

**PROGRESSIVE WITHDRAWAL VERSUS  
INTERMITTENT INTERRUPTION OF  
SEDATION DURING  
ELECTROCONVULSIVE THERAPY IN  
SUPER-REFRACTORY STATUS  
EPILEPTICUS**

**A multicenter randomized clinical trial**

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A les noves il·lusions*

*Sóc molt afortunat de tenir-vos a la meva vida*

## ABBREVIATIONS

SE	Status Epilepticus	ILAE	International League Against Epilepsy
NCSE	Non-convulsive Status Epilepticus	NMDA	N-methyl-D-aspartate
GABA	Gamma-aminobutyric acid	AED	Antiepileptic drugs
CNS	Central Nervous System	EMTs	Emergency medical technicians
CT	Computed tomography	MRI	Magnetic resonance imaging
TIA	Transient ischemic attack	ICU	Intensive care unit
ECG	Electrocardiogram	EEG	Electroencephalogram
BZD	Benzodiazepine	STESS	Status Epilepticus Severity Score
EMSE	Epidemiology based mortality score in status epilepticus	IPS	Intermittent photic stimulation
ACNS	American Clinical Neurophysiology Society	TIA	Transient ischemic attack
PRIS	Propofol infusion syndrome	mSCNC	Modified Salzburg consensus criteria for non-convulsive status epilepticus
SRSE	Super-refractory Status Epilepticus	TMS	Transcranial magnetic stimulation
ECT	Electroconvulsive therapy	RSE	Refractory Status Epilepticus
SEN	Sociedad Española de Neurología	CEIC	Comitè d'Ètica d'investigació Clínica
AE	Adverse Effect	SEEP	Sociedad Española de Epilepsia
FIRES	Febrile Infection-Related Epilepsy Syndrome	vEEG	Video-electroencephalogram
		NORSE	Non-convulsive refractory status epilepticus

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## 1. ABSTRACT

Status epilepticus (SE) is a neurological emergency associated with high mortality and numerous sequelae, requiring early identification and intervention. Despite epileptic seizures usually cease with benzodiazepines or other antiepileptic drugs, when cases exhibit refractoriness, the management becomes more challenging. Within the realm of refractoriness, we encounter refractory and super-refractory status epilepticus (RSE and SRSE respectively). RSE is defined when the seizure persists despite treatment with benzodiazepines and at least one antiepileptic drug. SRSE is characterized by the persistence of seizures after 24 hours of sedation. The therapeutic strategies available to treat SRSE are currently limited. Electroconvulsive therapy (ECT) has been recommended as a nonpharmacological option for treatment after other alternatives are unsuccessful. However, only case series have been published on their use in ceasing SRSE, which provides scarce evidence on their effectiveness and safety. Given the limited therapeutic options and considering the outcomes observed in published cases, it becomes apparent that assessing the efficacy of ECT to treat SRSE could be crucial in the future not only for the early control of the SE but also for the reduction of mortality and associated sequelae.

The main goal of our study is to analyze the efficacy of ECT in terminating super-refractory status epilepticus and to compare it based on the sedation protocol employed. We propose two sedation options: one involving interruption several hours before the ECT session, resuming once the session is completed, and another where sedation is progressively reduced as the patient undergoes ECT sessions, without abrupt interruption at any point. Our secondary objectives include analyzing and comparing the time required to achieve the termination of SE, assessing the degree of seizure control if termination is not achieved and evaluating the adverse effects and neurological sequelae of ECT with both sedation protocols.

For these purposes, we have designed a multicenter randomized clinical trial in which 408 patients will be consecutively and non-probabilistically recruited. The participants must be adults with SRSE scheduled to undergo ECT, with a one-year follow-up capability and without pre-existing cognitive impairment or memory loss. They will be randomized 1:1 into two intervention groups, with each group receiving ECT under either one of the mentioned sedation protocols. We will analyze clinical and electroencephalographic changes after each ECT session. In the favorable scenario of achieving the termination of SRSE, follow-up visits will be conducted to identify the presence or absence of long-term neurological sequelae and compare them according to the received sedation protocol

**Keywords:** super-refractory status epilepticus, epilepsy, electro-convulsive therapy, sedation management of status epilepticus, neurological sequelae.

## 2. INTRODUCTION

### 2.1 STATUS EPILEPTICUS

While a seizure is defined as a transient occurrence of signs and/or symptoms due to abnormal excessive and synchronous neuronal activity in the brain, status epilepticus (SE) is a condition resulting from the failure of the mechanisms responsible for seizure termination and/or from the initiation of mechanisms which lead to abnormally and prolonged seizures. As accurred as these definitions might seem, defining the point from which a seizure becomes a status epilepticus has always been a subject of conflict through the years (1).

It wasn't until 2015 when the International League Against Epilepsy (ILAE) proposed a new conceptual definition of status epilepticus. This definition established two operational dimensions (t1 and t2) to guide emergency management and treatment of prolonged seizures (1–3):

- **t1:** time from which the seizure control mechanisms are considered to have failed, so from this point onward, a patient experiencing a seizure is considered to be in status epilepticus and therefore the time when emergency treatment of SE should be started.
- **t2:** time from which it is considered that epileptiform activity may have long-term consequences, including alteration of neural networks, neuronal damage, and even death.

#### 2.1.1 CLINICAL CLASSIFICATION OF STATUS EPILEPTICUS

We can classify SE based on its semiology, using the presence or absence of prominent motor symptoms as the main differentiating axis.

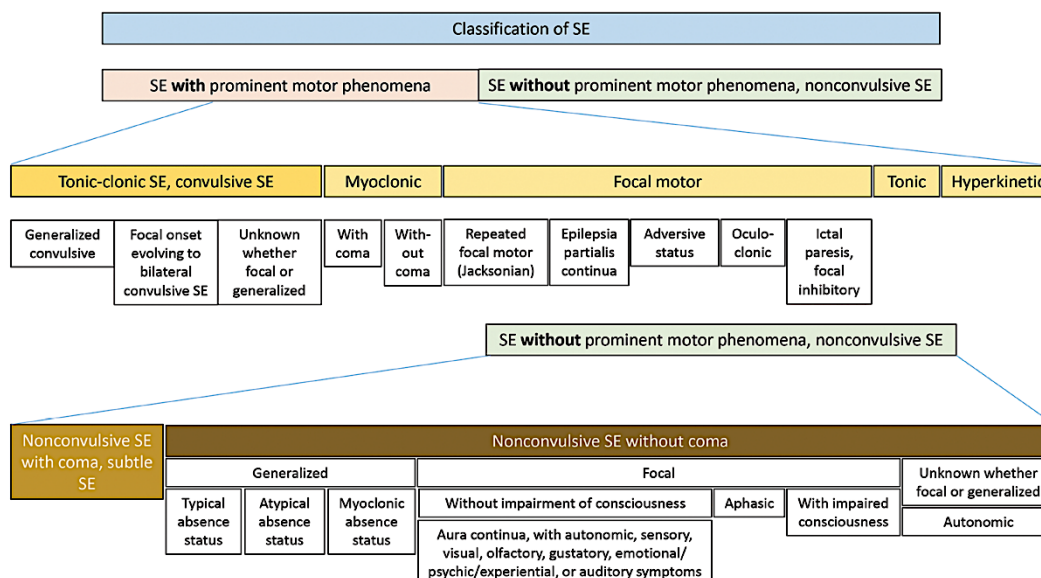


Figure 1: 2015 classification of status epilepticus by the ILAE (1,4)



The operational dimensions  $t_1$  and  $t_2$ , and therefore the emergency management, will be different depending on the type of status we are facing. That’s why it is crucial to identify and classify status properly on an early stage.

Table 1 (1)

Table 1. Operational dimensions with $t_1$ indicating the time that emergency treatment of SE should be started and $t_2$ indicating the time at which long-term consequences may be expected		
Type of SE	Operational dimension 1 Time ( $t_1$ ), when a seizure is likely to be prolonged leading to continuous seizure activity	Operational dimension 2 Time ( $t_2$ ), when a seizure may cause long term consequences (including neuronal injury, neuronal death, alteration of neuronal networks and functional deficits)
Tonic-clonic SE	5 min	30 min
Focal SE with impaired consciousness	10 min	>60 min
Absence status epilepticus	10-15 min <sup>a</sup>	Unknown

<sup>a</sup>Evidence for the time frame is currently limited and future data may lead to modifications.

SE can also be classified based on the clinical response to therapeutic management (3) (2):

- Early Status Epilepticus: seizure that fulfills status epilepticus operational criteria  $t_1$ .
- Established Status Epilepticus: SE that continues despite treatment with benzodiazepine.
- Refractory Status Epilepticus: SE that continues despite treatment with one benzodiazepine and at least one antiseizure medication administered in the right dose and well indicated.
- Super-refractory Status Epilepticus (SRSE): SE continues despite treatment with anesthetics >24 hours.

This classification can be found fully detailed when explaining the management of status epilepticus, but since it is mentioned on earlier parts of this project, I thought it could be useful to briefly explain it.

### 2.1.2 EPIDEMIOLOGY

The epidemiology data of SE has always been difficult to analyze due to the heterogeneity that existed in its definition. It wasn’t until 2015, when ILAE established the actual status definition and classification, that the epidemiological studies could start to be performed with a common understanding.

In Europe in 2015, the incidence of all types of status epilepticus in adults was 36.1 per 100.000 per year and 12.1 per 100.000 per year for nonconvulsive status epilepticus. The incidence of refractory status epilepticus was 7.2 per 100.000 adults per year while the incidence of super-refractory status epilepticus was 1.2 per 100.000 per year (5). All studies found a prominent increase with age on the incidence of status epilepticus in adults (2,5).

Mortality in status epilepticus is often a result of the ongoing epileptic activity and its consequences on neuronal networks and nervous system but also it is strongly related to its etiology. Anoxic damage and increasing age are some of the main factors associated with higher mortality whereas alcohol intoxication and antiepileptic drugs (AED) withdrawal are associated with lower mortality rates (6). In previous reviews of epidemiology on status epilepticus, mortality range in-hospital was found to be between 5.0% and 24.4% in established SE and between 4.6% and 39% on 30 days long status (7). One-year mortality rates were found to be 17-27% in refractory status epilepticus and 26-46% in super-refractory status epilepticus (8,9).

### 2.1.3 PATHOPHYSIOLOGY

Seizures represent the effect of abnormal synchronous discharges of progressively larger groups of connected neurons that lead to clinical manifestations. Although the inciting events of a seizure are yet to be found, it is known that its maintenance is due to an imbalance between an excess excitation and a decreased inhibition. Therefore, any etiology that disrupts the electrochemical gradient stability on neuronal membranes can cause a seizure. When discussing seizures pathophysiology, it is important to understand that glutamate is the main excitatory neurotransmitter and acts via N-methyl-D-aspartate (NMDA) subtype receptor and that gamma-aminobutyric acid (GABA) is the most common inhibitory neurotransmitter and acts via GABA<sub>A</sub> receptor (10).

It is clear that some endogenous seizure-terminating process must exist or every seizure would persist. However, even though several theories exist, the mechanisms that lead to these processes are yet to be known and, therefore, so does the exact pathophysiology of status epilepticus. In previous experimental models (11), a less potent response to GABA receptor agonists such as diazepam was found when administered later in the course of seizures than when given earlier. This suggests that, although many other processes are certainly involved in the development of SE, a change in number or sensitivity of GABA<sub>A</sub> receptors is very likely one of the main ones (11,12). Other factors such as the increasing in excitatory glutamate receptors, the alternations in excitatory and inhibitory neuropeptides (such as substance P and neuropeptide Y respectively) and other genetic and epigenetic changes are believed to play a part in the failure of these suppressing mechanisms (6,10,13). Although basic mechanisms of prolonged seizures are very similar, it is important to clarify that each type of SE has its own particularities. For example, the neuronal population involved in absence SE is the thalamocortical, and

it's synchronization depends mainly on GABAergic processes whereas in other simple and complex SE where the hippocampal formation neuronal population is involved, the excitation and synchronization depends mainly on glutamate receptors such as NMDA (14)

Neurologic injury in status epilepticus is mainly due to the excessive abnormal neuronal discharges that lead to excitotoxic mechanisms. When glutamate binds to the NMDA receptor under severely depolarized conditions of status epilepticus, the activity of this receptor is not properly regulated and it allows calcium and other ions to flow into the neuron. This flow of ions feeds back on itself, leading to a higher flow of ions into the cell and to the accumulation of high amounts of calcium, among others, which results in neuronal necrosis and delayed cell death (10).

#### 2.1.4 ETIOLOGY

Status epilepticus can be caused by a large group of etiologies (full list of etiologies that may cause SE can be found in Annex 1). This is why ILAE also classified SE using etiology as a main classificatory axis (1,2):

- **Known or symptomatic SE:** prolonged seizure caused by a known disorder which can be structural, metabolic, inflammatory, toxic, infectious or genetic. Known SE can be classified as it follows:
  - o Acute: SE occurring within 7 days of an acute disease (stroke, encephalitis, metabolic disorders, intoxication, drugs, etc) or 4 weeks of a head trauma.
  - o Remote: SE in an individual with prior (>7 days) neurological disease (stroke, encephalitis, metabolic disorders, etc), prior (>4weeks) head trauma or other prior systemic disease in absence of acute insult.
  - o Progressive: SE related to progressive diseases (brain tumor, dementias, neurodegenerative diseases, etc)
  - o Acute on remote: SE occurring in an individual with a previous brain disease due to an acute insult or trigger
  - o SE in defined electro-clinical syndromes or previous epilepsy with an acute trigger
- **Unknown or cryptogenic SE:** SE occurring in patients with no history of seizures and absence of any other neurological diseases.

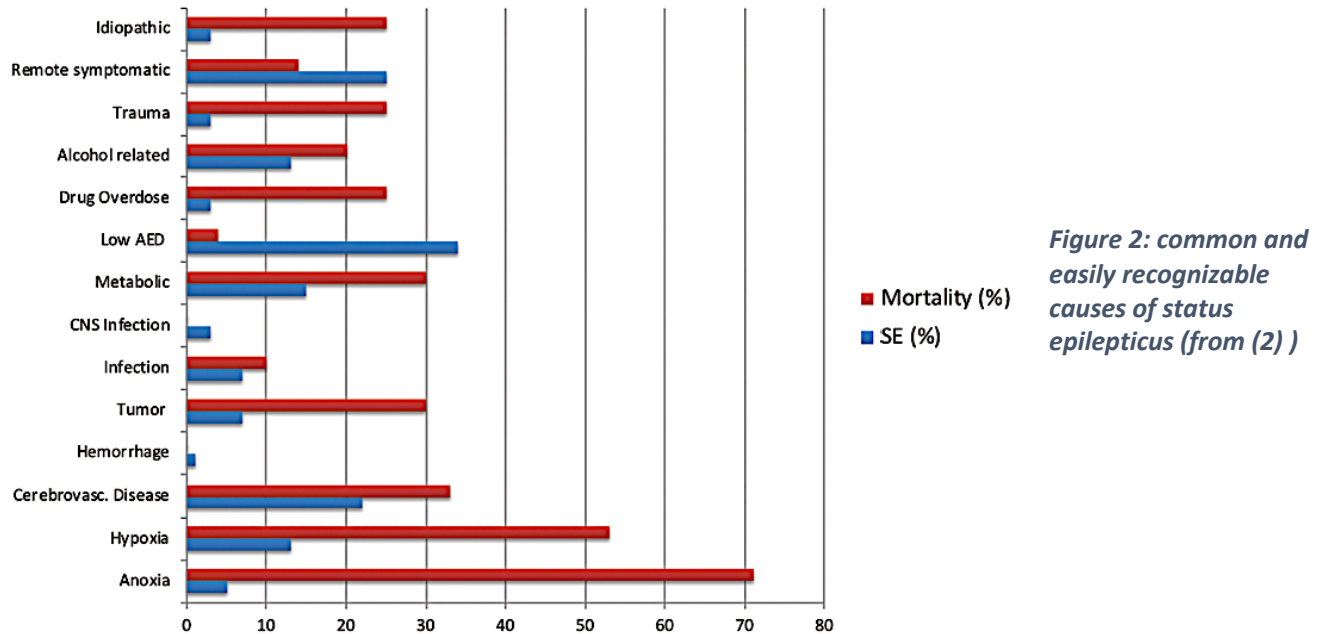


Figure 2: common and easily recognizable causes of status epilepticus (from (2) )

Studies show that cerebrovascular diseases, metabolic diseases, hypoxia, alcohol related, tumors and infections seem to be the most common causes of SE. However, in patients that were already being treated with AED, the most common cause of SE is the AED withdrawal or noncompliance (2,7,15).

