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Multicentre observational status-epilepticus registry: protocol for ICTAL

Gwenaelle Jacq,[1] Jonathan Chelly ,[2] Jean-Pierre Quenot ,[3] Pauline Soulier,[4] Olivier Lesieur,[5] Pascal Beuret,[6] Mathilde Holleville,[7] Cedric Bruel,[8] Pierre Bailly ,[9] Bertrand Sauneuf,[10] Caroline Sejourne,[11] Jean Philippe Rigaud,[12] Arnaud Galbois,[13] Marine Arrayago,[14] Gaetan Plantefeve,[15] Annabelle Stoclin,[16] David Schnell,[17] Candice Fontaine,[1] François Perier,[1] Wulfran Bougouin,[18] Nicolas Pichon,[19] Nicolas Mongardon,[20] Didier Ledoux,[21] Jean-Baptiste Lascarrou,[22] Stephane Legriel ,[1,23] Ictal Study Group

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For numbered affiliations see end of article.

Correspondence to
Stephane Legriel;
slegriel@ch-versailles.fr

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.

Trial registration number NCT03457831.

Strengths and limitations of this study

- The multicentre open cohort design including critically ill patients with convulsive, non-convulsive or psychogenic non-epileptic status epilepticus.
- The modular nature of the cohort with the establishment of satellite databases around the core set of variables.
- The multidisciplinary approach used by the IctalGroup research network.
- The inclusion criteria restricted to critically ill patients.
- The registry is on a modular-based structure that allows the establishment of satellite databases around the core set of variables.

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 insufficient 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 comparisons 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 presumedly 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 lacosamide 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 clinical 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 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 differentiate 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 information 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 clinical, 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 as 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[19] recently adapted American Clinical Neurophysiology Society's Standardized Critical Care EEG terminology (2021 version).[20] Thus, electrographic NCSE is defined as an electrographic seizure without prominent motor activity lasting at least 10 consecutive minutes or contributing at least 20% of any continuous 60 min recording. An electrographic seizure consists of epileptiform 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 electroclinical seizure activity despite second-line therapy.[21] Super-refractory SE is defined as persistent or recurrent SE 24 hours or more after anaesthesia induction, including cases occurring at reduction or withdrawal of the anaesthetics.[22] Finally, in CSE and NCSE presentation, SE resolution is considered when there is no electrical and/or electroclinical seizure.

PNESE is any paroxysmal event mimicking SE and manifesting as motor activity, behaviours, feelings or

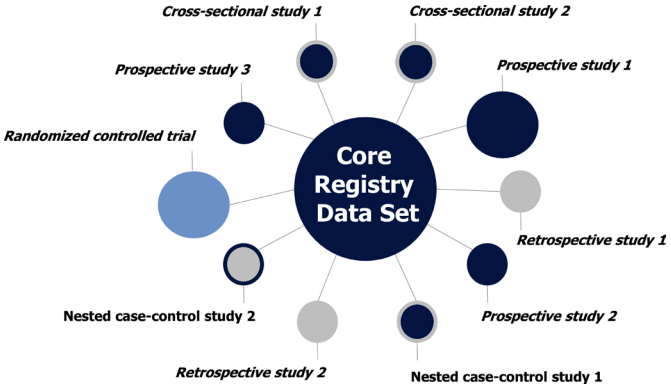

Figure 1 ICTAL Registry structure. The registry has a modular structure, with a vast core set of variables and the ability to attach satellite databases adding the variables needed to investigate specific issues. Possible study designs are indicated, with grey for retrospective studies, medium blue for prospective studies, light blue for interventional studies and dark blue for observational studies. The differences in the sizes of the circles reflect differences in the sizes of the satellite databases.

mental status alteration but not preceded by, coinciding with or followed by electrographic seizure activity.[23]

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.[24] They include demographic data, baseline autonomy, 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

