survivors and their caregivers, the relevant societies, and other researchers.

Trial registration number Australian New Zealand Clinical Trials Registry (ANZCTR) 12621001471875.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ *RESET Child Brain* is a prospective comprehensive study to investigate real-time seizure detection by bedside clinicians derived from a full 19 lead electroencephalography (EEG) in paediatric intensive care unit patients at risk of seizures.
⇒ Our study design will allow accurate estimation of sensitivity and specificity of quantitative EEG trend interpretation by bedside clinicians.
⇒ The pragmatic study design and training material for bedside clinicians makes this study reproducible.
⇒ Sensitivity and specificity for recognition of short (>10 s) seizures as well as clinically relevant events of >5 min and seizure burden >20% (12 min) will be described.
⇒ Limitation of this study include the single-centre design and that we will not assess if rapid seizure detection improves clinical outcomes.

INTRODUCTION

Context

In Australasia, paediatric intensive care unit (PICU) mortality has significantly dropped from 8%–18% to 2.5%–5% in the past 50 years.[1–3] Greater focus in paediatric critical care is on the PICU survivors. Specifically decreasing PICU-related and disease-related complications and their impact on morbidity and long-term outcome is the goal.[4–6] Secondary brain injury caused by systemic complications (hypotension, hypoxia, rapid shifts in carbon dioxide) or increased cerebral oxygen demand (fever, pain, seizures) has been postulated to add to post PICU morbidity and worsen functional outcomes. Especially at risk are the 20% of PICU children presenting with primary neurological disorders and the further 20% that are at risk of brain injury secondary to multiorgan failure.[7–9] Both primary and secondary brain injury increase the risk of seizures and status epilepticus.[10] Prolonged or repetitive seizures and status epilepticus have been shown to lead to moderate to severe long-term deficits.[4 5] This places a considerable burden on the patient, family and society. Timely seizure detection and management is therefore paramount.[11]

Given the increased vulnerability of the developing brain of a child, the impact of primary and secondary brain injury on the child, family, their socioeconomic situation and society is larger compared with adults.[12–16] In adults, post intensive care unit (ICU) morbidities are postulated to cost more than US$30 000 per patient within the first 2 years post ICU.[17 18] The associated actual healthcare costs for PICU patients where the majority is less than 2 years old are currently largely unknown.[18–21]

Electrographic seizures (ESz) are very common in PICU patients, especially in high-risk groups (coma plus risk factors including patients less than 2 years of age, hypoxic ischaemic encephalopathy, intracranial haemorrhage, supratentorial head injury or central nervous system (CNS) infection, stroke, autoimmune encephalitis, clinical seizures prior to electroencephalography (EEG)).[20–24] Cohort studies showed that 30%–40% of comatose PICU patients experience electrographic-only seizures (EOSz) when monitored with EEG.[23 25–28] Seizure burden and the presence of status epilepticus have been suggested as measurable indicators of risk for worse outcome.[11 19 20 23–25 29–31] A proposed mechanism for poorer outcome is that seizures increase metabolic demand, leading to higher potential for secondary brain injury.[30–3233 34] It is also known that delays to management of status epilepticus are associated with decreased medication effectiveness and decreased likelihood of seizure termination.[35 36]

Improved detection and treatment of seizures and electrographic status epilepticus (ESE) guided by EEG monitoring has been shown to improve response time to therapy and patient important outcomes including PICU and hospital length of stay in children admitted to PICU with altered level of consciousness due to all causes (see table 1 for terms and definitions).[11 18 20 23 24 30 37 38]

Current practice

Seizure detection on EEG requires a high level of expertise and the presence of a neurologist/epileptologist. An inherent delay from the acquisition of EEG data to the intervention exists as these resources are not available after hours in most centres.[39–43]

Other barriers and practical issues include higher likelihood of artefact in the PICU environment and need for robust interdisciplinary teamwork to overcome logistical challenges.[44]

Historically, the interpretation of the EEG has been solely the domain of highly trained EEG specialists, who analysed the data offline with substantial time delay in response time.[41]