### 2.1.5 MANAGEMENT OF STATUS EPILEPTICUS

When the seizing patient arrives to the emergency department, it is crucial to perform an exhaustive clinical history and physical examination as it follows:

Table 2 - EMERGENCY INITIAL DIAGNOSTIC MANAGEMENT OF SE (2,16,17)

<b>DETAILED CLINICAL HISTORY</b>	When performing the clinical history of a prolonged seizing patient it is vital to identify the circumstances surrounding the event and to obtain information from witnesses, bystanders and emergency medical technicians (EMTs). Important information includes when was the patient last seen well, if the seizure was witnessed by someone, if the patient has any history of trauma, neurosurgery, ischemic diseases or any other disease or condition that could possibly be an etiology of status epilepticus, if the patient has history of psychiatric diseases, if the patient has any comorbidity, which medication is taking the patient in case they're taking any (specially concerning AED), alcohol and drug consumption or if
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	<p>the patient has a preexisting epilepsy or has had previous seizures and, if they've had, if the current seizure has had any difference from the previous ones.</p> <p>In the clinical history it is also important to identify the circumstances surrounding the event such as what was the patient doing when the seizure started, if they have had any prodromal symptoms (behavior changes, mental instability, drowsiness, feeling of fear or hypersalivation to name some), how has the seizure started and how it progressed and the symptoms exhibited during the seizure.</p>
<p><b>PHYSICAL EXAMINATION</b></p>	<p>The physical examination of the seizing patient should include checking and vital signs (not only to manage and maintain them to ensure the patient's survival, but also because at times they can provide guidance towards the etiology of the seizure), a general inspection of skin and possible dysmorphias, an oral examination (if the patient's clinical presentation allows it) to check for lateral tongue bites, cardiovascular examination, pupil status, identify the specifics of the motor activity (if there is some), identify eye deviation (if there is some) and to perform neurological examination (as exhaustive as possible taking in consideration the patient's clinical presentation).</p> <p>Since seizures are often associated with injury, the patient should also be evaluated for both soft-tissue and skeletal trauma.</p>

While conducting a detailed medical history and physical examination, it is crucial to continuously monitor and stabilize the patient in case the epileptic seizure persists, leading to an onset of status epilepticus. In a status epilepticus scenario, it will be crucial to adhere to the "time is brain" principle, especially in SE with prominent motor activity. In a SE, symptomatic treatments with AED must be applied rapidly and, if needed, escalated toward anesthetics to prevent long-term consequences after t2 time point (2,18,19).

A proposed algorithm for the management of status epilepticus, which includes measures for monitoring, stabilization, and therapeutics, is detailed in *(Figure 3)*.

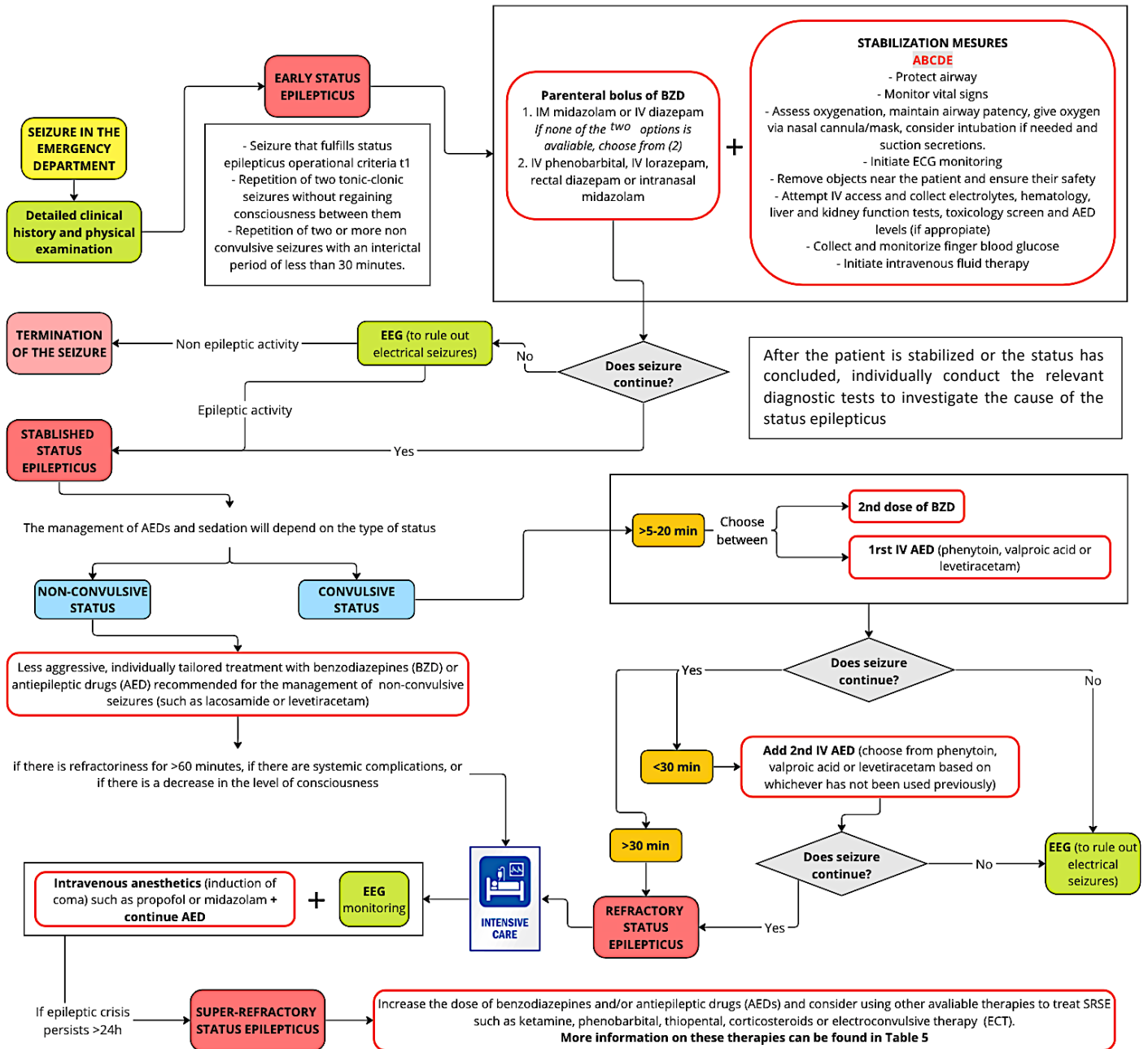


Figure 3: Algorithm for the management of status epilepticus (2,3,16,18,19)

Choosing an antiepileptic drug is a decision that should be made on an individualized basis. As explained in Annex 2, each drug has specific advantages and disadvantages which can justify choosing one AED over another one. In addition to the nature of the drugs, it is also important to consider the patient profile that needs to be treated. As observed in Annex 3, certain patient groups will require special considerations (2).

As it is pointed in Figure 3, other diagnostic tests (shown in Table 2) should be performed as soon as possible on an individualized basis to study the status etiology.

**Table 3 - DIAGNOSTIC TESTS CARRIED ON WHEN STUDYING SE (2,16,17)**

<b>LABORATORY STUDIES</b>	Laboratory studies in SE should include serum glucose levels, electrolytes, urea, nitrogen, creatinine, magnesium, calcium, complete blood count, pregnancy tests (in woman of childbearing age), AED levels (if taken), liver function tests, alcohol levels and drug-of-abuse screening. Nevertheless, the determination of other analytical parameters could be justified if there is a high clinical suspicion supporting it.
<b>ECG</b>	Cardiac monitorization, in addition to allowing the assessment of cardiac activity, can also sometimes prove insight into the seizure's etiology.
<b>NEUROIMAGING</b>	Neuroimaging is generally indicated in patients with a first-time nonfebrile seizure. Computed tomography (CT) changes acute management of patients with a new seizure in up to 17% of cases, this is why it is often carried on in the acute emergency management of the seizing patient. On the other hand, magnetic resonance imaging (MRI), although it is generally preferred by neurologists in evaluating first-time seizure for its high sensitivity on identifying small lesions, has not yet been evaluated in acute seizure management. Nevertheless, MRI will eventually be performed either during the acute management if deemed appropriate or later on for etiological diagnosis.
<b>LUMBAR PUNCTURE</b>	Lumbar puncture should be considered in patients with persistent altered mental status, fever or severe headache.
<b>ELECTROENCEPHALOGRAPHY (EEG)</b>	<p>Even though EEG's sensitivity varies depending on the timing and the location of the seizure focus, EEG is usually the definitive test for diagnosing and monitoring a seizure disorder, especially the non-convulsive ones.</p> <p>Since some observational studies found electrical activity in 25% of patients whose seizure was treated and thought to have terminated (20), literature suggest that, despite the technical and logistical difficulties, bedside EEG should be considered in the assessment of SE.</p>

During the initial management of status epilepticus, emergency physicians should also be able to distinguish whether the patient is having a seizure or is experiencing a condition that could mimic it (16,21). Some of the main conditions that should be considered in the differential diagnosis when facing a seizure, and the main clinical differences between them are:

*Table 4 - DIFFERENTIAL DIAGNOSIS OF A SEIZURE (21,22).* TIA stands for transient ischemic attack.

	Seizure	Syncope	Pseudo-crisis	TIA	Migraine
Eyes	Open	Open	Closed	Open	Open
Sphincter Relaxation	Yes	Yes/No	Yes/No	No	No
Loss of consciousness	Yes	Yes	Yes/No	No	No
Tongue bite	Lateral	Yes/No Tip of the tongue	No	No	No
Involuntary movements	Yes	Yes	Yes	No	No
Duration	Few minutes	Seconds	Minutes	Minutes	Minutes
Postictal period	Yes	No	No	No	No

Although clinical presentation and physical examination can guide you in the differential diagnosis, the primary tool to differentiate a true seizure from other conditions will be the EEG (2,17,21).

#### 2.1.6 AVAILIABLE THERAPIES TO TREAT SUPER-REFRACTORY STATUS EPILEPTICUS

The aims of treatment in super-refractory status epilepticus are **to control seizures**, mainly to prevent initial excitotoxicity (even though it should be recognized that after 24 hours of continuous or recurring seizures the excitotoxic processes causing cerebral damage are very likely already to have been initiated), **to provide neuroprotection** (an attempt to block the progression over time of the secondary processes triggered by initial excitotoxicity), **to avoid/treat systemic complications** of prolonged unconsciousness and of prolonged anesthesia and **to treat its underlying cause** (23).

Status epilepticus is usually treated with a range of therapeutic interventions that are tailored individually and often applied in an additive and stepwise manner (18,19,23). The therapeutic tools



employed or that could potentially be employed in the management of super-refractory SE (and the known mechanisms of action and primary adverse effects of some of them) are as follows:

**Table 5 - AVAILABLE THERAPIES TO TREAT SUPER-REFRACTORY STATUS EPILEPTICUS (2,19,23)**

ANAESTHETIC DRUGS			
TREATMENT	GENERALITIES	MECHANISM OF ACTION	ADVERSE EFFECTS
<b>THIOPENTAL AND PENTOBARBITAL</b>	Barbiturate anesthesia is the traditional anesthetic therapy for SE. Their tendency to rapid redistribute and to accumulate tends to result in long half-life in anesthesia (they require long recovery time). Strong anti-epileptic action.	Enhancing GABA(A) receptor activity Decreasing core temperature Neuroprotective effects Theoretical neuroprotective effect	Hypotension, cardiorespiratory depression, tendency to develop pharmacological tolerance and dependance, pancreatic dysfunction and hepatic dysfunction
<b>MIDAZOLAM</b>	Midazolam is the only benzodiazepine that has pharmacokinetic properties suitable for prolonged infusion without accumulation. Strong anti-epileptic action.	Enhancing GABA(A) receptor activity.	Strong tendency for rapid and acute tolerance and dependance to develop Hepatic and renal impairment Cardiorespiratory depression (less marked than barbiturates)
<b>PROPOFOL</b>	Versatile anesthetic with a very rapid onset and recovery. It's high responsiveness allows a great control of the level of anesthesia. It has no serious drug-drug interactions.	Enhancing GABA(A) receptor activity.	Hypotension and cardiorespiratory depression (at a lower rate than barbiturates and midazolam), Propofol infusion syndrome (PRIS) and drug induced involuntary movements.
<b>KETAMINE</b>	Anesthetic frequently postulated as an alternative for status epilepticus for its sympathomimetic action (this implies the absence of cardiodepressive or hypotensive properties)	Antagonism action at the NMDA receptor	Drug induced hypertensions and risk of neurotoxic effects (which needs to be further studied)

<p style="text-align: center;"><b>ANTIEPILEPTIC DRUGS</b></p>	<p>While in super-refractory status epilepticus, antiepileptic drugs may not seem to play as prominent a role as anesthesia, their administration is crucial during the status to provide adequate antiepileptic coverage upon sedation withdrawal.</p> <p>Further studies need to be performed on the role AED play in super-refractory status epilepticus and on the most appropriate or most effective anti-epileptic regimen. These studies are challenging to conduct due to patients in super-refractory status epilepticus often being treated with multiple medications, given the tendency of status epilepticus to spontaneously resolve and due to the delayed manifestation of both effects and adverse reactions.</p> <p>The most common adverse effects of antiepileptic drugs can be found in Annex 4.</p>
<p style="text-align: center;"><b>MAGNESIUM INFUSION</b></p>	<p>The infusion of magnesium sulfate has shown significant utility in controlling seizures of specific etiologies such as eclampsia, hypomagnesemia, and acute intermittent porphyria. Studies have proposed that its potential mechanism of action may involve the blockade of the NMDA receptor ; however, this hypothesis has not been conclusively demonstrated. It is common, due to a lack of research and evidence, to administer magnesium in super-refractory status epilepticus as it is considered safe and significant adverse effects have not been observed.</p>
<p style="text-align: center;"><b>PYRIDOXINE</b></p>	<p>Intravenous pyridoxine treatment forms the cornerstone for the resolution of super-refractory status epilepticus attributed to congenital pyridoxine metabolism disorders. Nevertheless, cases of super-refractory status epilepticus responsive to pyridoxine have been observed in patients without a diagnosis of congenital metabolic errors. Hence, despite the efficacy being notable in a limited number of cases, pyridoxine is routinely administered in super-refractory status, particularly in young patients.</p>
<p style="text-align: center;"><b>ANTI- INFLAMMATORY TREATMENT</b></p>	<p>Currently, corticosteroids and other forms of immunotherapy (such as immunoglobulins or plasma exchange) are not only employed in the treatment of immunologically mediated status epilepticus (for obvious reasons) but in cryptogenic cases as well. The use of these therapies in status epilepticus of uncertain etiology is motivated, on one hand, by the suspicion that cryptogenic cases are likely to have an immunological basis, possibly involving yet to be discovered autoantibodies. On the other hand, there is a suspicion that the persistence of status epilepticus may be attributed to inflammatory processes that occur in conjunction with sustained epileptic activity.</p>
<p style="text-align: center;"><b>KETOGENIC DIET</b></p>	<p>A ketogenic diet which leads to a consistent ketosis has shown to have both an anti-epileptic activity and an anti-inflammatory activity. However, even though ketogenic diet is a tool used in some cases (specially in severe childhood encephalopathies) conclusive experimental evidence on it's use in super-refractory status epilepticus is yet to be found.</p> <p>The ketogenic diet exhibits certain adverse effects that merit attention. These include metabolic acidosis, hypoglycemia, gastrointestinal effects (nausea, vomiting, and constipation),</p>

	<p>hyperlipidemia, hyponatremia, and weight loss. Monitoring is required while being in ketogenic diet for urinary and plasma ketones, electrolytes, glycemia, lipid profile, and hepatic function.</p> <p>Unlike other therapeutic options, the ketogenic diet presents numerous contraindications that restrict its usage. The primary contraindications include acute pancreatitis, severe metabolic acidosis, pregnancy, adynamic ileus, liver failure, kidney failure, disorders of fat metabolism, primary carnitine deficiency, carnitine palmitoyltransferase deficiency, carnitine translocase deficiency, porphyrias and pyruvate kinase deficiency. When initiating a ketogenic diet, it is important to consider potential interactions with other medications. This diet may interact with the following (66):</p> <ul style="list-style-type: none"> <li>- Propofol: increases the risk of propofol infusion syndrome.</li> <li>- Carbonic anhydrase inhibitors: increase the risk of metabolic acidosis.</li> <li>- Corticosteroids: increase insulin resistance and stimulate gluconeogenesis, thereby hindering ketosis.</li> <li>- Propylene glycol: stimulate lactic acidosis, thereby hindering ketosis.</li> </ul>
<p><b>HYPOTHERMIA</b></p>	<p>Hypothermia reduces metabolic rate, oxygen utilization, ATP consumption, glutaminergic drive, mitochondrial dysfunction, calcium overload, free radical production and oxidative stress, permeability of the blood-brain barrier and pro-inflammatory reactions. These mechanisms seem to be capable of reducing the damage caused by continuous epileptic activity. There are several studies that have tested the anti-epileptic action of hypothermia, and several show evidence of its efficacy. However, and since super-refractory status epilepticus' management is very complex and multifactorial, there is a lack of evidence to assert to what extent hypothermia can resolve super-refractory status. It is important to point out that even mild hypothermia has its own risks such as acid-base and electrolyte disturbances, disseminated intravascular coagulation, coagulation disorders, thrombosis, infections, cardiac arrhythmia, bowel ischemia and paralytic ileus.</p>
<p><b>EMERGENCY          NEUROSURGERY</b></p>	<p>Urgent neurosurgery has been employed as a last-line therapy in situations where there is radiological or electroencephalographic evidence of a focal lesion. However, in status epilepticus there are often widespread epileptogenic areas and, therefore, the outcome after emergency surgery is usually poor.</p> <p>Surgical procedures employed will depend on the type of lesion identified, with the most common being the focal resection of areas of cortical developmental malformation. The optimal timing for the implementation of surgical techniques is not entirely clear. Evidence suggests considering it in selected cases with status epilepticus lasting two weeks or more, although in some instances, interventions have been carried out earlier</p>

<b>ELECTRICAL AND MAGNETIC STIMULATION THERAPIES</b>	
<b>TRANSCRANIAL MAGNETIC STIMULATION (TMS)</b>	Transcranial magnetic stimulation uses a magnetic field to induce electric currents in specific areas of the brain. These electric currents are believed to be useful on stopping the epileptogenic activity just as they are on treating depression, obsessive-compulsive disorder and certain types of migraines. Due to its infrequent use in super-refractory status epilepticus, and given that its mechanism of action is contrary to that of anesthesia and antiepileptic drugs, it is doubtful that it will be incorporated in the future as a therapy with significant outcomes
<b>VAGAL NERVE STIMULATION</b>	Despite the mechanism of action not being fully understood, it is known that vagus nerve stimulation modulates neuronal activity. In the treatment of status epilepticus, the implantation of a vagus nerve stimulation device has shown effectiveness in some cases. However, due to the complex multifactorial management of status epilepticus, involving simultaneous administration of multiple therapies, there is insufficient evidence regarding the efficacy of vagus nerve stimulation in terminating the status
<b>DEEP BRAIN STIMULATION</b>	Deep Brain Stimulation (DBS) is a technique involving the implantation of electrodes in specific areas of the brain, which are connected to a pulse generator device typically subcutaneously implanted in the chest area. This cerebral stimulation allows for the modulation of neuronal activity in the stimulated regions and is occasionally used to treat neurological and psychiatric disorders such as Parkinson's disease, essential tremor, dystonia, treatment-resistant depression and some cases of obsessive-compulsive disorder. Further research is needed regarding its use in controlling super-refractory status epilepticus, as there are currently only publications regarding its efficacy in seizure control
<b>ELECTROCONVULSIVE THERAPY (ECT)</b>	Electroconvulsive therapy is the most extensively studied form of brain stimulation in the management of status epilepticus. Its antiepileptic effect, although not yet well-defined, is believed to be attributed to an increase in presynaptic GABA release that occurs following the tonic-clonic seizure or generalized epileptiform discharge induced by electroconvulsive therapy. Further information on ECT (including more detail on its mechanism of action and adverse effects) can be found in Section 3 of the introduction of this document.
<b>CEREBROSPINAL FLUID DRAINAGE</b>	There is a single recently published study regarding the use of cerebrospinal fluid drainage in the management of super-refractory status epilepticus. A highly favorable response was observed in this study, and it is suspected that it may be attributed to the removal of inflammatory substances, to an autonomic reflex caused by the drop of pressure or to the changes in intracerebral pressure, properly. It is postulated that this treatment tool could be combined with the intrathecal administration of highly effective antiepileptic agents, but further research on cerebrospinal fluid drainage is still required to draw definitive conclusions as proposed

### 2.1.7 PROGNOSTIC

Morbidity-mortality and complication rates of SE are somewhat challenging to determine due to the range of definitions that status epilepticus has had over the years. The extensive range of etiologies and therapeutic options also complicates drawing conclusions about the prognosis and sequelae of this. This is why obtaining prognostic tools is somewhat challenging within status epilepticus, as the prognosis tends to be individualized for each patient (24–26).

Several prognostic factors have been pointed to predict the outcome of status epilepticus. Of the prognostic factors proposed as predictors, the ones that are believed to be the most accurate are age, etiology, seizure duration and response to treatment (9,24–27).

*Table 6 – MAIN PROGNOSTIC FACTORS OF SE (8,9,26,27)*

<b>AGE</b>	Excluding neonatal period, status epilepticus prognosis and mortality mostly worsens with age.
<b>ETIOLOGY</b>	Etiology is considered to be the main determining prognostic factor. Patients with cerebral anoxia and acute symptomatic etiology (such as SE due to CNS infection) have a worse prognosis and a higher mortality rate. On the other hand, patients with SE due to noncompliance to treatment of changes of AED therapy have a better prognosis and a lower mortality rate.
<b>SEIZURE DURATION</b>	Seizure duration is associated with an increased mortality and worse prognosis but there is still no consensus in this finding since continuous EEG is not always available in order to monitorize seizure ending and duration in sedated and non-convulsive patients.
<b>RESPONSE TO TREATMENT</b>	One-year mortality rates are steamed to be 17-27% in refractory status epilepticus and 26-46% in super-refractory status epilepticus. Refractoriness to treatment has been associated to a worse prognosis, that's why refractory and super-refractory status epilepticus show a higher mortality and worse prognosis.

In the past years, new scores to predict the outcome of SE have emerged. The Status Epilepticus Severity Score (STESS) is a clinical score which predicts in-hospital mortality of patients with status epilepticus based on age, consciousness, history of previous seizures and the worst seizure type the patient's had.

Although this score is a good short term prognosis predictor, it's effectiveness in long term prognosis it is yet to be confirmed. In addition, STESS seems to have a low predictive value for status epilepticus with good outcome (9,28).

Epidemiology based mortality score in SE (EMSE) is a newer clinical score which also predicts in-hospital mortality of patients with status epilepticus based on age, etiology, comorbidities and EEG pattern. This score, although it needs further validation, has shown to be a better outcome predictor and to be valid and extrapolatable to a broader range of geographical and epidemiological realities than STESS (9,29).

The scores templates for both STESS and EMSE can be found in Annex 5.

The most common complications in patients during status epilepticus are arterial hypotension, pneumonia, arrhythmias, systemic and pulmonary hypertension, hypoxia, respiratory depression, hyperkalemia, rhabdomyolysis, infections, liver failure, renal failure, ileus and gastrointestinal disturbance, metabolic acidosis and pulmonary edema. These complications are not just related to the seizures themselves but also with the pharmacologic treatment and the prolonged stay in the ICU. This is why statuses that remain under sedation for a longer period (refractory and super-refractory SE) will be at a higher risk of complications (30).

Continuous epileptic activity may also lead to neurological sequelae. Secondary epilepsy in patients who didn't suffer from it (which may occur in 22-41% of established SE and in 87.5% of refractory SE), cognitive and/or functional deficits (which may occur in 21-61% of established SE and in 67% of super-refractory SE), behavioral problems and focal neurologic deficits are among the potential neurological consequences that a patient may experience after status epilepticus. It is important to specify that the risk of experiencing these sequelae largely depends on the etiology of the status, and that the risk increases with the refractoriness of the status (1,2,31-34).

## [2.2 ELECTROENCEPHALOGRAM \(EEG\)](#)

Electroencephalography is a cheap, painless and non-invasive functional exploration technique of the CNS which represents cerebral spontaneous electrical activity generated by the brain in real time. The origin of this electrical activity lies in the pyramidal cells of the cerebral cortex, but the entirety of electrical activity will depend not only on the integrity of these cells but also on the state of subcortical

structures such as the diencephalon, brainstem and the connections between the cortex and all these structures (35,36).

To perform it, electrodes are set up on the scalp according to the international 10-20 system (Annexe 6) to capture and analyze the frequency, characteristics, spatial distribution and state of cerebral electrical activity (35–37). The electrodes are combined in such a way that two different setups can be obtained:

- **Monopolar or referential montage:** records the electric voltage difference between one electrode placed in an active cerebral area and the reference electrode (which is placed in a neutral area such as the earlobe) or the average of all or some of the active electrodes (36).
- **Bipolar montage:** records the voltage difference between two electrodes placed in cerebral active areas (36).

EEG is currently indicated for evaluating clinical conditions such as epilepsy, alterations in the level of consciousness, impairment of higher cognitive functions, assessment of cerebral maturation in newborns and preterm infants and certification of brain death. In the field of epilepsy, EEG provides relevant information for the diagnosis, classification, and ongoing monitoring of patients with epileptic seizures. It is important to note that up to 50% of patients may have a normal EEG in the interictal period, and in some cases (especially with focal seizures), it can also be normal during the crisis itself. Therefore, to subject the patient to specific stimulations during the EEG that lower the epileptogenic threshold, such as hyperventilation, sleep deprivation, sleep or intermittent photic stimulation (IPS) can be useful to induce epileptic activity while performing the test, and in this way, to be able to analyze it using the EEG (35,36).

### 2.2.1 EEG in a super-refractory SE context

In the context of a super-refractory SE it is crucial to acknowledge that the patient will be sedated. The primary challenge in managing a patient with a prolonged epileptic crisis who has been sedated is to ascertain whether or not the patient is experiencing the seizure 24 hours after sedation and, therefore, if the patient is indeed experiencing a super-refractory SE (35,36,38). Determining whether a patient with refractory status epilepticus is in an epileptic crisis or not after 24 hours of sedation will depend on the clinical scenario in which we find ourselves. This scenario may include:

- **Patient who, after 24 hours of sedation, continues to exhibit a clinical seizure with prominent motor phenomena:** if EEG demonstrates epileptic activity corresponding to the clinical

manifestation, the patient will still be experiencing an epileptic crisis and, therefore, will be in a super-refractory status epilepticus situation (2–4,35,38).

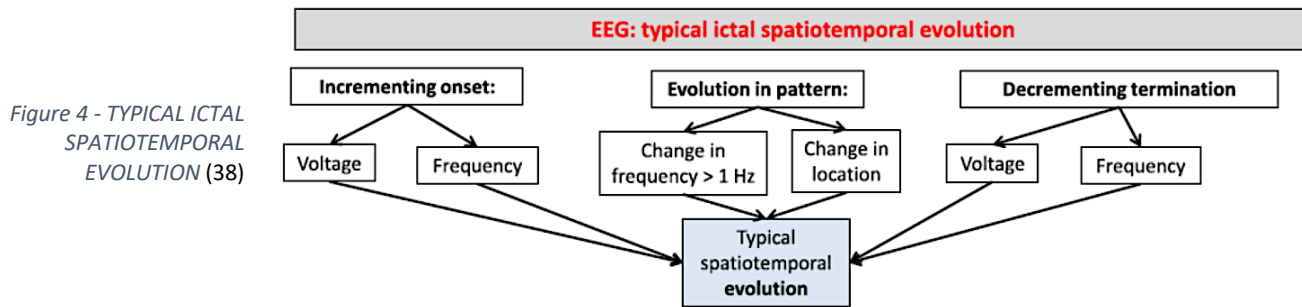
- **Patient who, after 24 hours of sedation, doesn't exhibit a clinical seizure with prominent motor phenomena** (*this includes patients who initially were in a non-convulsive SE and patients who were in a convulsive status epilepticus but sedation stopped them from manifesting predominant motor phenomena*): since the persistence of an epileptic crisis is necessary to categorize a patient as having super-refractory status epilepticus and a visible motor activity signs are not present, the mere presence of epileptic activity in an EEG 24 hours post sedation is insufficient to determine whether the patient is still experiencing status epilepticus or not. To distinguish between a clinical crisis and residual epileptic activity, an augmented evaluation of the electroencephalographic tracing must be carried on. Such evaluation shall be undertaken in accordance with the American Clinical Neurophysiology Society's (ACNS) modified Salzburg consensus criteria for non-convulsive SE (mSCNS) (*Table 5*) (2,35,38–40). If these criteria are fulfilled, the EEG findings will be deemed indicative of an epileptic crisis, thus signifying that the patient is in a super-refractory SE.

**Table 7 – mSCNC (38–40)**

<b>MODIFIED SALZBURG CONSENSUS CRITERIA FOR NON-CONVULSIVE STATUS EPILEPTICUS (mSCNC)</b>
<p>A. Patients without known epileptic encephalopathy who fulfill at least one of the following criteria:</p> <ol style="list-style-type: none"> <li>1. Epileptiform discharges (repetitive focal or generalized spikes, polyspikes, sharp waves, spike-and-waves or sharp-slow -wave complexes) &gt;2.5 Hz</li> <li>2. If epileptiform discharges are <math>\leq 2.5</math> Hz or, in case there are no epileptiform discharges, there is a continuous rhythmic delta-theta activity &gt;0.5Hz, one of the following should be fulfilled:               <ol style="list-style-type: none"> <li>a) Typical spatiotemporal evolution: one of the following must be fulfilled:                   <ul style="list-style-type: none"> <li>- Incrementing onset (increase in voltage with changes in frequency)</li> <li>- Decrementing termination (in voltage or frequency)</li> </ul> </li> </ol> </li> </ol>



- Evolution in pattern (change in frequency >1Hz and change in location).



b) Subtle clinical ictal phenomenon (facial twitching, gaze deviation, nystagmus, limb myoclonus, etc) during the EEG pattern mentioned above

c) EEG and clinical improvement after IV AED are applied

B. Patients with known epileptic encephalopathy, in addition to the criteria above, have to fulfill one of the following:

1. Increase in prominence or frequency when compared to baseline with observable change in clinical state.
2. Improvement of clinical and EEG features with IV AEDs

## 2.3 ELECTROCONVULSIVE THERAPY (ECT)

ECT is a well-known treatment used frequently in several psychiatric disorders. It consists of applying electrical stimulation to the brain under mild anesthesia, with specific frequency and intensity parameters and with a predetermined electrode montage with the intention of inducing a controlled generalized tonic-clonic seizure. ECT still faces some social resistance and continues to be linked to a perceived form of punishment for psychiatric patients. This perception couldn't be further from the truth, as ECT represents a safe and effective therapeutic tool for psychiatric disorders that are refractory to medical treatment and psychotherapy (41–44).

### 2.3.1 HISTORY OF ELECTROCONVULSIVE THERAPY

Although the practice of inducing convulsions to treat mental illness began in the 16<sup>th</sup> century, electroconvulsive therapy itself is no longer than 80 years old. It was first performed in 1938 by the

Italian psychiatrist Ugo Cerletti and his colleague Lucio Bini. At that time, it was believed that schizophrenia and other psychiatric disorders were caused by abnormal electrical activity in the brain, and ECT was thought to be able to help in restoring it to its normalcy. During the 1940s, ECT became a widely utilized treatment in the field of psychiatry, but as drugs for the treatment of psychiatric disorders were being developed, ECT gradually assumed a secondary role and became reserved for refractory cases (43,45,46).

Its role in the treatment of epilepsy and SE began when it was observed that psychiatric patients treated with ECT exhibited a higher epileptogenic threshold and a lower spontaneous seizure rate as they underwent it. Between 1950 and 1980, anecdotal cases were reported aiming to raise the seizure threshold and interrupt status epilepticus, but as AED emerged, the potential envisioned for ECT dissipated and it wasn't until the 90s when case reports of use of ECT in refractory SE again started reappearing. Most of these published case reports demonstrated promising results, but due to the low incidence and complex management of the condition, obtaining a level of evidence that allows for standardizing its use has not yet been possible to date. Although published cases have been increasing, and the results are promising, conducting further studies to strengthen the evidence still remains necessary (43,47,48).

### 2.3.2 MECHANISM OF ACTION

Although the specific mechanism of action by which ECT is beneficial in seizure control is still unknown, several studies with hypotheses on this matter have been published. Anticonvulsant properties of ECT are proposed to be due to direct or indirect modulation of inhibitory neurotransmitters, reducing seizure duration, increasing seizure threshold, modifying the expression of immediate ictal and postictal seizures, cerebral blood flow, glucose metabolism and EEG activity. This hypothesis of neurotransmitter modulation specifically revolves around GABA. It has been observed that following an induced generalized seizure, presynaptic release and transmission of GABA are enhanced, a phenomenon that would improve the control of neuronal hyperexcitability. Some later studies show that other anticonvulsant properties of ECT could rely on an elevation in the levels of inhibitory neuropeptides such as neuropeptide Y, somatostatin, or endothelin. These neuropeptides are believed to play a role in suppressing electrical activity, remodeling synaptic activity, promoting neurogenesis, and enhancing long-term neuronal plasticity, thereby imparting a certain anti-inflammatory action (48–50).

### 2.3.3. ADVERSE EFFECTS

ECT is usually well tolerated. Adverse effects (AE), while they can be self-limiting, are commonly mild and can be managed symptomatically (51).

- **General adverse effects:** headache (occurs in 26-85% of patients), which is usually mild and self-limiting, peaks within 2 hours, subsides within 24 hours and responds to conventional analgesics and triptans, myalgia and nausea.
- **Cardiac adverse effects:** bradycardia, hypotension and arrhythmias may occur immediately after the ECT stimulus. A sympathetic urge may occur if the induced seizure has a long duration, and it can cause tachycardia, hypertension, tachyarrhythmias and cardiac ischemia due to an increased myocardial oxygen demand. The occurrence of any cardiac AE during ECT may be as high as 7,5% (in healthy patients) and 55,0% (in patients with cardiac illness). Thankfully, with the institution of continuous heart rate, blood pressure and ECG monitoring cardiac AE have decreased. Analysis of mortality in large sets of patients receiving ECT suggests that cardiovascular death shortly after ECT is very rare and, in most cases, cannot be attributed to ECT per se (51–54).
- **Respiratory adverse effects:** the only respiratory AE reported in ECT aspiration leading to pneumonitis, neurogenic pulmonary edema and pulmonary embolism. However, they are rare (51).
- **Neurologic adverse effects:** neurological AE include an increasing on cerebral blood flow due to an increased oxygen demand during seizure and an increased vascular permeability, which may lead to temporary functional breakdown in the blood brain barrier. These changes may increase intracranial tension and sometimes cause benign brain edema. However, these complications mostly occur in patients with preexisting central nervous system lesions. Ischemic stroke and intracranial bleeding are very rare to occur during ECT (51,53).
- **Cognitive impairment:** related to a pre-ECT baseline status, medium to large short-term deficits are often found in executive functioning, in spatial problem solving and in global cognition after ECT. These deficits usually attenuate within time (51,55).
- **Memory loss:** ECT has different effects on verbal and nonverbal, episodic and semantic explicit memory. These include anterograde amnesia, retrograde (including autobiographical) amnesia

and subjective memory loss. Retrograde amnesia is arguably one of the most impactful AE since episodic and autobiographical memories are strongly tied to a sense of identity (51,55).

It is noteworthy that in a significant number of published cases of SRSE treated with ECT, patients experienced significant cognitive and/or memory impairment. Since the side effects of electroconvulsion have primarily been studied in the treatment of psychiatric patients (as they are the primary users of ECT), there is a lack of evidence to distinguish whether these adverse effects on cognition and memory could be attributed to ECT, to the prolonged epileptic activity or to a combination of both factors (41–44,56–59).

- **Death:** deaths directly or plausibly attributed to the electrical stimulus, seizure or anesthesia during ECT are estimated to be approximately 2-10 per 100,000 treatments. Cardiac and respiratory events are the most common causes of mortality related to ECT procedures. The deaths are commonly attributable to preexisting medical illness and anesthesia-related complications (60).
- **Others:** organic affective syndrome, transient treatment-emergent mania, manic switch, urinary bladder rupture, gastric rupture, vitreous detachment and bleedings.

#### 2.3.4 INDICATIONS

The main indications of ECT are (64):

- Treatment-resistant/refractory major depression
- Treatment-resistant/refractory schizophrenia
- Catatonia
- Acute Maniac Episode

While the use of ECT in the treatment of the mentioned psychiatric conditions is widely recognized, there are other disorders for which, although ECT is believed to be potentially beneficial, there is not yet sufficient evidence to warrant systematic use. Within the field of neurology, the diseases in which ECT could play a role as a treatment tool include Parkinson's disease, tardive dyskinesia, neuroleptic malignant syndrome, and, of particular interest in this document, refractory epilepsy (64,65).

#### 2.3.5 CONTRAINDICATIONS

Pheochromocytoma and elevated intracranial pressure with mass effect are absolute contraindications to ECT. Relative contraindications include elevated intracranial pressure without mass effect, cardiovascular conduction defects, hypertension, high-risk pregnancies, aortic and cerebral aneurysms (61,62).

### 2.3.6 REVIEW OF THE AVAILABLE PUBLICATIONS ON THE USE OF ECT IN THE MANAGEMENT OF SUPER-REFRACTORY STATUS EPILEPTICUS

The first published case series, which was published in 2012 on “Seizure: European Journal of Epilepsy”, shifted the paradigm of ECT. This series examined 11 cases of patients with super-refractory status epilepticus who underwent ECT, resulting in a highly favorable outcome. The **treatment was successful in 80% of cases, with complete functional recovery observed in 27% of cases** (41).

Four years later, the same journal published a systematic review comprising 14 retrospective descriptive articles, involving a total of 19 patients who underwent ECT for the treatment of refractory status epilepticus of various etiologies. A **reduction or control of seizures was observed in 57.9% of cases** but surprisingly, **satisfactory functional recovery was only noted in 3 out of the 13 patients for whom results were reported**. This review concluded that the application of ECT might have an impact on the control of prolonged seizures but its use was not recommended (56).

In 2010, a study was published that set the standard for ECT procedures in the subsequent years. In this study, the parameters were well-described, and an overall **favorable outcome was achieved in 2 out of the 3 cases**. The application protocol involved daily ECT sessions performed on consecutive days, with each session comprising at least three seizure inductions. Stimuli were applied at a mean intensity of 507mC (57).

In 2018, a study was published detailing the technical procedure used to administer ECT to 8 patients with super-refractory status epilepticus. Stimuli of 504mC were delivered with a bitemporal electrode montage. ECT sessions consisted of at least 2 stimulations (with a maximum of 3 based on the response to previous stimulations). In most cases, sessions were conducted daily, but the session frequency was individually determined based on each patient's clinical situation. **Favorable outcomes of improvement or control of epileptic activity were observed within 24 hours after ECT**, as assessed by electroencephalographic monitoring or clinical evidence, **in 63% of the cases** (43).

In 2011, an article was published recommending the reversal of anesthetic and antiepileptic agents prior to ECT administration, based on the hypothesis that these agents have a mechanism of action opposite to that of electrostimulation, thereby preventing an effective ECT (23). This idea was supported in 2018 with the publication of a study where a case of SRSE requiring ECT was reported. Anesthesia and antiepileptic medications were reduced prior to the application of ECT (only ketamine and levetiracetam

were maintained), and an intensity of 1,031mC was applied with a bitemporal electrode montage. Three stimuli were administered per session, with daily sessions for 4 consecutive days. A generalized seizure was successfully induced in all sessions, and **the patient eventually emerged from the status epilepticus** with relative functional capacity afterward since the **patient exhibited a considerable impairment in communicative abilities** in the follow-up months later (42).

In 2020, a case series was published where two patients were successfully treated with ECT after failing all pharmacological measures. Patient 1 underwent a total of 8 ECT sessions in 5 days within a 2 week-period. Stimuli were applied in a bitemporal montage, at a frequency of 50Hz and with an increasing intensity from 156mC to 416mC. All anesthetics and AEDs were maintained during ECT. His **status resolved**, and clinical improvement was observed two weeks after starting ECT. He did not participate in follow-up, so his **sequelae are unknown**. Patient 2 underwent total of 8 ECT sessions on consecutive days for 8 days. Stimuli were applied in a bitemporal montage, at a frequency of 50Hz and with an increasing intensity from 300mC to 768mC. **Seizures resolved** two weeks after starting ECT. **No sequelae were reported**. The conclusions were that ECT could have a role in terminating status after exhausting all pharmacological measures. However, the case series reported that larger prospective unbiased trials were required to yield more robust evidence in order to understand the role and benefits of ECT and to design a standardized regime of ECT for SRSE (58).

Also in 2020, a prospective review led by a Spanish team was published, proposing ECT as an adjunctive therapy following the failure of the initial anesthesia or barbiturate-induced coma, after two prior AED failures, including benzodiazepines. The review presented a methodological protocol detailing the procedure for inducing a seizure in each daily ECT session. The protocol involved optimizing antiepileptic treatment to minimal effective doses, administering them post-ECT session, and discontinuing the anesthetic treatment just before applying ECT (minimum of 30-60 minutes for propofol and 3-4 hours for midazolam). Fentanyl was maintained as an analgesic during the ECT session. The objective of each session was to induce a 20-second seizure. To achieve this, an initial stimulus of 500mC was applied, with the possibility of applying up to three stimuli (5 seconds at 60Hz each) per session, gradually increasing the intensity to a maximum of 1000mC. In sessions where no response was obtained with the initial

stimuli, non-electric stimuli (acoustic or oral caffeine 300-500mg) were applied to facilitate subsequent responses (44).

The patients were monitored using long-duration video-electroencephalogram (vEEG) recordings from 45 minutes before the session until 1-3 hours afterward. Ictal patterns were defined by rhythmic discharges or defined electrical seizures. Non-convulsive status epilepticus was defined according to the modified Salzburg consensus criteria for non-convulsive status epilepticus. In the event of ictal patterns or non-convulsive status, minimal doses of anesthetics were reintroduced, and ECT sessions were individualized (44).

ECT was administered on average 12 days after admission to the ICU, with a mean of 6.3 sessions per patient. Few clinical seizures were induced in response to stimulations, but **control of the status was achieved in all patients**. However, almost half of them experienced epileptic seizures in the subsequent months during the follow-up. The fact that status control was achieved despite not inducing clinical seizures suggests that the neuromodulatory effect on GABA and its receptors could be achieved without the need for a clinical convulsion. **Regarding sequelae, 2 out of the 6 patients did not exhibit any** (although it is worth noting that one of them passed away from pneumonia 6 months after emerging status, therefore it was not considered an adverse effect of ECT). Among the other 4 patients, all presented some form of mild or moderate neurological deficit (it is worth noting that one of the patients passed away due to comorbidities arising from the prolonged hospital stay, and that follow-up was impossible for another patient who ceased attending appointments or responding to phone calls). The conclusions were in line with previous reviews. It was concluded that ECT is a reasonable and feasible option in the treatment of SRSE which has to be considered in its treatment algorithm (44).

In 2023 a retrospective case series of 11 patients with SRSE was published. ECT was administered with a bitemporal stimulus electrode placement for all patients except one who presented with left focal SRSE and underwent a right unilateral montage due to history of left hemispherectomy without bone flap. Stimuli were applied at a 70Hz and with an intensity ranging from 501mC to 506,3mC. Anesthetic agents were weaned at least 2-4 hours prior to each ECT session and then restarted on an as-needed based on clinical judgement following the completion of a session. Each session consisted of 2-3 stimulations, and intervals between sessions were individualized based on the clinic situation of each patient. **Status resolution was achieved in all patients**, however, 6 of them recurred on a range of 8 to 51 days after

ECT and the **outcomes and sequelae at hospital discharge were mainly poor**. The conclusion in this case series were that ECT could be associated with the resolution of SRSE and improvement of highly ictal patterns on EEG. They also concluded that ECT on their population seemed safe and thus earlier initiation of ECT for SRSE should be considered (59).



### 3. JUSTIFICATION

Status epilepticus represents a therapeutic challenge today. Although the majority of SE cases respond to benzodiazepines and antiepileptic drugs (AED), when super-refractoriness emerges, management becomes very challenging. After benzodiazepines and AED fail, other available therapies for SRSE (which include magnesium infusion, pyridoxine, steroids and immunotherapy, ketogenic diet, hypothermia and electrical and magnetic stimulation therapies such as electroconvulsive therapy) can be attempted. However, the challenge lies in the fact that, despite it is believed that these therapies are safe and likely effective, there is insufficient supporting evidence due to a lack of studies as only a few case series have been published on this matter. Furthermore, the high mortality and morbidity of SRSE, despite its low incidence, emphasize the importance of increasing the level of evidence supporting the administration of any of these therapies (5,7–9).

Regarding the mentioned therapies, electroconvulsive therapy, although limited, is one of the most studied. There are some published case reviews that provide promising data regarding its efficacy in controlling super-refractory status epilepticus. All of them conclude that ECT could be effective in controlling prolonged seizures, but study designs providing a higher level of evidence are needed to extrapolate findings to clinical practice (41–44,56–59).

Understanding the mechanism of action of different therapies is crucial for optimizing their use in managing SRSE. ECT has demonstrated an increase in presynaptic GABA release after an induced generalized tonic-clonic seizure (49,50). It's important to note that patients in SRSE are consistently under sedation, and both anesthetic and AED function by inhibiting neuronal activity. While ECT also aims to reduce neuronal excitability, it necessitates the induction of a generalized seizure. Seizures result from synchronous neuronal hyperexcitation, so applying an electroconvulsive stimulus without modifying the inhibitory drugs given to a patient in status would be counterproductive as the mechanism of action of these drugs is antithetical to the induction of a seizure. Although it is widely accepted that the anesthetic and antiepileptic regimen should be adjusted during ECT administration, the optimal approach has not been conclusively demonstrated. Previous publications (23,42–44,59) have followed the trend of discontinuing the administration of anesthetics and (partially) of antiepileptics a few hours

before ECT to facilitate the seizure and reintroducing the withdrawn medication once the session is completed. Despite the evidence suggests that this protocol may already be effective, the neurology team at the epilepsy unit of Santa Caterina Hospital in Girona suspects that repeatedly withdrawing and reintroducing anesthesia medication might not be the best option. Instead, they propose a protocol of progressively reducing the medication without abruptly discontinuing it, so that in each ECT session, the patient is subjected to lower sedation, making it easier to induce the seizure. This new protocol has been implemented on two occasions in Santa Caterina Hospital. In one instance, despite observing electroencephalographic changes, adjunctive ECT was not sufficient to control the status. However, in the second case, adjunctive ECT following this new approach of anesthesia withdrawal proved effective in controlling the status. Detailed explanations of both cases can be found in Annexe 7.

The published evidence, along with the few contraindications and easily manageable adverse effects of ECT, encourage us to believe that researching ECT as a therapy for SRSE could be very profitable and have a positive impact on clinical practice.

Our study, which will be a randomized clinical trial, aims not only to fulfill the need for expanding evidence regarding the treatment of SE with ECT, but also seeks to address uncertainties regarding its administration protocol by comparing the efficacy and safety of two distinct sedation protocols during ECT sessions. The design of our study will allow for the consideration of confounding variables, avoidance of biases and more precise collection of clinical and therapeutic data, facilitating the derivation of results with greater evidence.

## 4. HYPOTHESIS

### 4.1 MAIN HYPOTHESIS

The progressive reduction of sedation is more effective than its intermittent discontinuation during electroconvulsive therapy in achieving cessation of super-refractory status epilepticus.

### 4.2 SECONDARY HYPOTHESES

Secondary hypotheses in this study are:

- The progressive reduction of sedation is more effective than its intermittent discontinuation during electroconvulsive therapy improving epileptic EEG activity in patients with super-refractory status epilepticus.
- The gradual sedation reduction protocol achieves a faster control of status epilepticus compared to an intermittent sedation discontinuation protocol when employing ECT in patients with super-refractory status epilepticus.
- The progressive reduction of sedation is no less safe than its intermittent discontinuation during electroconvulsive therapy in controlling super-refractory status epilepticus.
- The progressive reduction of sedation doesn't result in a higher occurrence of neurological sequelae than its intermittent discontinuation during electroconvulsive therapy in controlling super-refractory status epilepticus.

## 5. OBJECTIVES

### 5.1 MAIN OBJECTIVE

The main goal in the current study is to demonstrate greater efficacy of ECT when performing a gradual sedation reduction protocol compared to when using an intermittent sedation discontinuation protocol in achieving cessation of super-refractory status epilepticus.

### 5.2 SECONDARY OBJECTIVES

Secondary objectives in this study are:

- To demonstrate superior efficacy of ECT when performing a gradual sedation reduction protocol compared to when using an intermittent sedation discontinuation protocol in improving epileptic EEG activity in patients with super-refractory status epilepticus.
- To demonstrate that a gradual sedation reduction protocol achieves a faster control of status epilepticus compared to an intermittent sedation discontinuation protocol when employing ECT in patients with super-refractory status epilepticus.
- To compare the safety of ECT when performing the gradual sedation reduction protocol compared to when using intermittent sedation discontinuation protocol in the treatment of patients with super-refractory status epilepticus.
- To compare the neurological sequelae arising from the application of ECT when performing a gradual sedation reduction protocol versus when using intermittent discontinuation in the treatment of patients with super-refractory status epilepticus.

## 6. METHODOLOGY

### 6.1 STUDY DESIGN

To accomplish the objectives of this project, a randomized, multicentered, prospective, controlled clinical trial will be performed.

The study is designed to compare, as its main objective, two different sedation protocols to perform while applying ECT on a patient with a super-refractory status epilepticus. All patients will be treated with ECT and subsequently be monitored via EEG, but they will be randomized in a ratio 1:1 into one of the following groups:

- Group 1: patients with super-refractory status epilepticus to whom **ECT will be applied with an intermittent interruption of sedation around ECT sessions.**
- