

Seizure Prophylaxis Versus Epilepsy Prevention After Acquired Brain Injury: A Cross-Sectional ClinicalTrials.gov Registry Analysis, 2000-2026

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Abstract

Background

Seizures after acquired brain injury create distinct therapeutic questions: early seizure prophylaxis, treatment of acute symptomatic seizures, and prevention of late epilepsy. These endpoints are often conflated, although early seizure suppression does not establish disease-modifying antiepileptogenesis.

Methods

We performed a cross-sectional ClinicalTrials.gov registry analysis of studies first posted from January 1, 2000, through June 18, 2026. Four disease-specific seizure-related search blocks were deduplicated by NCT number and adjudicated into a primary seizure-management cohort or sensitivity/monitoring cohort. Data were extracted from ClinicalTrials.gov export files and final adjudicated CTG Excel workbooks. In response to clinical-review priorities, we added NCT-specific extraction of completed pharmacologic trials, antiseizure medication or study-drug dosing when explicitly present in registry fields, seizure-control endpoints, follow-up windows, and clinical, EEG/cEEG/ECOG, and MRI/CT/imaging markers.

Results

Searches yielded 1,054 exported records; after removal of duplicate NCT numbers, 878 unique records were screened. Final adjudication retained 85 primary-cohort studies and 39 sensitivity/monitoring records; 754 records were excluded. Reviewer agreement was substantial to almost perfect across inclusion, disease category, seizure-focus category, and intervention type (kappa range, 0.787–0.897). Primary-cohort activity was concentrated in brain tumor/neurosurgery (27/85, 31.8%) and traumatic brain injury (23/85, 27.1%). Trial focus included late epilepsy prevention (26/85, 30.6%), acute seizure prophylaxis (25/85, 29.4%), acute symptomatic seizure treatment (23/85, 27.1%), and monitoring/characterization or other ASM-use studies (11/85, 12.9%). Drug/ASM interventions accounted for 46/85 (54.1%). Among 26 completed trials eligible for registry results-reporting assessment, 11 (42.3%) had posted results. Completed medication/study-drug trials were clinically heterogeneous, and explicit dose fields were sparse and NCT-specific.

Conclusions

The registered evidence-generating pipeline for seizures after acquired brain injury is clinically important but fragmented. Future trials should separate acute seizure suppression from late epilepsy prevention, enrich enrollment using etiology-specific seizure-risk markers, predefine how clinical seizures, EEG/cEEG/ECOG, and imaging guide prophylaxis decisions and duration, and improve dose-level and results reporting.

Clinical trial registration

Clinical trial number: not applicable. This manuscript is a cross-sectional registry analysis and was not itself a clinical trial. NCT01463033 is an included ClinicalTrials.gov registry record; its ClinicalTrials.gov first-posted/registration date was November 1, 2011.

Key points

- ClinicalTrials.gov seizure-related trials after acquired brain injury frequently mix acute prophylaxis, acute symptomatic seizure treatment, and late epilepsy prevention, although these are different clinical and biological endpoints.
- Drug/ASM trials dominate the portfolio, but registry dose reporting is sparse; explicit dose information was limited to NCT-specific records such as levetiracetam 55 mg/kg/day, perampanel dose records, vigabatrin renal-adjusted dosing, eslicarbazepine acetate 800 mg versus placebo, and a ketamine sensitivity/monitoring ECOG record.
- Clinical seizure assessment, EEG/cEEG/ECOG, and MRI/CT/imaging were used inconsistently, supporting the need for etiology-specific trial selection criteria and endpoint definitions.

Background

Seizures and epilepsy after acquired brain injury are clinically important but methodologically difficult endpoints. Acute symptomatic seizures occur in close temporal association with a systemic or brain insult, whereas epilepsy implies a durable predisposition to recurrent unprovoked seizures [1, 2]. This distinction matters because a trial that reduces early seizures during an index hospitalization has not necessarily demonstrated antiepileptogenesis or prevention of late epilepsy.

The clinical context varies substantially across disease states. Post-stroke epilepsy risk is shaped by stroke severity, cortical involvement, early seizures, and hemorrhagic features; risk models such as SeLECT and CAVE illustrate the movement toward individualized risk stratification [3–5]. TBI remains a prototypical acquired cause of epilepsy, yet classic randomized trials showed that phenytoin reduces early post-traumatic seizures without preventing late post-traumatic epilepsy [6–9]. Recent TBI guidance continues to emphasize uncertainty in patient selection, choice of medication, and duration of prophylaxis [10–12].

Stroke, intracerebral hemorrhage, subarachnoid hemorrhage, brain tumors, neurosurgery, CNS infection, and hypoxic brain injury generate different seizure-risk mechanisms and different clinical decisions. Contemporary ICH and SAH guidance cautions against indiscriminate prophylaxis and prioritizes clinical or electrographic seizure recognition [13–15]. Similarly, brain tumor and neurosurgical guidance has repeatedly questioned routine prophylactic antiseizure medication in seizure-naïve patients [16–18].

The central question is not simply whether seizure-related trials exist, but whether the registered evidence pipeline distinguishes what it is trying to accomplish. We therefore analyzed ClinicalTrials.gov records from 2000 to 2026 to map disease populations, seizure-related objectives, medications and doses when available, outcome and follow-up choices, use of clinical/EEG/imaging markers, completion status, and registry results reporting.

Methods

Study design and data source

We performed a cross-sectional registry analysis of ClinicalTrials.gov records. The study used publicly available trial-level registry data and did not involve patient-level identifiable information. Reporting was informed by STROBE principles for observational analysis, the RECORD statement for studies using routinely collected registry data, and PRISMA-style flow reporting for record selection [24–26].

ClinicalTrials.gov was accessed on June 18, 2026. Eligible first-posted dates ranged from January 1, 2000, through June 18, 2026. Records were exported from the ClinicalTrials.gov search interface and deduplicated by NCT number. Registry fields included status, dates, title, conditions, summary, interventions, sponsor/collaborators, design features, eligibility, outcome measures, locations, and available results-reporting fields [27, 28]. The source of extraction for all added clinical datapoints was the ClinicalTrials.gov export files and final adjudicated CTG Excel workbooks, not the manuscript document.

Search strategy and eligibility

Four disease-specific search blocks were used to improve sensitivity while preserving interpretable disease categories: stroke/hemorrhage; traumatic brain injury/head injury; brain tumor/craniotomy/neurosurgery; and neurocritical illness including subarachnoid hemorrhage, intracerebral hemorrhage, encephalitis, hypoxic-ischemic brain injury, coma, and neurocritical care. Each block was combined with a standardized seizure-related search string including seizure, epilepsy, epileptogenesis, seizure prophylaxis, acute symptomatic seizure, status epilepticus, nonconvulsive seizure, post-traumatic epilepsy, post-stroke epilepsy, postoperative seizure, antiepileptic, antiseizure, anticonvulsant, and named ASMs.

Studies were eligible if the registry record described an acquired brain injury population and a seizure-related purpose. We excluded primary epilepsy trials unrelated to acquired brain injury, chronic antiseizure-drug trials in established epilepsy without a qualifying neurologic injury exposure, febrile seizure studies, neonatal-only hypoxic injury or neonatal seizure studies, basic science/nonhuman studies, and non-neurologic ICU seizure studies unless a qualifying acquired brain injury was clearly present.

Study selection, classification, and clinical deep-dive extraction

Records underwent two-stage screening followed by manual adjudication using a predefined coding dictionary. The final primary analytic cohort included trials of acute seizure prophylaxis, late epilepsy prevention, treatment of acute symptomatic seizures, antiseizure-medication use after acute neurologic injury, and clinically linked seizure monitoring or characterization when the registry record directly informed post-injury seizure management. Seizure detection, EEG-based monitoring, remote monitoring, neuromonitoring, and related adjunct studies retained outside the primary analytic cohort were summarized separately as a sensitivity/monitoring cohort.

In addition to the main registry variables, we performed a clinically oriented deep dive of completed primary-cohort medication/drug trials and dose-containing pharmacologic records. NCT-specific fields included etiology, seizure-focus category, drug/ASM or comparator, dose if explicitly present in the registry export, treatment or follow-up duration, seizure-control endpoint, results posting, and use of clinical seizure assessment, EEG/cEEG/ECOG, or MRI/CT/imaging. Dose was not inferred from standard clinical practice; it was recorded only when present in the uploaded CTG export/deep-dive workbook or verified registry record.

Reviewer validation was performed on a set of candidate included, sensitivity, and borderline excluded records. Reviewers classified inclusion status, disease category, seizure-focus category, and intervention type. Disagreements were resolved by consensus. Percent agreement and unweighted Cohen kappa were calculated.

Statistical analysis

Categorical variables were summarized as counts and percentages. Enrollment was summarized using median and interquartile range because enrollment was right-skewed. Registration trends were summarized by calendar year and prespecified eras. Cross-tabulations were used to summarize disease category by seizure-focus category and temporal era by disease category, seizure focus, and intervention type. Exploratory chi-square tests were interpreted cautiously because several expected cell counts were small. Data organization and screening adjudication were performed in Microsoft Excel. Descriptive statistics, cross-tabulations, exploratory chi-square analyses, and reviewer-agreement analyses were performed in Jamovi version 2.7.34 and checked against the final adjudication workbook and original ClinicalTrials.gov export files.

Results

Search yield and reviewer validation

The four ClinicalTrials.gov search blocks yielded 1,054 exported records. After removal of 176 duplicate NCT records, 878 unique records were screened. Final adjudication retained 85 studies in the primary analytic cohort and 39 additional records in the sensitivity/monitoring cohort; 754 unique records were excluded (Fig. 1).

In the reviewer-validation set ($n = 269$), all four coded fields matched exactly for 232/269 records (86.2%). Variable-specific agreement was 87.4% for inclusion/exclusion status ($\kappa = 0.787$), 92.2% for disease category ($\kappa = 0.884$), 90.3% for seizure-focus category ($\kappa = 0.853$), and 91.8% for intervention type ($\kappa = 0.897$).

Primary cohort and clinical evidence-pipeline structure

Among the 85 primary-cohort studies, brain tumor/neurosurgery (27/85, 31.8%) and TBI (23/85, 27.1%) were the largest disease categories, followed by ischemic/unspecified stroke (11/85, 12.9%), CNS infection/encephalitis (8/85, 9.4%), and hypoxic-ischemic injury/coma (6/85, 7.1%). The median enrollment was 88.5 participants (IQR, 30–267; enrollment available for 84/85 studies). Fifty-nine studies (69.4%) were interventional and 26 (30.6%) were observational.

Trial focus included late epilepsy prevention (26/85, 30.6%), acute seizure prophylaxis (25/85, 29.4%), acute symptomatic seizure treatment (23/85, 27.1%), and monitoring/characterization or other ASM-use studies (11/85, 12.9%). TBI trials were primarily late epilepsy prevention or acute prophylaxis studies, whereas brain tumor/neurosurgery trials more often addressed acute symptomatic seizure treatment or perioperative seizure prophylaxis. Stroke-related trials were fewer and concentrated in late epilepsy prevention or post-stroke epilepsy. CNS infection/encephalitis and hypoxic-ischemic injury/coma were represented largely by acute symptomatic seizure treatment, seizure characterization, or monitoring-linked studies (Table 1; Fig. 2).

Table 1
Primary-cohort trial focus by acquired brain injury category and clinical interpretation.

Disease category	Acute seizure prophylaxis	Late epilepsy prevention	Acute symptomatic seizure treatment	Monitoring/characterization/other ASM use	Total	Clinical interpretation
Brain tumor/neurosurgery	9	2	12	4	27	Largest category; mainly perioperative prophylaxis and tumor-related seizure treatment.
TBI	9	14	0	0	23	Dominated by late epilepsy prevention and acute prophylaxis; early and late objectives must be separated.
Ischemic/unspecified stroke	1	9	1	0	11	Mostly late epilepsy prevention/post-stroke epilepsy; risk enrichment is essential.
CNS infection/encephalitis	0	0	6	2	8	Primarily acute symptomatic seizure treatment/characterization.
Hypoxic-ischemic/coma	1	0	2	3	6	Acute treatment and EEG-linked characterization predominate.
ICH/hemorrhagic stroke	2	0	1	0	3	Small evidence stream despite high clinical relevance.
SAH	2	1	0	0	3	Few trials; prophylaxis and late prevention remain distinct clinical questions.
Mixed neurocritical illness	1	0	0	1	2	Heterogeneous; requires prespecified stratification.
Mixed acquired brain injury/stroke	0	0	0	1	1	Sparse registry representation.
Other acquired brain injury/subdural hematoma	0	0	1	0	1	Single-record category; descriptive only.
Total	25	26	23	11	85	Portfolio mixes acute prophylaxis, treatment, late prevention, and monitoring/other studies.
<i>Note: Disease and focus categories were coded from registry title, condition, summary, intervention, and outcome fields. Composite or granular seizure-focus labels were collapsed into dominant analytic categories.</i>						

Medication strategy, completed trials, dosing, outcomes, and follow-up

Drug/ASM interventions accounted for 46/85 (54.1%) of primary-cohort studies. The most frequently named medication was levetiracetam (30 trial-level mentions), followed by phenytoin/fosphenytoin (8), lacosamide (7), valproate/valproic acid (6), and perampanel (5); other named ASMs/study drugs accounted for 14 additional mentions, including eslicarbazepine as a single mention. Medication counts were non-mutually exclusive trial-level mentions and should not be summed to the number of drug/ASM trials. Because intervention type was coded using the adjudicated analytic category, named medication counts could include records classified under broader intervention categories when the registry intervention-type field was not coded as Drug/ASM.

Among the 27 completed primary-cohort studies, 15 were selected for the completed medication/study-drug deep dive. These records were distributed across brain tumor/neurosurgery (6/15), TBI (3/15), ICH/hemorrhagic stroke (2/15), mixed neurocritical illness (1/15), SAH (1/15), hypoxic-ischemic/coma (1/15), and ischemic/unspecified stroke (1/15). Their focus was acute seizure prophylaxis in 6/15, acute symptomatic seizure treatment in 6/15, and late epilepsy prevention in 3/15. Ten of 15 had posted ClinicalTrials.gov results.

Explicit dosing was sparse and NCT-specific. In primary-cohort records, dose fields were available for levetiracetam in NCT01463033 (55 mg/kg/day for post-traumatic epilepsy prevention), perampanel in completed tumor-related seizure-treatment record NCT02363933 and terminated primary-cohort dose record NCT04650204, vigabatrin in NCT04772547, and eslicarbazepine acetate in NCT06597084 (ESL 800 mg vs placebo). In the sensitivity/monitoring cohort, ketamine dosing was available in NCT07165262, an intraoperative ECoG pharmaco-activation study rather than an ASM prophylaxis or epilepsy-prevention trial. Most other completed ASM records did not provide dose-level detail in the exported registry fields (Table 2).

Table 2

NCT-specific pharmacologic/deep-dive records: completed primary-cohort medication trials plus dose-containing primary and sensitivity records.