Newer EEG analysis tools, quantitative EEG (QEEG), mathematically transform raw EEG to be displayed at the bedside in real time as trends to assist clinicians in EEG interpretation.[45] The most frequently used forms are amplitude integrated EEG (aEEG) and colour density spectral array (CDSA). aEEG displays a time-compressed

Table 1 Common terms and definitions

Term	Definition
Electrographic seizure (ESz)	An abnormal paroxysmal electrographic event that differs from the background activity, last longer than 10 s (shorter if associated with clinical change), has a plausible electrographic field, and evolves in frequency, morphology or spatial distribution. ESzs may be either electroclinical or subclinical.[53 60]
Electroclinical seizure (clinical seizure, convulsive seizure)	A seizure that is coupled with clinical manifestations and time-locked to an EEG pattern (note: EEG pattern does not need to fulfil ESz criteria) OR an ESz and clinical improvement with an antiseizure medication.[53 60]
Electrographic-only seizure (subclinical seizure, non-convulsive seizure)	An ESz that occurs without any clinical manifestation.[54 55]
Electrographic status epilepticus (ESE)	An uninterrupted ESz lasting 10 min or longer OR recurrent seizures totalling 12 min (seizure burden 20%) in any 1-hour period with or without clinical manifestations.[53 60]
EEG background	The predominant EEG background activity during the first hour of continuous video-EEG monitoring as well as over the whole recording categorised as: normal or sedated sleep; slow and disorganised; discontinuous or burst suppression; or attenuated and featureless.[21 37 61–63]
Seizure burden	Duration of seizures (in seconds) in any electrode, focal, or diffuse.[11]
Anti-seizure medication (antiepileptic drug) ASM (AED)	A medication given by oral or parenteral routes, in single or regular doses, to treat or prevent seizures.
Patient at risk of seizures	Defined as brain injury and unexplained coma or unable to assess clinically (especially patients less than 2 years of age, HIE, intracranial haemorrhage, supratentorial head injury or CNS infection with coma, clinical seizures prior to EEG, stroke, autoimmune encephalitis); see online supplemental appendix 1

CNS, central nervous system; HIE, hypoxic ischaemic encephalopathy.

trend of EEG amplitude and is used primarily in neonatal ICUs.[46] CDSA displays the frequency and power of the EEG signal over a time compressed scale, different trends can be chosen. Bedside utility for these modalities to detect seizures recognisable by critical care providers has only been suggested in children following cardiac arrest, and comatose adults in ICU.[47 48] They have not been evaluated for real-time seizure detection in comatose critically ill children. Prospective studies testing QEEG in the point-of-care context to improve external validity have been suggested.[49] Provision of robust education and training components and inclusion of all PICU patients requiring cEEG for seizure detection have been identified as priorities.[49]

International studies suggest that monitoring high-risk patient groups could be cost-effective.[50 51] Our study aims to address the knowledge gap regarding the sensitivity and specificity of seizure detection by QEEG in comatose children in PICU.

Study hypothesis

Our primary hypothesis is that, compared with the gold standard of neurologists interpreting cEEG, bedside nurses interpreting QEEG can accurately determine the presence or absence of seizures and status epilepticus and accurately quantify the number of seizures. This in turn will be associated with a shorter time to seizure recognition.

Our secondary hypotheses are:

- Accuracy will improve if the neurologist validates at least one seizure during the real-time cEEG recording (print-out of validated seizure provided to bedside nurse) and/or if seizures are present on cEEG.
- QEEG experts (neurophysiologists and/or neurologists with training in EEG and QEEG) can accurately detect seizures on QEEG compared with seizure detection by neurologists on cEEG (gold standard) and this in turn will be more accurate then QEEG interpretation by bedside nurses interpreting QEEG in real time.

To test the primary hypothesis, we will determine the sensitivity, specificity, positive predictive value and negative predictive value of QEEG ESz and status epilepticus detection by bedside users compared with cEEG interpreted by a neurologist. Further, we will determine the time from seizure occurrence and/or status epilepticus occurrence to recognition (first QEEG entry vs first cEEG annotation or electronic medical record entry). Finally, we will determine if validation of seizures as true positive events by the neurologist at least once during the cEEG recording, the presence of seizures in the recording or QEEG expert review are associated with higher sensitivity and specificity of QEEG-based seizure recognition.

METHODS AND ANALYSIS

Study protocol

This is a prospective, single-centre observational cohort study in children at risk for seizures in a tertiary paediatric mixed surgical and medical 36-bed PICU with more than 1800 admissions per year in Brisbane, Australia.

The study started on the 1 July 2020 with an interim analysis planned once data collection on the first 40 EEG studies is complete. Recruitment to the study will conclude after 80 EEG studies have been analysed; however, the sample size will be reviewed at the time of the interim analysis. cEEG recordings obtained in comatose PICU patients identified as 'at risk of seizures' clinically will be eligible for inclusion (table 2).

All children receiving cEEG monitoring will be notified to the study personnel before commencement and the EEG will be analysed by QEEG if inclusion criteria are fulfilled and no exclusion criteria present.

Measurement of exposures

EEG and QEEG measurements

PICU EEGs will be recorded digitally (Compumedics Limited, Grael 4K-EEG, Abbotsford, Victoria, Australia) as per international standard[52] with electrodes placed according to the 10–20 system.

All eligible EEG recordings in the PICU will be analysed in real time with the QEEG tools built into the Magic Marker software (V.P14, Persyst Development Corporation, Prescott, AZ). QEEG panels (comprehensive P12) will be visible on a bedside monitor as part of the EEG recording and display the most recent 1 hour epoch (figure 1).

PICU nurses will undergo a short (<10 min) QEEG face-to-face training complimented by digital training material. If applicable, a 1-hour QEEG panel printout containing the patient's most recent seizure(s) will be displayed next to the bedside EEG acquisition monitor,

Table 2 Inclusion and exclusion criteria

Inclusion criteria	EEG recording ≥1 hour ≤18 years of age Admission to study PICU Identified as at risk of seizures (defined as brain injury and unexplained coma or unable to assess clinically, patient at risk of seizure definition, see online supplemental appendix)
Exclusion criteria	EEG recording ≤1 hour Patients with decompressive craniectomy or injury to head that prevents placing of electrodes Allergy to EEG glue QEEG software not available on relevant EEG machine

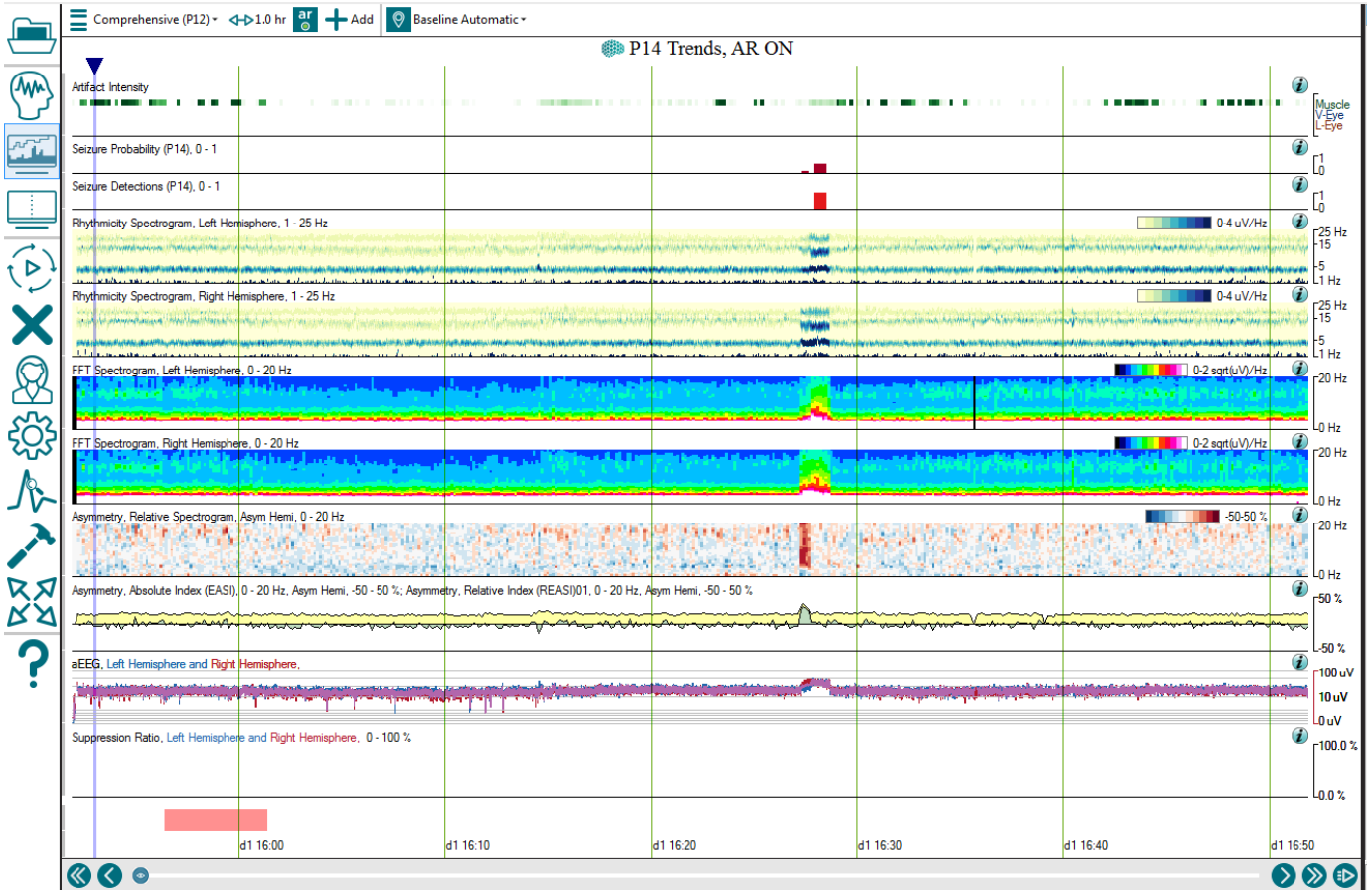

Figure 1 1-hour window of QEEG trends as displayed at bedside.

and nurses will be instructed to identify similar patterns. For the duration of their shift, the nurses will assess the QEEG trend for seizures and status epilepticus at least on an hourly basis and annotate significant events on the QEEG. An event will be classified as 'certain seizure on QEEG' if at least three trends (seizure probability >50%, seizure print in rhythmicity spectrogram and fast Fourier transformation (FFT) trend, concordant focal or generalised change asymmetry spectrogram, change in amplitude in aEEG) are indicative of seizure. The nurses will mark 'status epilepticus certain' on QEEG if one seizure lasts longer than 10 min and/or multiple seizures occur per hour making up more than 10 min (this is chosen as the markers on persyst are 10 min increments displayed as 60 min window and is in keeping with the current ESE definitions).[53–55] Given that 80 EEG studies are expected to be included, the study PICU employs approximately 200 registered nurses, and some EEG studies will run for more than one nursing shift, we anticipate that between 50 and 150 nurses will participate in the study. To ensure that the bedside teaching is reproducible, the same educational materials will be used by MW, the research coordinator (LS) or one of three nurse educators. Comprehension of the materials will be assessed throughout the education sessions, with participants asked to identify events on example slides. If seizures or status epilepticus are suspected, the treating senior PICU doctor will be notified. Management will be based on usual hospital protocols including involving the on-call neurologist when clinically appropriate. This process is in keeping with comparable practice improvement projects that rely on best practice care standards.

To compare the accuracy of seizure recognition from QEEG by nurses and QEEG experts, the QEEG will be analysed offline by QEEG experts (neurologist or EEG scientist), events will be classified as 'certain seizure on QEEG' if at least three trends (seizure probability >50%, seizure print in rhythmicity spectrogram and FFT, concordant focal or generalised change asymmetry spectrogram, change in amplitude in aEEG) are indicative of seizure.

Independent EEG and QEEG assessors will be blinded to nursing assessments and patient details.

