Multicentre observational status-epilepticus registry: protocol for ICTAL

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ABSTRACT

Introduction Status epilepticus (SE) is a common life-threatening neurological emergency that can cause long-term impairments. Overall outcomes remain poor. Major efforts are required to clarify the epidemiology of SE and the determinants of outcomes, thereby identifying targets for improved management.

Methods and analysis ICTAL Registry is a multicentre open cohort of critically ill patients with convulsive, non-convulsive or psychogenic non-epileptic SE. Observational methods are applied to collect uniform data. The goal of the ICTAL Registry is to collect high-quality information on a large number of patients, thereby allowing elucidation of the pathophysiological mechanisms involved in mortality and morbidity. The registry structure is modular, with a large core data set and the opportunity for research teams to create satellite data sets for observational or interventional studies (eg, cohort multiple randomised controlled trials, cross-sectional studies and short-term and long-term longitudinal outcome studies). The availability of core data will hasten patient recruitment to studies, while also decreasing costs. Importantly, the vast amount of data from a large number of patients will allow valid subgroup analyses, which are expected to identify patient populations requiring specific treatment strategies. The results of the studies will have a broad spectrum of application, particularly given the multidisciplinary approach used by the IctalGroup research network.

Ethics and dissemination The ICTAL Registry protocol was approved by the ethics committee of the French Intensive Care Society (#CE_SRLF 19-68 and 19-68a). Patients or their relatives/proxies received written information to the use of the retrospectively collected and pseudonymised data, in compliance with French law. Prospectively included patients receive written consent form as soon as they recover decision-making competency; if they refuse consent, they are excluded from the registry. Data from the registry will be disseminated via conference presentations and peer-reviewed publications.

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INTRODUCTION

Status epilepticus (SE) is a common life-threatening neurological emergency in which prolonged or multiple closely spaced seizures can result in long-term impairments.1 SE can occur with or without involuntary motor contractions, the two forms being known as status epilepticus with prominent motor symptoms (CSE) and status epilepticus without prominent motor symptoms SE (NCSE), respectively.1

Despite regularly updated national and international management guidelines, SE remains associated with considerable mortality and morbidity, with little progress over the last three decades.2 The proportion of patients who die in the hospital is about 20% overall and 40% in patients with refractory CSE.3 Morbidity is more difficult to evaluate, as adverse effects of SE are often difficult to differentiate from those attributed to the cause of SE. Our experience suggests that nearly 50% of patients may experience long-term functional impairments.4 Very few randomised controlled trials have addressed the management of SE, and most of them investigated the efficacy of first-line or second-line treatments,5-9 resulting in a
dearth of information on neuroprotective strategies.10
We urgently need to identify new therapeutic targets to
improve the outcomes of SE. One means to achieving
this goal consists in collecting epidemiological data about
patients with SE at all stages of management.11

Delayed recognition of CSE with delayed treatment
initiation is associated with worse patient outcomes.12 13
Moreover, when first-line antiseizure medication (ASMs)
fail to stop CSE, benzodiazepines are often given in insuf-
ficient dosages.14 Among second-line ASMs, none has
been proven better than the others in shortening seizure
duration. Many new ASMs have been introduced over the
last two decades, but few, recent, head-to-head compar-
sions of new versus old and therefore less costly ASMs are
available.15 Despite this lack of evidence, newer ASMs are
being increasingly prescribed based on their presumably
better safety profile.16 According to a 2019 metanalysis,
the old and inexpensive ASM phenobarbital may provide
the fastest termination of benzodiazepine-resistant SE but
may raise safety concerns, whereas valproate and lacos-
amide may have the best safety profiles.17 A randomised
controlled trial comparing levetiracetam, fosphenytoin
and valproate for benzodiazepine-resistant CSE found no
superiority of one drug over the others in stopping clin-
ical seizures and improving consciousness within 60 min.7
Lacosamide, which was introduced in 2008, may share
with the widely used and far older drug phenytoin a poor
cost/effectiveness ratio as compared with levetiracetam,
valproate or phenobarbital.17 Importantly, independent
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valproate or phenobarbital.17 Importantly, independent
associations have been reported between the use of newer
ASMs and increases in refractory SE, new-onset disability
and in-hospital death.16

The current management of SE is highly standardised
as opposed to being tailored to specific clinical patterns.
The causes of SE vary widely, and different causes may
require different treatments to optimise patient outcomes.
Vast patient registries that collect information on causes,
treatments and outcomes of SE would help to differenti-
tate patient subgroups requiring different treatments.18

One of the endeavours undertaken by our research
network IctalGroup (ictalgroup.org) is the establishment
of a large multicentre registry of critically ill patients with
SE, the ICTAL Registry. The objective of this article is
to describe the goals and methodology of this registry.

METHODS AND ANALYSIS
ICTAL Registry objectives
The ICTAL Registry collects observational data on adults
admitted to intensive care units (ICUs) at multiple
healthcare institutions for CSE, NCSE or psychogenic
non-epileptic SE (PNESE).

The primary objectives are to record extensive informa-
tion on the causes, circumstances of onset, clinical and
electroencephalographic (EEG) patterns, treatments,
adverse treatment effects and outcomes in adults with
CSE, NCSE or PNESE. These data will allow us to identify
different patient phenotypes that may require different
treatments.

The secondary objectives are to provide the data
needed for nested-cohort studies using a variety of designs
including cohort multiple randomised controlled trials;
observational cross-sectional, prospective or retrospective
studies and patient-reported outcome studies. We plan to
develop severity scores. We will also develop a cohort of
patients willing to receive invitations to participate in clin-
cal, translational or basic-science studies.

Design and patients
The ICTAL Registry collects retrospective data (from
January 2005 to December 2017) and prospective data
(from January 2018 onward) from 23 ICUs in France.
Expansion to international centres is planned.

All patients admitted to any of the participating ICUs
with any seizure activity are screened for eligibility by
the ICU physicians around the clock and 7 days a week.
Inclusion criteria are age 18 or older and admission to
any of the participating ICUs for CSE, NCSE or PNESE
defined below. Patients with post-anoxic SE are not
included.

Definitions
We use the standard definition of CSE as either 5 min’
continuous clinical motor seizures or at least two motor
seizures less than 5 min apart with no return to baseline
in the interval.1

NCSE is defined according to the Salzburg Consensus
Criteria recently adapted American Clinical Neurophys-
iology Society’s Standardized Critical Care EEG termi-
nology (2021 version).20 Thus, electrographic NCSE is
declared as an electrographic seizure without prominent
motor activity lasting at least 10 consecutive minutes
or contributing to least 20% of any continuous 60 min
recording. An electrographic seizure consists of epilepti-
form discharges at more than >2.5 Hz on average, for at
least 10 s (>25 discharges in 10 s) or of any pattern lasting
at least 10 s and exhibiting typical morphology, frequency
and amplitude.19 20 Electroclinical NCSE is electrographic
NCSE accompanied with a clinical symptom coinciding
with the electrographic seizure and consisting for instance
in mental status alteration, without prominent motor
activity. In this case, patients may only demonstrate subtle
clinical symptoms including face twitching, eye deviation
or nystagmus.

Refractory SE is defined as persistent clinical and/or
or electroclinical seizure activity despite second-line
therapy.21 Super-refractory SE is defined as persistent or
recurrent SE 24 hours or more after anaesthesia induc-
tion, including cases occurring at reduction or withdrawal
of the anaesthetics.22 Finally, in CSE and NCSE presenta-
tion, SE resolution is considered when there is no elec-
trical and/or electroclinical seizure.

PNESE is any paroxysmal event mimicking SE and
manifesting as motor activity, behaviours, feelings or
Figure 1 ICTAL Registry structure. The registry has a modular structure, with a vast core set of variables and the ability to attach satellite databases adding the variables needed to investigate specific issues. Possible study designs are indicated, with grey for retrospective studies, medium blue for prospective studies, light blue for intervention studies and dark blue for observational studies. The differences in the sizes of the circles reflect differences in the sizes of the satellite databases.

Sample size and recruitment
Given the observational nature of the registry and objectives including patient participation in nested-cohort studies, determining a sample size appropriate for a given between-group comparison would not be appropriate. Thus, the ICTAL Registry will aim to include as many patients as possible to provide sufficient statistical power for many comparisons. We plan to include at least 1000 patients in our open cohort. We expect 10 years to be needed to achieve this goal. Follow-up will be 1 year initially and will be subsequently extended to 5 and 10 years. The expected duration of the research programme is therefore 10 years after the inclusion of the last participant.

Data collection
For each patient, the registry collects a set of core variables. Over time, as the registry data or other new events suggest clinical questions requiring specific studies, additional data to allow such studies will be obtained. Figure 1 is a graph showing these satellite data sets and examples of the types of investigations they will allow.

A standardised case report form is used for each patient (figure 2). The form includes definitions of variables (see below) and data validation rules. The core variables were chosen based on an adaptation of Utstein-style guidelines. They include demographic data, baseline autonomic, history of epilepsy, comorbidities and characteristics of the current episode (circumstances of onset, dates and times of onset and of seizure control, clinical features of the seizures, prehospital and hospital care providers and timing of all given ASMs and adjuvant antiseizure or supportive treatments). Seizure duration is determined based on the prehospital, emergency-room and ICU records. In patients with an unknown timing of onset of SE, seizure duration was estimated as time from seizure discovery until the end of seizure. We also collect on-scene clinical findings recorded at any time during the early management (Glasgow Coma Scale (GCS) score, systolic blood pressure, heart rate, respiratory rate, pulse oximetry, glycaemia and body temperature), initial complications (eg, respiratory distress, shock, cardiac arrhythmias, aspiration pneumonia, rhabdomyolysis, lactic and/or respiratory acidosis, acute renal failure).

Variables included in the ICTAL Registry core data set
- Demographic data
- Information on the history of epilepsy
- Comorbidities
- Baseline function
- Clinical features of the seizures and other clinical findings
- Symptomatic management (including ASMs and supportive care)
- On-scene complications (respiratory distress, shock, cardiac arrhythmias, aspiration pneumonia, rhabdomyolysis, lactic and/or respiratory acidosis, acute renal failure)

Figure 2 ICTAL registry core data set. ASMs, antiseizure medication; EEG, electroencephalographic; GOS, Glasgow Outcome Scale; ICU, intensive care unit; LODS, Logistic Organ Dysfunction Score; SAPS II, Simplified Acute Physiology Score version II; SE, status epilepticus; STESS, Status Epilepticus Severity Score.
international guidelines.20 The following data describing the ICU and hospital care are also collected: severity and description of SE and organ failures according to the STESS score, Simplified Acute Physiology Score II (SAPS-II) and Logistic Organ Dysfunction (LOD) score and use of mechanical ventilation, inotropic support and/or renal replacement therapy.

Follow-up data are recorded for all registered patients not known to have died before or after discharge. The Glasgow Outcome Scale (GOS) score and functional impairments at ICU and hospital discharge are collected. The same data are then obtained during telephone interviews 90 days and 1 year after SE onset. Up to two attempts are made to contact each patient, on separate days, during and out of office hours. After two unsuccessful calls, information is sought from the family, general practitioner or neurologist. If no information can be obtained, the hospital charts are reviewed for follow-up data.

Data quality control
For each patient entered into the registry, the data are manually verified by an IctalGroup member and any queries are resolved with participating-centre investigators. For patients with missing data, the available information is checked again to ensure that only high-quality data are kept in the registry. When data are missing, out-of-range or inconsistent, the IctalGroup coordinator routinely contacts the participating-centre investigator to obtain clarification. Outcome data recorded at ICU and hospital discharge then 90 days and 1 year after SE onset are routinely verified. The registry data are regularly checked against source data, and random audits are conducted every 100 included patients by the IctalGroup coordinator.

Data security
The Ictal Registry complies with the standards set by the French health authorities (INDS #MR5821231120 and #MR0314241018) and the General Data Protection Regulation (GDPR) 2016/679 of European Union law aimed at protecting the confidentiality of personal data. According to the GDPR, all data are pseudonymised, that is, made unattributable to a specific patient without additional information. Only the participating-centre investigator can identify the patients managed at that centre, using a mapping table of inclusion numbers.