Cohort/status	NCT	Etiology / focus	Medication or comparator	Dose in CTG export	Clinical endpoint / follow-up	Markers / results
Primary completed	NCT00004817	TBI; acute seizure prophylaxis	Phenytoin; valproate sodium	Not reported	Safety/tolerability and post-traumatic seizure prevention intent; follow-up unclear in export	Marker not explicit; results not posted
Primary completed	NCT00571155	Brain tumor/neurosurgery; acute symptomatic seizure treatment	Levetiracetam	Not reported	Feasibility, efficacy, safety, and tolerance around neurosurgical intervention; 1 year	Clinical seizure assessment; results not posted
Primary completed	NCT00618436	Mixed neurocritical illness/TBI/SAH; acute prophylaxis	Levetiracetam vs phenytoin	Not reported	Seizure incidence up to 6 months; functional outcomes at discharge, 3 and 6 months	Clinical seizure assessment; results posted
Primary completed	NCT00629889	Brain tumor/neurosurgery; acute symptomatic seizure treatment	Levetiracetam; pregabalin	Not reported	Survival without status epilepticus, impaired-consciousness seizures, AED add-on, or discontinuation; 12 months	Safety/tolerability emphasis; results not posted
Primary completed	NCT01115959	ICH/hemorrhagic stroke; acute symptomatic seizure treatment	Valproic acid vs placebo	Not reported	Number of seizures during 1-month study drug period and 1-year follow-up; NIHSS outcome	Marker not explicit; results not posted
Primary completed	NCT01137110	SAH; acute seizure prophylaxis	Brief vs extended levetiracetam	Not reported	In-hospital seizures from admission to discharge	Marker not explicit; results posted
Primary completed	NCT01463033	TBI; late epilepsy prevention	Levetiracetam	55 mg/kg/day	Post-traumatic epilepsy at 2 years; adverse events during 30-day treatment	Marker not explicit; results posted
Primary completed	NCT01673828	TBI; late epilepsy prevention	Allopregnanolone injection vs placebo	Not reported	Safety/tolerability and late prevention-oriented outcomes; 6 months	Marker not explicit; results posted
Primary completed	NCT02276053	Brain tumor/neurosurgery; acute symptomatic seizure treatment	Lacosamide adjunctive therapy	Not reported	Responder outcome in brain tumor-related epilepsy; 28 days to 6 months	Functional/cognitive relevance; results posted
Primary completed	NCT02334722	Brain tumor/neurosurgery; acute prophylaxis	Levetiracetam	Not reported	Neurotoxicity scale change; baseline to 6 weeks/follow-up	Safety/tolerability emphasis; results posted
Primary completed	NCT02363933	Brain tumor/neurosurgery; acute symptomatic seizure treatment	Perampanel	2 mg start; titrate to 8 mg; taper 6/4/2 mg then stop	At least 50% seizure reduction during maintenance; 2–24 week windows	Clinical seizure assessment; results posted
Primary completed	NCT02631759	ICH/hemorrhagic stroke; acute prophylaxis	Levetiracetam vs placebo	Not reported	Clinical/electrical seizure on 48-hour EEG; early/late clinical seizures to 12 months; mRS/NIHSS/CT edema	Clinical + EEG + MRI/CT; results posted
Primary completed	NCT04497142	Brain tumor/neurosurgery; acute prophylaxis/mechanistic	Perampanel + standard of care	Not reported	Peritumoral HFO rate on ECoG; seizure freedom to progression or 12 months	ECoG + MRI/CT; results posted
Primary completed	NCT04772547	Hypoxic-ischemic/coma; acute electrographic seizure treatment	Vigabatrin	CrCl > 50: 4500 mg; CrCl 30–50: 2250 mg; CrCl < 30: 1125 mg	Serum absorption by 3 hours; delivery within 48 hours; 6-month follow-up element	EEG/cEEG-linked results posted
Primary completed	NCT06597084	Ischemic/unspecified stroke; late epilepsy prevention	Eslicarbazepine acetate	ESL 800 mg vs placebo	Anti-epileptogenic/post-stroke epilepsy prevention outcomes across 7 days to 18 months	Clinical + EEG; results posted
Primary terminated / dose-containing	NCT04650204	High-grade glioma; focal seizure treatment	Perampanel + standard	4 mg daily	> 50% focal seizure reduction at 3 and 6 months;	Clinical seizure frequency; results posted

Note: Dose is reported only when explicitly present in ClinicalTrials.gov export/deep-dive fields. NCT04650204 was a terminated primary-cohort dose-containing record; NCT07165262 was a sensitivity/monitoring ECoG/anesthetic pharmaco-activation record and not an ASM prophylaxis or epilepsy-prevention trial.

Cohort/status	NCT	Etiology / focus	Medication or comparator	Dose in CTG export	Clinical endpoint / follow-up	Markers / results
			antiseizure-drug context		survival/neuropsychological outcomes; terminated record	
Sensitivity/monitoring / dose-containing	NCT07165262	Brain tumor surgery; intraoperative ECoG pharmac-activation	Ketamine during intraoperative ECoG vs fentanyl context	0.5 mg/kg	ECoG spike activation, blood pressure, heart rate, and recovery-time measures; not seizure prophylaxis or epilepsy prevention	ECoG; active/not recruiting
<i>Note: Dose is reported only when explicitly present in ClinicalTrials.gov export/deep-dive fields. NCT04650204 was a terminated primary-cohort dose-containing record; NCT07165262 was a sensitivity/monitoring ECoG/anesthetic pharmac-activation record and not an ASM prophylaxis or epilepsy-prevention trial.</i>						

Seizure-control outcomes varied by etiology and objective. Registry endpoints included seizure incidence, seizure freedom/control, seizure frequency, late seizure or epilepsy occurrence, status epilepticus, EEG/electrographic seizure burden, need for additional ASM, safety/tolerability, and functional or cognitive outcomes with seizure/ASM relevance. Follow-up windows ranged from acute in-hospital or 48-72-hour periods to 6 weeks, 20–24 weeks, 6–12 months, 18 months, and 2 years. Outcomes were not pooled because endpoint definitions, populations, interventions, and follow-up windows were clinically heterogeneous.

Clinical, EEG, and imaging markers

Clinical seizure assessment was explicitly mentioned in 24/85 primary-cohort records, EEG/cEEG/ECoG in 26/85, and MRI/CT/imaging in 20/85. Clinical seizure assessment was used for seizure incidence, recurrence, seizure freedom/control, time to seizure, and treatment response. EEG/cEEG/ECoG was used for electrographic seizure detection, nonconvulsive seizure burden, perioperative hyperexcitability, ICU monitoring, and EEG-linked outcomes. Imaging was used primarily to define injury substrate or risk context, including cortical involvement, hemorrhage, tumor/neurosurgical context, structural injury, or postoperative substrate. These markers were clinically relevant but were not applied as a uniform validated algorithm for deciding prophylaxis initiation or duration (Table 3).

Table 3
Clinical seizure, EEG/cEEG/ECoG, and MRI/CT/imaging markers used in the primary cohort.

Marker	Count	How used clinically in the registry portfolio	Decision-making limitation
Clinical seizure assessment	24/85	Clinical seizure incidence, recurrence, seizure freedom/control, time to seizure, and treatment response	Directly meaningful but may miss subclinical or nonconvulsive seizures
EEG/cEEG/ECoG	26/85	Electrographic seizure detection, nonconvulsive seizure burden, perioperative hyperexcitability, HFO/ECoG markers, ICU monitoring	Monitoring duration and protocol intensity varied; not a validated stand-alone surrogate for late epilepsy prevention
MRI/CT/imaging	20/85	Defined injury substrate, cortical involvement, hemorrhage/tumor/neurosurgical context, edema, mass effect, or risk-enrichment substrate	Generally used for risk context or eligibility rather than as a standardized rule for ASM duration
Combined clinical + EEG	12/85 outcome categories	Captured both bedside clinical seizures and electrographic seizure burden	Stronger acute ascertainment, but still heterogeneous across etiologies
Imaging/risk-context without explicit seizure ascertainment	8/85 outcome categories	Characterized structural risk substrate	Does not directly measure seizure occurrence
Unclear ascertainment	9/85 outcome categories	Registry record did not clearly state how seizures were measured	Should be reported as a registry-data limitation
<i>Note: Marker categories are non-mutually exclusive and reflect registry field extraction, not standardized clinical protocols.</i>			

Completion, discontinuation, results reporting, and sensitivity cohort

Twenty-seven primary-cohort studies were completed (27/85, 31.8%), 26 were recruiting, not yet recruiting, active but not recruiting, or enrolling by invitation (30.6%), 15 had unknown status (17.6%), and 17 were discontinued (17/85, 20.0%). Among studies that were completed or discontinued, the discontinuation proportion was 17/44 (38.6%). Among completed primary-cohort studies, 26 had a primary completion date on or before June 18, 2025 and were eligible for results-reporting assessment; one completed study lacked a primary completion date and was excluded. Eleven of 26 eligible completed trials (42.3%) had posted ClinicalTrials.gov results.

The 39-record sensitivity/monitoring cohort was clinically distinct from the primary seizure-management cohort. It was dominated by seizure detection, EEG-based monitoring, remote monitoring, and multimodal neuromonitoring studies: 33/39 records (84.6%) were device/EEG/monitoring interventions. Twenty-four sensitivity-cohort records (61.5%) were first posted during 2020–2026, suggesting that seizure detection and monitoring represent a growing complementary evidence stream rather than direct prophylaxis or antiepileptogenesis trials.

Discussion

This ClinicalTrials.gov registry analysis shows that seizure-related trial activity after acquired brain injury is clinically meaningful but fragmented. The key finding is not simply that 85 primary-cohort trials were identified, but that these trials were distributed across different disease populations, seizure-related objectives, intervention strategies, marker choices, dosing detail, follow-up windows, and reporting practices. This is clinically important because acquired brain injury is not a single disease state, and seizure risk, mechanisms, consequences, and feasible trial endpoints differ substantially across injury types.

The central implication is that seizure prevention after acquired brain injury should not be treated as a single endpoint. Acute seizure prophylaxis, treatment of acute symptomatic seizures, and prevention of late epilepsy represent different clinical and biological objectives. A trial that reduces early provoked seizures during an acute hospitalization does not necessarily demonstrate modification of epileptogenesis or prevention of late unprovoked seizures. This distinction is especially important in TBI and stroke, where early seizure risk and late epilepsy risk overlap but are not identical.

The completed medication-trial deep dive makes this distinction more clinically visible. Completed medication/study-drug records included early prophylaxis, acute symptomatic seizure treatment, and late-prevention/antiepileptogenesis-oriented trials. Three completed records in the extracted cohort had a late-prevention orientation, underscoring how limited the completed antiepileptogenesis evidence base remains. Dose reporting was inconsistent; where doses were available, they were NCT-specific rather than portfolio-wide. Therefore, the manuscript should not imply a coherent dose-response evidence base across etiologies. Instead, the clinical message is that future trials need standardized exposure reporting, seizure ascertainment, follow-up windows, and clearly separated acute versus late endpoints.