Each cEEG will be reviewed offline by two independent paediatric neurologist (SM, MW) and seizure onset and duration will be annotated using published criteria.[11] Annotations will be exported for analysis purposes. If there is disagreement between the cEEG interpretation consensus will be obtained by combined review and agreement between the two research reporting neurologists. The reporting doctors will be blinded to QEEG results, indication and neuroimaging findings. As knowledge of current and preceding medications, clinical events, and event button presses is important to EEG interpretation, this information will be provided.

Clinical EEG annotations that form part of the EEG record will be available for analysis to determine time to seizure recognition as per standard care.

Each recording will be placed into the same categories: no seizures, seizures present: 1–10 seizures, or >10 seizures. The absolute number and duration of seizures per hour will also be recorded. The predominant EEG background activity during the first hour of cEEG as well as over the whole recording will be categorised as normal or sedated sleep, slow and disorganised, discontinuous or burst suppression, or attenuated and featureless.

The spatial extent of the seizures (focal, defined as ≤4 unilateral electrodes involved, hemispheric, defined as unilateral but >4 electrodes involved, or generalised/bilateral), stereotypical events and duration (seizure burden) will be determined from the corresponding conventional EEG segments. Spike amplitude will be determined and recorded as the average amplitude during ESzs as ≤50 µV or >50µV.

Accurate diagnosis of seizures on QEEG review will be defined as the same event scored on cEEG expert review as a seizure identified by ICU nurse (true positive). Timestamping within 5 min of each other will be accepted as accurate. Accurate diagnosis of status epilepticus on QEEG review will be defined as the same event scored on cEEG expert review as a status epilepticus (true positive). Timestamping within 1 hour of each other will be accepted as accurate.

Data collection

Data will be collected from EEG request forms and the electronic medical record to determine eligibility at time of enrolment. Data collection will include QEEG and cEEG interpretation as well as clinical data on completion of EEG recording and at time of discharge (online supplemental appendix 2).

Statistical analysis plan

Demographic and clinical characteristics of the cohort will be presented using mean (SD), median (IQR) and frequency (percent), dependent on the distribution of the variable under investigation.

The primary hypothesis (accuracy of bedside nurses interpreting QEEG for identification of seizures and status epilepticus) will be assessed using sensitivity, specificity, positive predictive value and negative predictive value, comparing to conventional cEEG review by neurologists as the gold standard. Ninety-five per cent CIs will be reported for each measure. The following definitions will be used for the components required for calculation of these statistics:

- Seizure:
  True negative: no seizure event/s recorded on QEEG within the 1-hour epoch, with no seizure event/s recorded on cEEG for the same time period.
  False negative: no seizure event within the 1-hour QEEG epoch, with one or more seizure event/s recorded on cEEG for the same time period.
  False positive: seizure event recorded on QEEG with no seizure event on cEEG within a 5 min interval.
  True positive: seizure event recorded on QEEG within 5 min of a seizure on cEEG.
- Status epilepticus:
  True negative: no status event/s recorded on QEEG within a 1-hour epoch, with no status event/s recorded on cEEG for the same time period.
  False negative: no status event within a 1-hour QEEG epoch, with status event recorded on cEEG for the same time period.
  False positive: status event recorded on QEEG with no status event on cEEG within a 1-hour interval.
  True positive: status event recorded on QEEG within 1 hour of a status event on cEEG.

A subgroup analysis will be conducted for seizures lasting >5 min based on the cEEG reading by the neurologist, as these events would be considered clinically significant.

Time from onset of status epilepticus as marked by the research neurologist offline to time recognised by bedside clinician using QEEG will be captured.

A similar analysis will compare QEEG experts (EEG technician and/or neurologist blinded to raw EEG data) interpretation of QEEG offline and neurologists interpreting raw EEG (secondary hypothesis). Inter-rater reliability for seizure detection for bedside clinician reviewing QEEG in real-time and offline review of QEEG by experts will be calculated. Additionally, a sensitivity analysis will be undertaken for the primary hypothesis excluding children who have no seizures recorded on both cEEG and QEEG, and multivariable models will be used to adjust for baseline demographic and clinical characteristics. Additionally, QEEG experts will mark duration of the event on QEEG; this will be compared with event duration marked on cEEG.