Other important measures further improve data security. The registry data are accessible only to authorised individuals who need the access for logistic or scientific purposes. The pseudonymised data are stored on a secure local server approved for hosting health data. In accordance with French law on the protection of data on individuals, the patients will be allowed to access and to delete their data should they so wish.

General management of SE in the participating centres
All participating centres follow current guidelines for the management of SE.21 22 In France, each first responder team includes a physician. ASM therapy and efforts to identify the cause are started on-scene. Patients with SE receive at least one first-line intravenous ASM (clonazepam, diazepam, midazolam and/or lorazepam).8 If the seizures persist, a second-line intravenous ASM is chosen among fosphenytoin, phenytoin, sodium valproate, levetiracetam and phenobarbital, based on specific indications and contraindications.9 26 Patients with refractory SE are given an intravenous bolus of an anaesthetic (propofol, midazolam, sodium thiopental or ketamine), which is repeated until seizure cessation, at which point a continuous intravenous propofol infusion is started.27 When seizure cessation is not obtained (uncontrolled refractory and/or super-refractory SE), additional anaesthetic drugs and adjuvant treatments such as therapeutic hypothermia,10 a ketogenic diet28 and/or an anaesthetic gas can be used. Intravenous second-line ASMs are switched to their oral equivalents as soon as possible. Patients with a known history of epilepsy are given their previous treatment enterally or parenterally. It is important to note that the first-line, second-line and third-line treatments listed here are indicative and may in the future not be limited to today’s approved options. These treatments are given according to current national or international guidelines.

Patients whose GCS score remains less than eight despite first-line anticonvulsant therapy receive endotracheal mechanical ventilation, which is started on-scene if needed. A deep coma may be related to the postictal state or to subtle electrographic SE, and patients with refractory SE requiring anaesthetic drug administration are intubated.29 30 Patients with aspiration pneumonia and respiratory failure or shock also receive endotracheal mechanical ventilation, after rapid-sequence induction with various combinations of anaesthetic agents (etomidate, propofol, ketamine, or thiopental) and neuromuscular blocking agents (succinylcholine or rocuronium).

The prevention of secondary brain injury relies on maintaining normothermia, blood glucose between 0.8 and 1.4 g/L, PaO2 ≥ 80 mm Hg and SaO2 ≥ 95%, PCO2 between 35 and 40 mm Hg, mean arterial pressure between 70 and 90 mm Hg and serum sodium between 138 and 142 mmol/L; in addition, the head of the bed is elevated to 45°.31

Etiological investigations are started at the same time as the treatment. They include a thorough initial and daily physical examination including a special attention to the nervous system parts and functions. Tests are performed for carbon monoxide poisoning, hypoxia and hypercapnia and metabolic disturbances (eg, hypoglycaemic, hypocalcaemia, hyponatraemia, uremia and hypomagnesemia). CT of the brain is performed routinely. In patients with previously treated epilepsy, serum ASM assays are performed if appropriate to determine whether the levels are within the therapeutic range. As dictated by the clinical setting, tests are performed for disorders such as porphyria and thyroid dysfunction and/or for toxic substances (alcohol, cocaine, amphetamines and tricyclic or serotoninergic antidepressants). A lumbar puncture is performed in patients with a fever, neck
stiffness, an immunodeficiency or negative findings from all other etiological investigations. MRI may be considered if the other etiological investigations are negative. The aetiology is diagnosed jointly by the intensivists and consultant internists and neurologists. Continuous or sequential EEG monitoring is performed routinely as soon as possible, and is particularly valuable in patients with a deep coma, long-lasting postictal state and/or progression to refractory SE.

The future
One of the purposes of the ICTAL Registry is to allow nested observational and interventional studies (figure 1). The collection of core data followed by that of satellite data as dictated by the identification of unresolved issues will make these studies easier, faster, and less costly.

Once the cohort is established in France, partnerships with international research teams will be sought. The case report form of the cohort will be translated into the relevant languages, notably English and Spanish. The database will remain located in France and subject to the data-security requirements set by French law. Data transfers outside France will occur only as part of scientific research projects and after obtaining approval from the competent authorities.