The marker analysis also changes the clinical interpretation. Clinical seizures, EEG/cEEG/ECOG, and MRI/CT/imaging were each present in only a subset of primary-cohort records. Clinical seizure endpoints are directly meaningful but can miss nonconvulsive events. EEG/cEEG/ECOG can capture electrographic seizure burden, ICU seizures, and perioperative hyperexcitability, but monitoring duration and protocols varied. Imaging identifies structural risk substrate but was generally not used as a standardized rule for prophylaxis duration. Future trial protocols should prespecify how these modalities define eligibility, risk enrichment, treatment duration, and outcomes.

The medication-centered composition of the portfolio is expected, but it provides only a partial view of the field. Levetiracetam dominated the registry landscape, while phenytoin/fosphenytoin, lacosamide, valproate, and perampanel appeared less frequently. Newer-generation ASMs such as lacosamide and perampanel were present, and eslicarbazepine appeared in one eligible post-stroke epilepsy-prevention record; however, brivaracetam and cenobamate were not detected as eligible primary-cohort ABI prophylaxis or epilepsy-prevention records in this extracted portfolio. Future exploration of newer or third-generation ASMs should not be framed as indiscriminate substitution for existing practice. It should be tested in etiology-specific, risk-enriched populations with endpoints matched to acute seizure control, acute symptomatic seizure treatment, or late epilepsy prevention.

The 39-study sensitivity/monitoring cohort provides a complementary view of the field. These records were not combined with the primary cohort because many addressed seizure detection, EEG monitoring, seizure characterization, or management-adjacent workflows rather than direct prophylaxis or epilepsy prevention. Nevertheless, they are clinically relevant because improved seizure detection may help identify high-risk patients for future prevention trials.

Finally, discontinuation and incomplete registry results reporting limit the usable evidence base. Among completed or discontinued primary-cohort trials, 38.6% were discontinued, and among eligible completed trials, only 42.3% had posted ClinicalTrials.gov results. Prior ClinicalTrials.gov analyses have similarly shown persistent incomplete or delayed results reporting across clinical research [29–32]. For post-injury seizure care, unpublished or unposted results can obscure lessons about feasibility, endpoint selection, medication tolerability, and patient selection.

Overall, the field does not simply need more trials. It needs disease-specific trials whose inclusion criteria, markers, treatment duration, dosing, outcome definitions, and follow-up windows match the biological question being asked. Table 4 provides an etiology-specific framework for selecting patients and aligning clinical, EEG, and imaging markers with the intended prophylaxis or prevention endpoint.

Table 4
Etiology-specific selection criteria for future seizure prophylaxis and epilepsy-prevention trials after acquired brain injury.

Etiology	Pertinent selection criteria for future prophylaxis/prevention trials	Markers to prioritize	Clinical design implication
TBI	Moderate-severe TBI, cortical contusion, intracranial hemorrhage, depressed skull fracture, early seizure, ICU/cEEG indication	CT/MRI injury pattern; clinical seizure; EEG/cEEG	Separate 7-day early prophylaxis from true late post-traumatic epilepsy prevention
Ischemic stroke	Cortical stroke, large infarct, severe stroke, hemorrhagic transformation, early seizure	MRI/CT; stroke severity; clinical seizure; EEG when mental status is abnormal	Avoid unselected prophylaxis cohorts; enrich for high-risk cortical/severe stroke
ICH	Lobar/cortical hemorrhage, larger hematoma, early clinical seizure, electrographic seizure, depressed mental status	CT/MRI; clinical seizure; cEEG	Target high-risk or EEG-positive patients rather than blanket prophylaxis
SAH	High-grade SAH, MCA aneurysm or cortical blood burden, hydrocephalus, infarction, intracerebral hematoma, early seizure	CT/CTA; clinical seizure; EEG/cEEG	Separate short-term prophylaxis from long-term epilepsy prevention
Brain tumor/neurosurgery	Supratentorial/cortical tumor, glioma, craniotomy, perioperative cortical irritation, preoperative seizure vs seizure-naïve status	MRI; operative context; clinical seizure; EEG/ECOG when used	Separate treatment of tumor-related epilepsy from prophylaxis in seizure-naïve surgical patients
CNS infection/encephalitis	Encephalitis, cortical involvement, acute symptomatic seizures, status epilepticus, EEG abnormalities	MRI; infection diagnosis/CSF context; clinical seizure; EEG/cEEG	Often an acute treatment or seizure-burden question rather than pure late prevention
Hypoxic-ischemic coma	Post-anoxic electrographic seizures, status epilepticus, malignant EEG patterns, coma severity	cEEG; neurologic exam; MRI/CT when available	EEG is central, but outcome interpretation is confounded by global prognosis
Mixed neurocritical illness	Clearly defined ABI subgroup, structural brain injury, ICU seizure-risk features, standardized seizure definitions	Clinical seizure; cEEG; CT/MRI	Do not pool etiologies without prespecified stratification
<i>Note: This table translates the registry gaps into a clinically oriented future-trial design framework.</i>			

Limitations

This study has limitations. ClinicalTrials.gov does not capture all global trial activity and may miss studies registered only in other registries. Registry entries may be incomplete, inconsistently updated, or ambiguous, and classification required manual interpretation of title, condition, summary, intervention, and outcome fields. Results posted on ClinicalTrials.gov do not capture all journal publications, and publication-linking was not exhaustively adjudicated beyond registry-listed publication references. The 2026 registration year was incomplete at data access. Several categories contained small cell counts, so cross-tabulated patterns and exploratory chi-square tests should be interpreted descriptively.

A specific limitation of the clinically oriented deep dive is that medication dose, treatment exposure, and numerical seizure-control outcomes were incompletely reported in the exported registry fields. Therefore, dose ranges were presented only for NCT-specific records in which the uploaded ClinicalTrials.gov export/deep-dive workbook explicitly reported dose. The analysis describes the registered evidence-generating landscape rather than the clinical efficacy of any prophylactic or preventive strategy.

Conclusions

In this ClinicalTrials.gov registry analysis, seizure-related trials after acquired brain injury were clinically meaningful but fragmented. The field has generated substantial activity, particularly in TBI and brain tumor/neurosurgery, but fewer trials were directed toward stroke, hemorrhage, infection, hypoxic-ischemic injury, and mixed neurocritical-care populations. Most importantly, the current portfolio mixes acute seizure prophylaxis, acute symptomatic seizure treatment, late epilepsy prevention, and monitoring-oriented studies, even though these address different clinical and biological questions. Future acquired-brain-injury seizure trials should be risk-enriched, etiology-specific, explicit about whether they target early seizure control or late epilepsy prevention, and designed with transparent dose-level, marker-level, follow-up, and results reporting built into the protocol.

Abbreviations

ABI
acquired brain injury
ASM
antiseizure medication
CNS
central nervous system
CTG
ClinicalTrials.gov
EEG
electroencephalography

ECoG
electrocorticography
ICH
intracerebral hemorrhage
IQR
interquartile range
NCT
National Clinical Trial number
SAH
subarachnoid hemorrhage
TBI
traumatic brain injury.

Declarations

Ethics approval and consent to participate

Not applicable. This study was conducted in accordance with the Declaration of Helsinki, as applicable to secondary analyses of publicly available registry data. It analyzed publicly available trial-level registry records from ClinicalTrials.gov and did not involve human participants, identifiable human data, human tissue, or patient-level data.

Consent for publication

Not applicable.

Clinical trial registration

Clinical trial number: not applicable. This manuscript is a cross-sectional registry analysis and was not itself a clinical trial. NCT01463033 is an included ClinicalTrials.gov registry record; its ClinicalTrials.gov first-posted/registration date was November 1, 2011.

Availability of data and materials

All data generated or analyzed during this study are included in this article and its additional files. Source registry records are publicly available from ClinicalTrials.gov. Additional files include the final included records, raw CTG exports, reviewer agreement file, and completed-trial/deep-dive extraction files.

AI-assisted language editing

During manuscript preparation, AI-based tools were used only for language editing and grammar clarification. All scientific content, data interpretation, statistical outputs, and final wording were reviewed and approved by the authors.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

VS and AC contributed equally as co-first authors. VS conceived the study, designed the search and coding framework, led data curation and adjudication, performed the statistical analyses, and drafted the manuscript. AC provided senior clinical and methodological supervision, directed the clinically oriented completed-trial and marker/dose integration, interpreted findings, and critically revised the manuscript. JHC and OD contributed to screening, coding validation, data verification, and critical revision. All authors reviewed and approved the final manuscript.

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Figures

Figure 1. ClinicalTrials.gov record flow and analytic cohorts

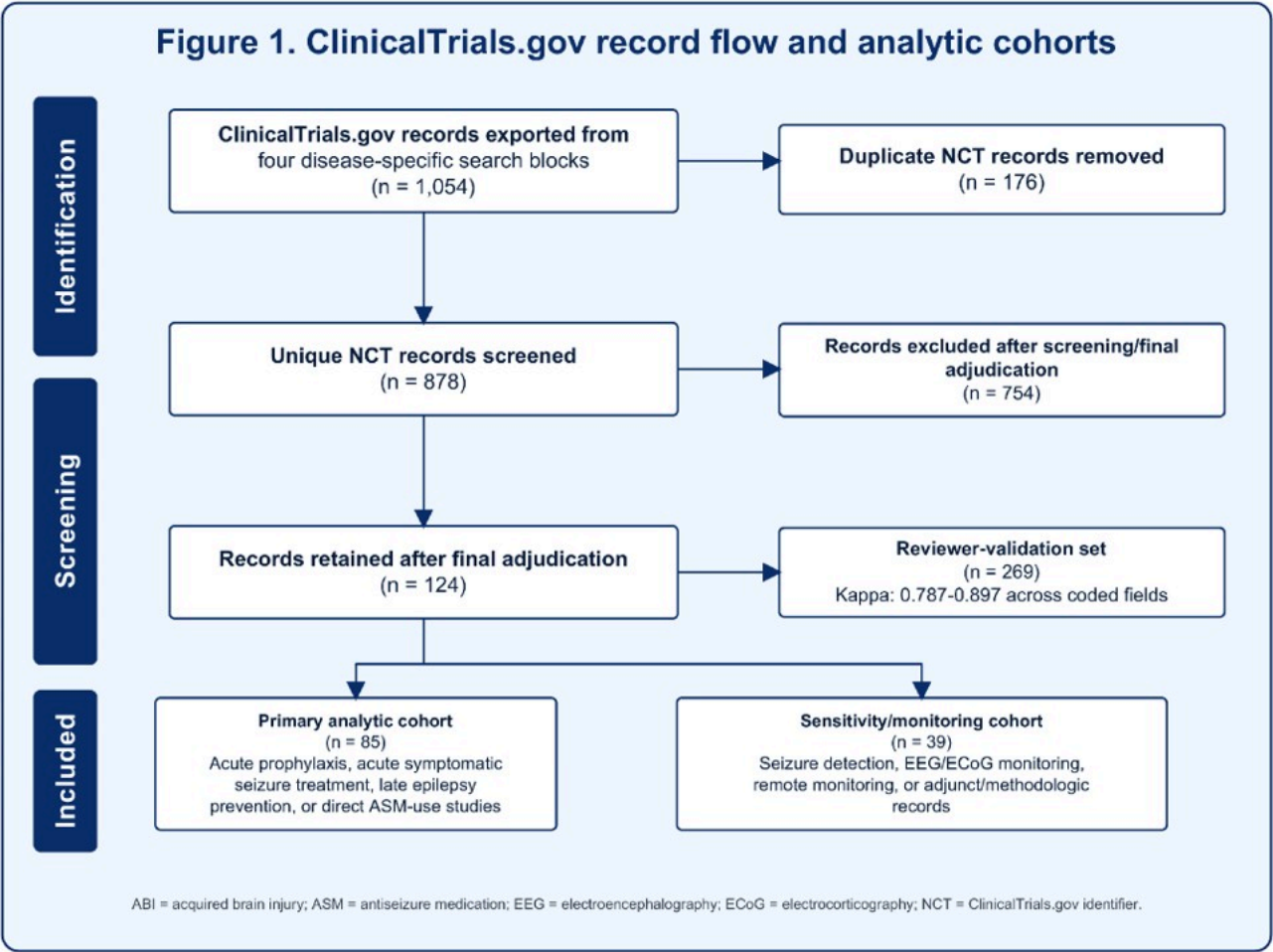
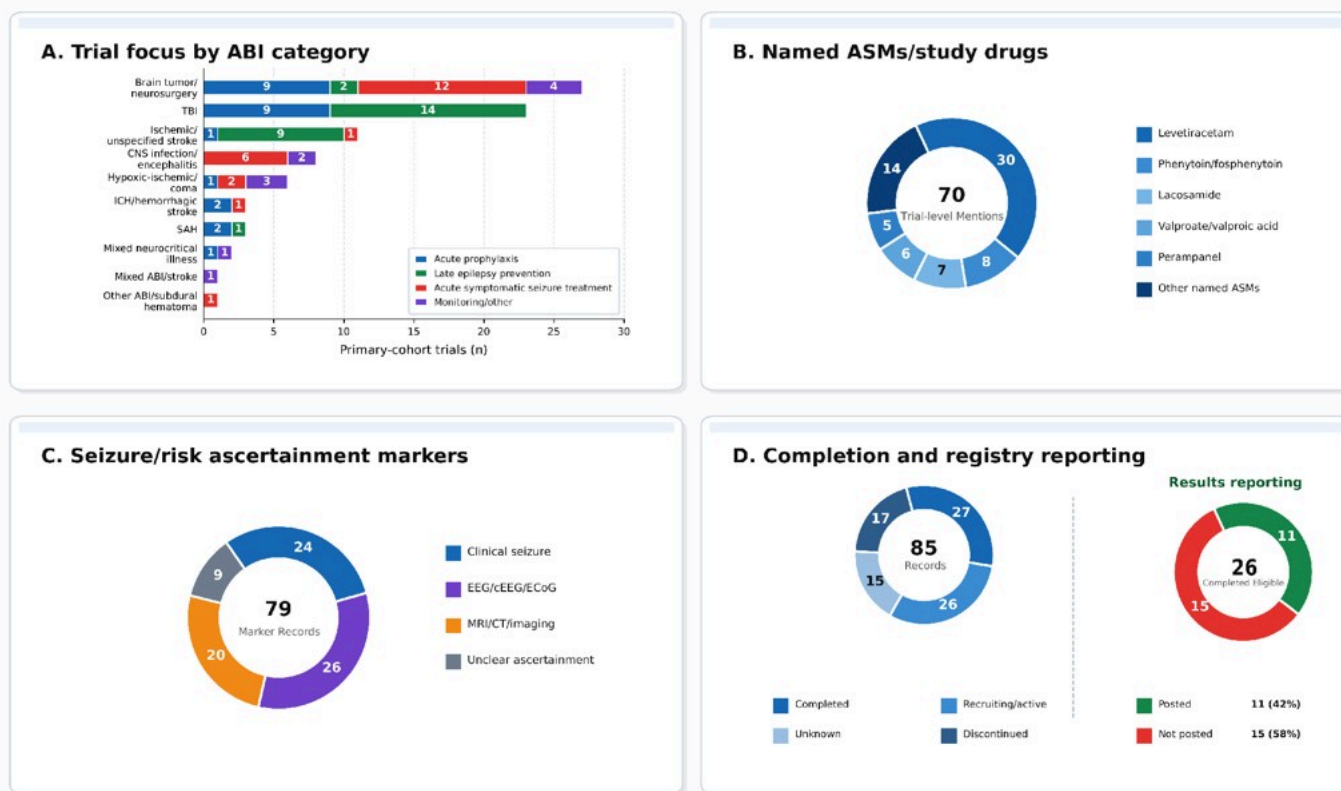


Figure 1

See image above for figure legend

Figure 2. Clinical architecture of the registered ABI seizure-trial pipeline



ABI = acquired brain injury; ASM = antiseizure medication; EEG = electroencephalography; ECOG = electrocorticography.

Figure 2

See image above for figure legend