Temporal analyses will be used to determine whether validation of seizures by a neurologist during the real time recording impacts the and accuracy of seizure detection on QEEG.

Temporal analysis models will be used to determine the association between cEEG seizure category (no seizures, seizures present: 1–10 seizures, or >10 seizures), spatial extent of seizures and QEEG versus cEEG seizure confirmation.

The primary analysis will test the ability of nurses to detect individual events (seizures or status epilepticus) compared with conventional cEEG reviewed by neurologists. To address variation in seizure frequency between patients, the analysis will be repeated testing the ability of the nurses to correctly classify each 1-hour EEG epoch as seizures present or absent. This will also allow the results to be compared with a study of the accuracy QEEG in adult ICU patients.[48]

Time to seizure recognition will be recorded for QEEG review and will be compared with standard practice (EEG review).

Analyses will be undertaken in Python (Python Software Foundation, Wilmington, Delaware) and StataSE

(StataCorp Pty). Statistical significance will be set at the 0.05 level, and no modification for multiple comparisons will be made. Missing data will be reported in the results of the trial.

Sample size analysis

In our institution, we observed subclinical seizures in 29 of 105 children on cEEG over a period of 12 months (unpublished audit data) and the mean cEEG duration was 7 hours. This proportion is similar to international studies.[11 31 39 56 57]

Other centres have reported lower rates of patient with subclinical seizures if all comatose patients are monitored, hence our decision to define the patient at risk of seizure categories in our institutional EEG monitoring pathway (online supplemental appendix).[27]

There is no validated and comparable paediatric data available. Based on our institutional baseline data (unpublished), it is assumed that 30% of patients will have one or more seizures present, sensitivity of QEEG seizure detection by clinicians will be approximately 85% and specificity will be approximately 90%. To calculate 95% (CIs) around the sensitivity and specificity estimates with a CI width of 10%, the sample size needed for sensitivity is 80 patients assuming each EEG will have approximately 9 to 18 1-hour epochs. An interim analysis will be undertaken once 40 participants have completed data collection to ascertain the frequency of children with no seizures to ensure the sample size assumptions are met. If required, at this timepoint the sample size will be recalculated based on the proportion of children experiencing at least one of more seizures as well as based on the sensitivity and specificity.

ETHICS AND DISSEMINATION

Ethics approval for this study was obtained with waiver of consent from the Children's Health Queensland Human Research Ethics Committee (HREC/19/QCHQ/58145). The EEG recordings are obtained for clinical reasons consistent with standard clinical practice while the research aims to determine the accuracy of seizure detection using QEEG. This study will be performed in accordance with the ethical principles of the Declaration of Helsinki, ICH GCP for Guidance on Good Clinical Practice and NHMRC National Statement on Ethical Conduct in Research Involving Humans[52 55] and has been registered with the Australian New Zealand Clinical Trials Registry (ACTRN12621001471875) pre-results. Results will be made available to the funders, critical care survivors and their caregivers, the hospital board, relevant societies, and other researchers on reasonable request following publication in a peer-reviewed journal.

Data management and oversight

Study investigators and the study coordinator will take responsibility for the conduct of RESET child brain. Study investigators will supervise the day-to-day operations of the project and are responsible for ensuring that the International Council For Harmonisation Of Technical Requirements for Pharmaceuticals for Human Use - Good Clinical Practice (ICH-GCP) guidelines are followed.

Members of the *RESET Child Brain* research team from the University of Queensland will monitor the data at 3 monthly intervals. Monitoring will ensure protocol compliance, proper study management and timely completion of study procedures.

Ongoing surveillance and adherence to the study protocol (intervention fidelity) will be monitored by the principal investigator and clinical research nurse (CRN) during weekly audits

Streamlined data collection instruments and procedures will be used. All other data will be collected by the CRN onto the case report form directly from the source data. Data will be entered into the electronic data platform REDCap, hosted by The University of Queensland.[58 59]

Data storage and security

Identifiable information will be stored on institutional network drives with firewalls and security measures in place. Hard copy records will be stored in a locked cabinet in a secure location.

Access to records and data will be limited to study personnel. Study data will be deidentified and a master linking log with identifiers will be kept and stored separately from the data.

Results will be made available to the funders, critical care survivors and their caregivers, the relevant societies, and other researchers. The datasets used and/or analysed during the current study as well as the training package are available from the corresponding author on reasonable request. Publication of results is planned in a peer reviewed journal.

Patient and public involvement statement

The authors thank the PICU nurse education team, the EEG technician team and our patients and families for their valuable comments on drafts of this protocol.

Methodological issues

Our prospective study design in which variables are reliably measured over time will provide stronger evidence for feasibility of this real-time seizure detection model than could be obtained from a retrospective design or offline assessment models.

Although our hypothesis that EOSz can be detected by PICU clinicians in a point of care fashion is exploratory, it is based on evidence from other patient populations. If our hypothesis is true, QEEG would provide an easy way of identifying patients at risk of secondary brain injury due to seizures who may benefit most from early intervention.

Based on reasoning from previous studies in PICU patients, if accurate, our real-time seizure detection method would provide a way to identify vulnerable patients that may benefit most from intervention strategies. This could decrease the risk of additional cognitive

impairment and secondary epilepsy and potentially transform cEEG into a feasible neuroprotective strategy.

The primary limitation of this study is its single centre design and potential for missing data (QEEG not commented on, EEG study lost) that would challenge the internal and external validity of reported results from RESET child brain. However, our research team has extensive experience in achieving high recruitment rates and data integrity in other studies of children that are critically ill receiving new interventions. Strategies to minimise missing data will include the appropriate training and support of experienced study personnel, accurate and timely capture and entry of data, streamlined IT solutions and the utilisation of a standardised database.

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Contributors The study concept and design were conceived by MW, KG, ASchibler, ASlater and SM. LS, SG, JH and MW will conduct screening and data collection. Analysis will be performed by KG. MW prepared the first draft of the manuscript. All authors provided edits and critiqued the manuscript for intellectual content.

Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The datasets used and/or analysed during the current study as well as the training package are available from the corresponding author on reasonable request.

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Supplementary/Appendix:

Appendix 1: Patient at risk of seizures categories (EEG monitoring pathway)

Strong recommendations:

I) patients with persistently altered mental status after seizures,
II) patients with acute supratentorial brain injury with altered mental state,
III) PICU patients without primary brain injury and fluctuating or unexplained alteration in mental status.

Weak recommendations

IV) patients at risk of seizures that are under pharmacological paralysis
and
V) paroxysmal events suspected by PICU personnel to be seizures.

Specifically, at CHQ:
PICU patients that are comatose or intubated and ventilated and cannot be safely lightened for clinical assessment or infants aged less than 2 years where one of the following risk factors is present:

1. suspicion of non-convulsive seizures among encephalopathic patients (with or without concomitant muscle relaxation):

2. Recent clinical seizure or SE with delayed return to baseline conscious state (>60 min after seizure medication); earlier if clinical evidence of continued seizures or clinical concerns

3. Encephalopathy with suspicion of electrographic seizures – especially autoimmune encephalitis

4. Recent stroke (ischemic, haemorrhagic, sinovenous thrombosis = CSVT) with clinical seizures

5. Recent stroke (ischemic, haemorrhagic, sinovenous thrombosis) in children < 5 years of age with or without clinical seizures

6. Known Epilepsy diagnosis and high risk of subclinical seizures

7. Structural brain abnormality with high risk of subclinical seizures

8. ECMO with suspicion of seizures or brain injury

9. Recent cardiac procedure with suspicion of seizures in infants < 2 years of age

10. Suspected electrographic seizures in patients with unexplained altered mental status

11. Intracranial haemorrhage including TBI, SAH, ICH

12. Acute brain injury and prolonged use of muscle relaxants (e.g. drowning, neonatal HIE, recent cardiac arrest)

13. neonatal HIE patients in PICU for other reasons within 5 days of their acute insult

