

# BMJ Open Mapping spreading depolarisations after traumatic brain injury: a pilot clinical study protocol

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## ABSTRACT

**Introduction** Cortical spreading depolarisation (CSD) is characterised by a near-complete loss of the ionic membrane potential of cortical neurons and glia propagating across the cerebral cortex, which generates a transient suppression of spontaneous neuronal activity. CSDs have become a recognised phenomenon that imparts ongoing secondary insults after brain injury. Studies delineating CSD generation and propagation in humans after traumatic brain injury (TBI) are lacking. Therefore, this study aims to determine the feasibility of using a multistrip electrode array to identify CSDs and characterise their propagation in space and time after TBI.

**Methods and analysis** This pilot, prospective observational study will enrol patients with TBI requiring therapeutic craniotomy or craniectomy. Subdural electrodes will be placed for continuous electrocorticography monitoring for seizures and CSDs as a research procedure, with surrogate informed consent obtained preoperatively. The propagation of CSDs relative to structural brain pathology will be mapped using reconstructed CT and electrophysiological cross-correlations. The novel use of multiple subdural strip electrodes in conjunction with brain morphometric segmentation is hypothesised to provide sufficient spatial information to characterise CSD propagation across the cerebral cortex and identify cortical foci giving rise to CSDs.

**Ethics and dissemination** Ethical approval for the study was obtained from the Hennepin Healthcare Research Institute's ethics committee, HSR 17-4400, 25 October 2017 to present. Study findings will be submitted for publication in peer-reviewed journals and presented at scientific conferences.

**Trial registration number** NCT03321370.

## INTRODUCTION

Spreading depression, now known as cortical spreading depolarisation (CSD), was first described by Aristides A.P. Leão in 1944 as the suppression of spontaneous cerebral cortical electrical activity.<sup>1,2</sup> CSDs are characterised by excitatory waves of depolarisation followed by electrical silence of cerebral cortical neurons and glia. Concomitant with the passage of a depolarising wave, action potentials and synaptic transmission are inhibited over a

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This is a pilot feasibility study of a new spatial method for extended recording of cortical spreading depolarisation after traumatic brain injury.
- ⇒ In a limited sample size of 10–20 patients, we will surgically place four multielectrode arrays and measure electrocorticography, to be monitored over the course of multiple days.
- ⇒ This study uses a novel computational approach for mapping spreading depolarisations.

region of the cortex. CSDs propagate at a slow rate of a 1–8 mm/min<sup>3</sup> across contiguous cortical grey matter which exhibits an electrical discharge that produces a change in the extracellular potential of approximately –10 to –20 mV.<sup>4</sup> The large, transient disturbances in extracellular potential are detected using direct current (DC) amplifiers in concert with cortical surface electrodes, a phenomenon known as DC shift,<sup>1</sup> which marks the passage of CSD waves. The current gold standard for CSD detection is invasive neuromonitoring with a single subdural strip electrode.<sup>1,5</sup>

CSDs produce massive changes in the extracellular concentrations of potassium, chloride, glutamate and glucose, as well as dendritic swelling, altered cerebral metabolic rate of O<sub>2</sub> consumption and a vascular hyperaemic response.<sup>6–8</sup> The cascade of events leads to cytotoxic oedema formation.<sup>9,10</sup> The vasomotor response initially consists of arteriolar vasoconstriction followed by a longer period of hyperaemia triggered by the release of glutamate and nitric oxide.<sup>6,11</sup> In a physiological setting, hyperaemia delivers metabolic substrates necessary for recovery of neuronal membrane homeostasis.

When CSDs occur in injured tissue, a variation of the haemodynamic response occurs, with an accentuation of the hypoperfusion state and blunting of the hyperaemic response known as spreading ischaemia or the inverse haemodynamic

response.<sup>3 6 12 13</sup> The haemodynamic inversion becomes increasingly pronounced as brain tissue is more metabolically compromised. Sustained neuronal depolarisation triggers an acidic, hyperkalaemic environment that promotes vasoconstriction, leading to further reduction in nutrient supply and upregulation of factors that lead to increased blood brain barrier permeability and vasogenic oedema.<sup>11 14</sup> The sequence of CSDs followed by the inverse haemodynamic response creates a pathological feed-forward cycle which facilitates further CSD events. As a result, regions of focal infarct may expand significantly during the subsequent secondary injury induced by repeated CSD events, as has been demonstrated in traumatic brain injury (TBI), stroke and aneurysmal subarachnoid haemorrhage (SAH).<sup>15 16</sup>

At the time that Leão described the CSD phenomenon, he hypothesised that propagating focal seizures were related phenomena and that they are generated by similar cellular mechanisms.<sup>2</sup> Subsequently, seizures have been described to promote an extracellular milieu supportive of CSD events and vice-versa. Both seizures and CSD events arise from abnormal neuronal activity in excitotoxic states that ultimately results in a synchronisation of hyperexcitable neurons.<sup>11 14 17</sup> CSDs and electrographic seizures occur in cortical slice preparations after induction of CSDs.<sup>11 18</sup> Seizures and CSDs also occur together in the human brain. Fabricius *et al* analysed the electrocorticography (ECoG) recordings of 63 patients after acute brain injury and found that 32 patients exhibited CSDs within 10 days of ECoG electrode implantation. Seizures and CSDs were both observed in 10 patients.<sup>18</sup> A similar study found coincident CSD and seizure activity in 14/103 patients while CSDs occurred in the absence of seizures in 58/103 patients.<sup>19</sup> While evidence for coupling of CSDs and seizure activity in the injured human cerebral cortex has been reported, further investigation is required to define the coexistence of seizures and CSDs after TBI as well as to determine what cause-and-effect relationship, if any, might exist between these pathological states.

ECoG recording in humans after TBI demonstrates an early (~48 hours) increased incidence of CSD clusters with a less pronounced, longer latency clustering of CSDs at days 6–8 postinjury (this second peak is more pronounced after aneurysmal SAH).<sup>20–22</sup> Other factors associated with a higher probability of CSDs are lower mean arterial pressure, lower cerebral perfusion pressure and higher core body temperatures.<sup>22</sup> Subdural and subarachnoid blood volume are also associated with CSD events.<sup>23 24</sup> The early recognition of CSDs is crucial for improved management of TBI as CSD clusters are independently associated with unfavourable Extended Glasgow Outcome Scale scores at 6 months in patients with acute TBI.<sup>19 23</sup>

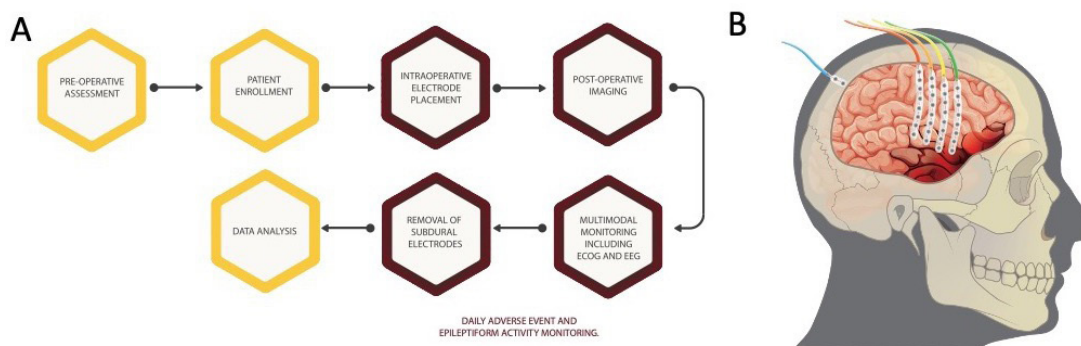
In animal models, CSD waves exhibit irregular wave patterns and propagation speeds which vary depending on structural barriers such as veins and sulci. Broken radial, irregular cycling, reverberating and reentrance patterns have been described.<sup>25 26</sup> In human cerebral cortex CSD propagation paths observed after SAH have

been modelled yielding estimates of SD propagation velocity.<sup>10</sup> The modelling of SD propagation in human cortex has proven challenging in part due to limitations of currently available brain segmentation algorithms which are not well suited for use in the setting of significant structural pathology.<sup>10</sup> The limitations are further compounded by the current standard CSD monitoring strategy (ie, a single strip electrode) which affords limited spatial resolution of cortical activity.<sup>1 27–31</sup> Whether, and to what extent CSD initiation and propagation may be distorted by structural injuries and reduced energetic substrates is unknown as CSDs have not been electrically mapped in relation to structural injuries in patients with TBI.

With the exception of several large trauma centres, current standard medical care does not include application of continuous electroencephalography (EEG) or ECoG monitoring in patients with TBI.<sup>32</sup> The current standard for invasive neuromonitoring after TBI was largely developed prior to the understanding of the contribution of CSD to secondary brain injury and may be inadequate for optimising outcomes after brain injury.<sup>33</sup> Determination for continuous EEG monitoring is based on clinical suspicion for seizures due to ongoing, unexplained altered mental status, fluctuating mental status, unexplained clinical paroxysmal events and for monitoring effectiveness of seizure treatment, among other indications.<sup>34</sup> The approach to seizure monitoring in critically ill patients is accepted practice despite a 34% prevalence of seizures in patients requiring neuro intensive care unit (ICU) level care<sup>35 36</sup> with the majority (approaching 90% in comatose patients) of epileptiform activity detected with EEG or ECoG without clinically overt seizure activity.<sup>18 36</sup> Patients with TBI are among the largest critically ill patient populations to be affected by the lack of routine continuous monitoring of brain activity. Early post-traumatic seizures (seizures occurring within 7 days of brain trauma) are a well-known complication of TBI. The incidence of early post-traumatic seizures is as high as 26% with more than half of the seizures being non-convulsive and diagnosed exclusively by EEG.<sup>35 37 38</sup> Thus, the current management of patients requiring neuroICU care may lead to delayed recognition and treatment as well as potentially missed detection of seizures.

The early recognition and treatment of post-traumatic seizures is paramount, as post-traumatic seizures lead to secondary brain injury, worsen outcome and significantly increase the risk of developing late post-traumatic seizures and post-traumatic epilepsy.<sup>21 35 37</sup> Furthermore, seizures during hospitalisation for TBI are independently associated with longer hospital stays, posthospitalisation discharge to a nursing facility, as well as a higher likelihood of mortality.<sup>35 39</sup>

This study is designed to evaluate the feasibility of characterising the spatiotemporal dynamics of CSDs and evaluate these dynamics with respect to structural brain lesions and physiology of patients with TBI by using a multielectrode array combined with novel analytical algorithms.



**Figure 1** Overview of the major events from patient selection to data analysis for proposed study (A) and schematic of the subdural strip electrodes used for the study (B). Note, strip electrodes include 4, 8 contact recording electrodes placed on the cortical surface and a single 2 contact ground electrode placed in the subgaleal space.

Furthermore, by extending the duration of continuous neuromonitoring beyond 7 days, the study affords the opportunity to improve the current understanding of the incidence of CSDs after TBI. A secondary objective of the study is to identify epileptiform activity and characterise the spatiotemporal relationship of epileptiform activity with CSD events.

## METHODS AND ANALYSIS

### Aim and setting

In this pilot, prospective, observational study, we aim to determine the feasibility of using four electrode strips to identify CSDs as well as their propagation characteristics in space and time (figure 1). The study is being conducted in the surgical ICU of a level 1 trauma centre with continuous monitoring by neurocritical care staff. Based on the goal of a pilot trial, the target sample size for the study is 10–20 participants. The ultimate number of patients enrolled is contingent on the incidence of CSD events observed in the initial participants given that CSDs occur in approximately 56% of patients with TBI.<sup>1</sup> The rationale for performing a pilot study is that the proposed approach to invasive neuromonitoring as well as the computational techniques employed in the trial are novel. Therefore, the feasibility of implementing these techniques in a larger trial requires preliminary evaluation.