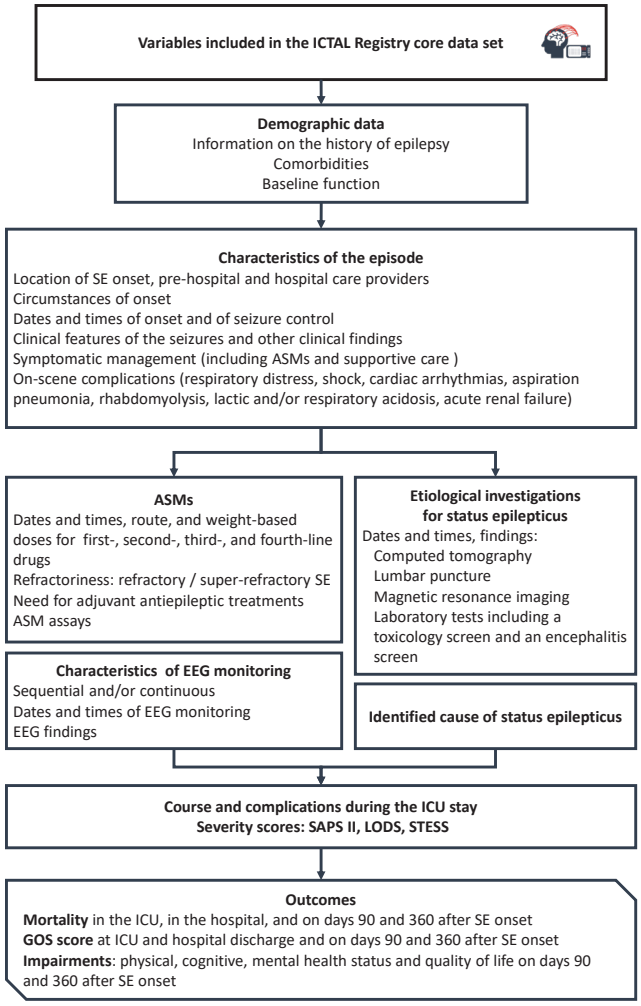

Figure 2 ICTAL registry core data set.ASMs, antiseizure medication; EEG, electroencephalographic; GOS, Glasgow Outcome Scale; ICU, intensive care unit; LODS, Logistic Organ Dysfunction Score; SAPs II, Simplified Acute Physiology Score version II; SE, status epilepticus; STESS, Status Epilepticus Severity Score.

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 arrhythmia, aspiration pneumonia, rhabdomyolysis, lactic and/or respiratory acidosis and acute renal failure). The core variables also include the findings from etiological investigations (CT, lumbar puncture, MRI and laboratory tests including a toxicology screen) and the final identified cause of SE. Special attention is paid to treatment-related complications (eg, respiratory and/or cardiac side effects of ASMs, haemodynamic side effects of anaesthetics and airway-management difficulties). The characteristics (sequential and/or continuous) and results of EEG monitoring are collected according to the most recent

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 (GDRP) 2016/679 of European Union law aimed at protecting the confidentiality of personal data. According to the GDRP, 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 centrs

All participating centres follow current guidelines for the management of SE.[21 25] 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.[7 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 diet[28] 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, PaO_2 ≥80 mm Hg and SaO_2 ≥95%, PCO_2 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, hypoxemia and hypercapnia and metabolic disturbances (eg, hypoglycaemic, hypocalcemia, hyponatremia, 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 serotonergic 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,[32] and is particularly valuable in patients with a deep coma, long-lasting postictal state and/or progression to refractory SE.[33–35]

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.[18] 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.