14. Acute supratentorial brain injury with altered mental state (moderate/severe TBI (accidental or NAI), CNS infections, recent neurosurgical procedures, brain tumours, HIE, sepsis associated encephalopathy)

Appendix 2: Data collection parameters and source

Table 3. Variables and definitions

Variable	Definition	Data collection
QEEG		
Seizure (no clinical) certain	≥ 3 QEEG trends indicative of seizure, no observed clinical manifestations	QEEG comment
Seizure (clinical) certain	≥ 3 QEEG trends indicative of seizure, observed clinical manifestations	QEEG comment
Status epilepticus (no clinical) certain	≥ 3 QEEG trends indicative of seizure, lasting > 10 min OR multiple seizures occur per hour making up more than 10 min, no observed clinical manifestations	QEEG comment
Status epilepticus (clinical) certain	≥ 3 QEEG trends indicative of seizure, lasting > 10 min OR multiple seizures occur per hour making up more than 10 min, observed clinical manifestations	QEEG comment
QEEG screened hourly	Bedside clinician has assessed QEEG 1-hour epoch	QEEG comment
Time to seizure recognition QEEG	Date/time stamp of seizure certain comment on QEEG	QEEG comment
Seizure event verified by neurologist	Date/time stamp of seizure confirmed comment on QEEG	QEEG comment
Event confirmed “not seizure” by neurologist	Date/time stamp of Event confirmed “not seizure” comment on QEEG	QEEG comment
EEG		
EEG duration	EEG start and stop date/time	EEG annotation
Seizures present (yes/no)	Clinical or subclinical seizures present on cEEG expert review	EEG annotation
Seizures clinical (yes/no)	Clinical manifestations present on video or annotations	EEG annotation
Seizure duration	Seizure onset and offset	EEG annotation
Seizure duration category	< 1 min 1-5 min > 5 min	EEG annotation
Spatial extension of seizure	focal (≤ 4 unilateral electrodes involved) hemispheric (unilateral but > 4 electrodes involved) generalized/bilateral (bilateral, > 4 electrodes involved)	EEG annotation
Electrographic status epilepticus	a single seizure lasting > 10min or recurrent seizures totalling > 10 min in any 1-h period (hourly seizure burden > 10%)	EEG annotation
Status epilepticus clinical (yes/no)	Clinical manifestations present on video or annotations	EEG annotation
EEG background category	normal or sedated sleep slow and disorganized discontinuous or burst suppression attenuated and featureless	EEG annotation

Time to seizure recognition cEEG	Date/time stamp of seizure annotation on cEEG	EEG annotation
Spike amplitude	average amplitude during electrographic seizures as ≤ 50 μV or > 50μV.	EEG annotation
Patient characteristics		
Gender	Male, female	EEG request form
Age	Years, months, days	EEG request form
Primary diagnosis or indication for cEEG	Refractory status epilepticus Encephalopathy with suspicion of electrographic seizures Recent stroke (ischemic, haemorrhagic, sinovenous thrombosis) Epilepsy (history of seizures) Structural brain malformation ECMO and suspicion of brain injury Cardiac procedure and suspicion of brain injury Traumatic brain injury (TBI) Non-accidental injury (NAI) CNS infection (meningitis/encephalitis) Recent neurosurgical procedure (postoperative craniotomy) Brain tumour Hypoxic-ischemic encephalopathy (HIE) Sepsis associated encephalopathy	EEG request form
Primary discharge category/factor for risk of seizures	systemic disease, acute seizures, acute brain injury	Electronic medical record
Time to seizure recognition chart	Date/time stamp of chart entry referencing seizure recognition and/or management	Electronic medical record
Hospital length of stay (LOS)	Date/time of hospital admission and discharge	Electronic medical record
PICU LOS	Date/time of PICU admission and discharge	Electronic medical record
Adverse events	Pressure areas related to EEG electrode placement	Electronic medical record

EEG: electroencephalogram; cEEG: continuously monitored electroencephalogram; QEEG: quantitative electroencephalogram; ECMO: extracorporeal membrane oxygenation; CNS: central nervous system; PICU: paediatric intensive care unit; LOS: length of stay