The secondary goal of the study is characterisation of the relationship between CSD events and epileptiform activity. Given the larger spatial resolution afforded by the multielectrode array, the relationship between epileptiform activity and CSD may be better characterised than it has in previous studies utilising a single strip electrode recording configuration.<sup>18 19</sup>

### Patients

All patients who present through the emergency department or on direct transfer to the neurosurgery service with TBI requiring neurosurgical intervention are eligible for screening. The inclusion criteria are age 18 years or older, diagnosis of TBI, and recommendation to undergo craniotomy/craniectomy for evacuation of

mass effect or due to refractory elevation of intracranial pressure. Exclusion criteria include contaminated head wound, TBI lesion requiring posterior fossa decompression, known or suspected systemic bacterial infection and pregnancy. Multiple traumas, penetrating head injuries or other pre-existing diseases are not exclusions to study enrolment.

### Patient and public involvement

Patients and/or the public were not involved in the design of the trial protocol.

### Placement of cortical electrodes

Trained neurosurgery staff will place four 1×8 contact (linear array) subdural electrode strips (PMT Corporation, Chanhassen, MN) in a grid formation on the cerebral cortical surface. The electrode strip array consists of 8 platinum electrodes each 3 mm in total diameter and 10 mm distance between electrode centres. The goal is to place the electrodes in an orientation that positions contacts across injured and normal appearing brain tissue (figure 1B). A 1×2 contact strip (4.5 mm distance between electrodes) ground electrode is placed in the subgaleal space near the cranial defect. The electrode leads are tunnelled 3–5 cm away from the primary surgical incision through stab incisions in the scalp. The procedure is identical to that reported for a single electrode.<sup>1</sup> The incisions are closed in the usual fashion and patients are admitted in the neurosurgical care unit. Once critical care is no longer clinically indicated, the subdural electrodes are removed at the bedside via the scalp defect that the electrode lead was tunnelled through by applying gentle traction.<sup>1</sup>

### Multimodal neuromonitoring and ECoG acquisition

Postneurosurgical care and continuous bedside monitoring are provided in the surgical ICU. As the standard of care, intracranial pressure, mean arterial pressure, cerebral perfusion pressure and brain tissue oxygen monitoring are monitored in addition to the acquisition of continuous ECoG recordings as long as invasive neuromonitoring is clinically indicated. Monopolar ECoG recordings are acquired from the 32 recording electrodes

against the subgaleal reference using the Neuralynx ATLAS neurophysiology amplifier system (Neuralynx, Bozeman, MT) with Persyst Continuous Monitoring software (Persyst, Solana Beach, California, USA) for interpretation of DC-coupled ECoG recordings. Signals are sampled at 16 kHz using a 0.0–4.0 kHz band-pass filter. If significant charge build-up occurs during continuous acquisition, the acquisition is altered to a near-DC configuration with a 0.01 to 4 kHz band-pass filter. The dynamic range of the amplifier was set to  $-128$  mV to  $+128$  mV. Daily monitoring includes reporting of any adverse events.