Patient and public involvement
Patients were not directly involved in the development of the study protocol.

Ethics and dissemination
The ICTAL Registry protocol was approved by the ethics committee of the French Intensive Care Society (#CE_SRLF 19-68 and 19-68a). Patients or their relatives/proxies received written information to the use of the retrospectively collected and pseudonymised data, in compliance with French law. Prospectively included patients receive a written consent form as soon as they recover decision-making competency; if they refuse consent, they are excluded from the registry.

The ICTAL Registry is being created and maintained by the IctalGroup, a non-profit organisation of physicians, nurses and other healthcare professionals dedicated to teaching and research in neurocritical care. The IctalGroup is responsible for managing and coordinating the database and for conducting the statistical analyses of the registry data.

Data from the registry will be disseminated via conference presentations and peer-reviewed publications.

DISCUSSION
The development of the ICTAL Registry is a major collaborative initiative aimed at allowing retrospective and prospective studies of mechanisms associated with short-term and long-term outcomes, notably disabilities, in critically ill patients with SE. The large size of the cohort, the breadth and quality of the data and the inclusion of patients over time should result in management changes capable of improving the currently poor outcomes of SE. The data collected for each patient include potential demographic and biological risk factors and health events occurring over time. Whereas closed cohorts collect longitudinal data in a population determined at a given time point, our registry will remain open to the inclusion of all adults with non-postanoxic SE newly admitted to the participating ICUs. Thus, real-life information on unselected patients will be obtained, whereas randomised trials are done in selected populations. The large number of participating ICUs and future involvement of international centres will ensure strong external validity. Moreover, the considerable sample size combined with potent statistical tools such as propensity-score matching will provide robust statistical results despite the observational nature of the data.

The modular nature of the cohort with the establishment of satellite databases around the core set of variables provides room for almost real-time responsiveness to the data collected thus far and to changes in epidemiological circumstances. These satellite databases will allow a broad diversity of study designs. The vast core database will limit the amount of additional data needed for the satellites, thereby substantially reducing study times and costs. Finally, the creation of satellite databases will be open to investigators from multiple disciplines (eg, neurophysiologists, neurologists, emergency physicians, resuscitators, rehabilitation physicians, family physicians, nurses, physiotherapists and occupational therapists), which constitutes a major advantage since patients with SE require both organ support and also antiseizure treatment, EEG monitoring (continuous whenever possible), laboratory tests and imaging studies to identify the cause and treatment of the cause. Also, patients recovering from SE are managed in neurology wards or rehabilitation units and, after discharge, by acute care physicians.

The ICTAL Registry will allow conducting cohort multiple randomised controlled trials. This type of trial consists in testing interventions within large longitudinal cohorts and has the advantage of minimising recruitment difficulties and costs. Other trial-within-cohorts designs will be possible, including cross-sectional observational studies and longitudinal outcome studies. Patient inclusion into studies based on the ICTAL Registry will be subject to the obtaining of informed written consent, in compliance with regulations. Finally, the ICTAL Registry data will be open to sharing with other registries focused on SE or on other conditions, thereby promoting international collaboration.

The ICTAL Registry will allow evaluations of associations linking specific components of management, such as very early initiation of EEG monitoring, to outcomes. Some of these management components may apply to all patients with SE. However, a major goal of the ICTAL Registry is to separate patient subgroups that differ regarding the management strategies associated with the best outcomes. The large number of patients and
extensive spectrum of collected variables are expected to allow valid subgroup comparisons. This patient-centred approach has the potential for suggesting tailored treatments capable of improving outcomes.

Our study has several potential limitations. First, the extent to which our future findings apply to the full spectrum of patients with convulsive status epilepticus is unclear. Some patients may have died prior to medical intervention and others may have recovered fully without needing ICU admission. However, we focus here on the precise population of patients who require intensive care management, which represents a gap in the literature and is the main interest of our registry. Second, the variety of types of EEG monitoring from one service participating in the registry to another may consider a recruitment and potentially a management bias. However, this is a reality of real patient management that many services are faced with. Moreover, it is also an opportunity to compare outcomes according to management modalities. This variability will allow us to address this issue which is discussed in the literature.

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