Author affiliations
[1]Service de réanimation et unité de soins continus, Centre Hospitalier de Versailles, Le Chesnay, France
[2]Service de réanimation, Centre Hospitalier Intercommunal Toulon La Seyne sur Mer, Toulon, France
[3]Réanimation médicale, CHU Dijon, Dijon, France
[4]Service de réanimation, Groupe Hospitalier Sud Ile-de-France, Melun, France
[5]Service de réanimation, Centre hospitalier de la Rochelle, La Rochelle, Nouvelle-Aquitaine, France
[6]Service de Réanimation et Soins Continus, Centre Hospitalier de Roanne, Roanne, Rhône-Alpes, France
[7]Department of Anesthesiology and Critical Care, AP-HP, Paris, Nord, France
[8]Service de réanimation, Groupe hospitalier Paris Saint Joseph, Paris, France
[9]Médecine Intensive Réanimation, CHU de Brest, Brest, France
[10]Service de réanimation, Centre Hospitalier Louis Pasteur de Cherbourg, Cherbourg-Octeville, Basse-Normandie, France
[11]Service de réanimation, Hôpital de Béthune, Beuvry, France
[12]Service de réanimation, Centre Hospitalier de Dieppe, Dieppe, Haute-Normandie, France
[13]Intensive Care Unit, Claude Galien Private Hospital, Quincy-sous-Senart, Île-de-France, France
[14]Department of Intensive Care, Cannes Hospital, Cannes, France
[15]Service de Médecine Intensive Réanimation, Centre Hospitalier d'Argenteuil, Argenteuil, Île-de-France, France
[16]Service de réanimation, Instituy Gustave Roussy, Villejuif, France
[17]Service de réanimation, Hospital Centre Angouleme, Angouleme, Poitou-Charentes, France
[18]Intensive Care Unit, Jacques Cartier Private Hospital, Massy, France
[19]Service de réanimation, Centre Hospitalier de Brive, Brive-la-Gaillarde, France
[20]Service de Médecine Intensive-Réanimation, Hôpital Henri Mondor, Creteil, Île-de-France, France
[21]Department of Intensive Care, University Hospital of Liege, Sart, Belgium
[22]Service de Médecine Intensive Réanimation, CHU Nantes, Nantes, Pays de la Loire, France
[23]University Paris-Saclay, UVSQ, INSERM, Team « PsyDev », CESP, Villejuif, France

Twitter Jonathan Chelly @Chellyjonathan, Jean-Pierre Quenot @Quenot and Stephane Legriel @stlegriel

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Collaborators Ictal Study Group: Coralie Marjolet (Centre Hospitalier de Versailles); Louison Feyrit (Centre Hospitalier de Versailles); Gabriel Obert (Centre Hospitalier de Versailles); Lea Jacot (Centre Hospitalier de Versailles); Sonia Garrigou (Groupe Hospitalier Paris Saint Joseph); Roxane Bai (Groupe Hospitalier Paris Saint Joseph); Camille Prudat (Groupe Hospitalier Paris Saint Joseph); Carole Ouisse (Centre Hospitalier Universitaire de Nantes); Diane Maugars (Centre Hospitalier Universitaire de Nantes); Jack Richecoeur (Centre Hospitalier de Beauvais); Didier Ledoux (Centre Hospitalier Universitaire de Liège); Audrey Massard (Centre Hospitalier Universitaire de Dijon); Mathilde Godard (Centre Hospitalier Universitaire de Dijon); Mathilde Audry (Centre Hospitalier Universitaire de Dijon); Ludivine Garrier (Centre Hospitalier Universitaire de Dijon); Magaly Noel (Centre Hospitalier du Cotentin); Guillaume Duhommet (Centre Hospitalier du Cotentin); Alice Langlois (Centre Hospitalier de La Rochelle); Julie Noublanche (Centre Hospitalier de La Rochelle); Sonia Garrigou (Groupe Hospitalier Paris Saint Joseph); Sybille Merceron (Centre Hospitalier de Versailles).

Contributors SL and GJ conceived, designed and supervised the study and wrote the first draft of the manuscript. GJ, JC, J-PQ, PS, OL, PB, MH, CB, PB, BS, CS, JPR, AG, MA, GP, AS, DS, CF, FP, WB, NP, NM, DL J-BL and SL reviewed the manuscript for important intellectual content and approved the final submitted version.

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ORCID iDs
Jonathan Chelly http://orcid.org/0000-0002-8198-1239
Jean-Pierre Quenot http://orcid.org/0000-0003-2351-682X
Pierre Bailly http://orcid.org/0000-0001-8187-8672
Stephane Legriel http://orcid.org/0000-0003-4782-6734

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