### Standard of care and seizure monitoring

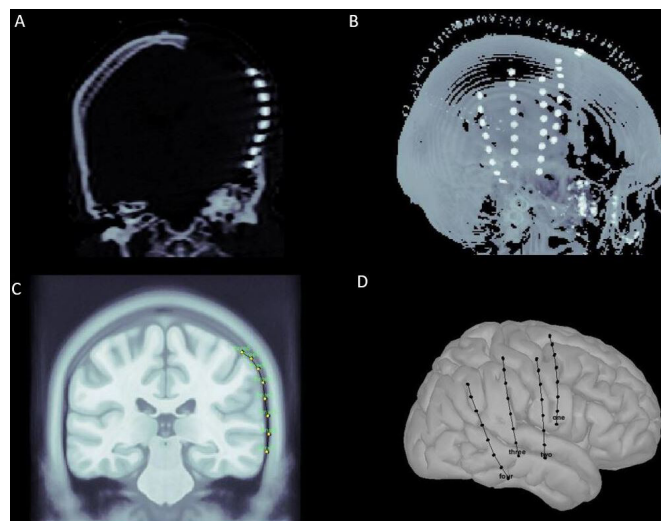
Participants enrolled in this study undergo continuous ECoG monitoring for as many days clinically possible in the ICU. Patient stay will not be prolonged for recording unless medically indicated. ECoG recordings will be reviewed daily for evidence of epileptiform activity, and therefore, subclinical seizures are more likely to be detected and treated at an early stage compared with patients with TBI not enrolled in the study, providing a possible direct benefit to participants enrolled in this study.

### Data analysis and mapping CSDs

CSD events are identified offline by their characteristic negative shift of the slow potential recorded with a DC-coupled amplifier and an associated reduction in the amplitude of spontaneous cortical activity or characteristic sequential DC changes in two or more adjacent electrodes within 10 min of each other based on the criteria recommended by the Co-Operative Studies on Brain Injury Depolarisations.<sup>1 5</sup> Characteristics of CSD events including the duration and amplitude of DC shift, depression pattern and propagation rate, as well as individual electrode sensitivity and specificity will be computed. The CSD characteristics will be correlated to structural lesions (defined by brain imaging), epileptiform discharge, intracranial pressure, mean arterial pressure, cerebral perfusion pressure, peripheral capillary oxygenation and brain tissue oxygenation.

The use of multiple electrode arrays affords improved spatial resolution of cortical activity compared with a single six contact linear electrode array. Therefore, the likelihood of identifying and characterising the origination and propagation of the CSDs is increased. The novel approach to capturing CSDs is anticipated to allow the development of models of CSD propagation as well as localisation of foci of CSD initiation.

CSD foci will initially be localised using electrophysiological data. A cross correlation of ECoG signals is performed across all electrode pairs followed by a Granger causality analysis to determine the directionality of signal propagation across the electrodes.<sup>40</sup> A two-dimensional (2-D) plane will be constructed based on interelectrode distances. This will allow the CSD epicentre and propagation of CSD waves to be characterised in 2-D space. Reconstruction of the cortical surface using a standard MRI



**Figure 2** Brain segmentation pipeline (A) Reference thresholded CT input is first inverse segmented to obtain a crude brain structure with cortical electrodes identified (B). This segmentation is transformed and projected to a standard MRI template to appreciate anatomical landmarks using SPM 12 toolbox in Brainstorm (C, D).<sup>56 57</sup>

template and the post-operative head CT is performed using Brainstorm.<sup>41</sup> First, DICOM files of the post-operative CT are loaded into the three-dimensional (3-D) slicer.<sup>42–45</sup> The volume is then coregistered with a standard MRI template using SPM 12 toolbox.<sup>46</sup> Visualisation of electrode configuration is then marked and labelled in the postoperative CT in 3-D. An example registration and mapping is shown in figure 2.

After the postoperative CT brain segmentation has been performed, the 2-D surface constructed with the electrophysiological recordings is overlaid on the 3-D brain segmentation so that the CSD foci and propagation characteristics are correlated with brain morphology and structural injuries.

### ETHICS AND DISSEMINATION

The trial is approved by the Hennepin Healthcare Research Institute's Institutional Review Board (Reference number: HSR 17-4400) and performed in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice (ICH E6) and the code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46). Written informed consent is obtained from study participants or their legally authorised representatives prior to enrollment.

Study participants are monitored for adverse events throughout the study. The principal investigator will record all reportable events occurring after enrollment until 7 (for non-serious adverse events) or 14 days (for serious adverse events) after the last day of study participation. Adverse events will be followed for outcome information until resolution or stabilisation. Study participants are followed daily during enrollment. After electrode removal, there is no further planned follow-up.

Safety oversight is under the direction of the principal investigators, aided by the coinvestigators and collaborators. Patients are monitored in the ICU with close supervision. ECoG recordings will be reviewed daily for evidence of seizure activity. Adverse events will be reviewed monthly and addressed to correct safety issues. Safety events are reported to the Institutional Review Board. Aggregate adverse event data will be reported twice per year as patient data is available to the Institutional Review Board.

Study findings will be submitted for publication in peer-reviewed journals. In addition, study findings will be presented at scientific conferences. Deidentified participant data will be made available on reasonable request.

## DISCUSSION

Achieving the aims of this pilot study: implementation of long-term multielectrode monitoring of CSDs, mapping of CSDs and identification of epileptiform activity in relation to CSD events would support the feasibility of a full-scale trial. An appropriately powered study would provide the means to unambiguously identify the origin of CSDs, at-risk brain regions relative to CSD origins and the time course of CSDs post injury. Furthermore, a large data set with CSDs mapped from a diverse range of cortical pathology at high spatial resolution could serve as the basis for the development of automated algorithms for CSD detection.

The time-course of CSD incidence following TBI is well characterised within 24–72 hours after injury.<sup>20–22</sup> However, the frequency of CSD events beyond approximately 7 days postinjury is less well understood. The limited understanding of the CSD time course is due in part to the design of prior studies which, except in the case of SAH,<sup>1 10</sup> discontinued invasive neuromonitoring at or before 7 days.<sup>19 22 28 46–49</sup> Another barrier to determining the natural history of CSDs after TBI is current clinical practice which emphasises early cessation of invasive neuromonitoring and transfer out of the ICU.<sup>33</sup> Based on the time-varying distribution of CSDs post-TBI as well as preclinical data,<sup>50</sup> the duration of invasive neuromonitoring should be extended to improve the understanding of the fundamental time-course of CSDs.<sup>15 28</sup> Elucidating the time-course of CSDs is important as it will inform the therapeutic window for interventions to minimise secondary injury after TBI.

Preclinical studies demonstrate that CSDs arise independently from several different foci<sup>49</sup> and exhibit independent wave morphology.<sup>25 26</sup> However, multiple CSD foci and their spatial distribution have not been specifically investigated in clinical trials.<sup>1 19 22 28 49 50</sup> By using an alternative recording method to capture CSDs with higher resolution and creating a model for different TBI presentations, our goal is to build on prior studies and determine the spatiotemporal properties of CSDs. By achieving the study goals of defining the spatiotemporal properties of CSDs and the time course of CSD events

post-injury, the next step is the development of an automated CSD detection algorithm.

Identifying the topology of CSD origins has important therapeutic implications. For example, one putative therapeutic approach to minimising CSDs after TBI is blocking the NMDA receptor.<sup>51–53</sup> Inhibition of NMDA receptors more effectively blocks CSDs in healthy brain tissue compared with ischaemic tissue.<sup>54</sup> If initiation of CSDs always occurs in penumbral tissue then targeting of the N-methyl-D-aspartate (NMDA) receptor may not be the most effective approach to minimising secondary injury after TBI. Another hypothesis to consider is that CSDs in penumbral tissue originate in other brain regions, and through re-entrant pathways, propagate through ischaemic tissue and return to the site of injury. In either case, the differential effects of other therapeutic agents evaluated for effective CSD blockage may similarly occur. Therefore, improved understanding of CSD dynamics after TBI may guide the selection of therapeutic targets.

## CSDs and seizures

CSD and seizure activity are classified as distinct phenomena though they co-occur in patients with severe TBI.<sup>18 53</sup> Modelling of neuronal activity suggests that CSD, mixed seizure and CSD states as well as terminal anoxic depolarisation are events in a continuum.<sup>17</sup> By increasing the ECoG recording period, our goal is to define the spatiotemporal relationship between seizures and CSDs after brain injury. Moreover, daily review of the ECoG recordings allows adjustments of AEDs to treat subclinical seizures. The goal of the study is not to evaluate the relationship between post-TBI CSD incidence and development of epilepsy, though prior studies have established a link between early CSDs and late epilepsy after SAH.<sup>21</sup>

Commonly used AEDs, such as levetiracetam, may differentially affect CSD and seizure activity. Though the mechanism of levetiracetam is not fully understood, it is known that levetiracetam inhibits glutamatergic neurotransmission<sup>55 56</sup> and in hippocampal slices reduces spontaneous NMDA-induced epileptiform bursts.<sup>57–59</sup> The pathophysiological basis of CSD and astroglial impairment involves the sensitisation of NMDA receptors to small changes in interstitial glutamate, facilitating further release of glutamate and  $K^+$ .<sup>8 15</sup> Could the excitotoxic effects of glutamate in the origins of CSDs be modified with the use of this anti-convulsant and other glutamate/NMDA receptor modulating drugs? An *in vitro* study demonstrated that NMDA receptor antagonists blocked both epileptiform activity as well as CSDs<sup>56</sup> and *in vivo* NMDA receptor blockade diminished the secondary phase of CSD attenuating core infarct volume.<sup>50</sup> Additionally, a derivative of valproic acid reduced CSD events,<sup>11</sup> and ketamine reduces CSDs.<sup>51 53</sup> Interventions to ameliorate or prevent CSDs is an area of active investigation and is beyond the scope of the current trial. However, since it is the standard of care for patients with TBI in our centre to receive prophylactic and therapeutic treatment for seizures with levetiracetam, some



insight might be obtained into the relationship between seizures, CSD and the use of glutamate-inhibiting drugs.

### Study limitations

As this is a feasibility study with an expected small heterogeneous cohort of patients, several limitations related to the study design might be encountered:

1. Population heterogeneity: bimodal age distribution and injury heterogeneity can limit intersubject reproducibility.<sup>59</sup> Older individuals exhibit lower CSD incidence<sup>18 55</sup> and higher CSF/brain ratios that may reduce signal-to-noise resulting in lower sensitivity of CSD detection. Furthermore, the spectrum and severity of injury varies widely among the TBI population.
2. Temporal heterogeneity: time since injury at which patients are enrolled, implanted and monitored will define the window of CSDs that is captured. While the goal of this study is to extend monitoring beyond 7 days, this might not be feasible for patients that don't require extended ICU stays or for those that deteriorate rapidly.
3. Electrode location heterogeneity: positioning of electrodes will depend on the site of injury as well as the geometry of the craniotomy, therefore, electrodes are unlikely to be anatomically aligned between patients.
4. Coincident CSD and epileptiform activity: given the limited sample size of the pilot study, the number of CSDs in close temporal proximity to epileptiform activity may be limited. Without a sufficient number of coincident CSDs and epileptiform activity, characterisation of the spatiotemporal relationship of these events may not be possible with a high degree of certainty.
5. CSD modelling challenges: brain reconstructions for CSD modelling may be hindered by severe structural injuries that distort sulci/gyri anatomy. Furthermore, previous attempts to reconstruct CSD propagation in injured human cortex have proven challenging given the limitations of currently available brain segmentation software combined with the limited spatial resolution of the recording configurations used to monitor for CSDs.<sup>10</sup>

### TRIAL STATUS

The trial opened for enrolment and is currently recruiting patients.

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**Contributors** SWC conceived the study, participated in the study design, obtained funding, was responsible for preparing and revising the manuscript and is the principal investigator. IPP participated in study design as well as preparation and revision of the manuscript. AN and DC were responsible for assisting with brain segmentation, editing and revising the manuscript. MCP conceived the study, participated in the study design, and was responsible for revising the manuscript. DPD conceived the study, participated in the study design, obtained funding and was responsible for preparing and revising the manuscript. All authors read and approved the final manuscript.

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**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not applicable.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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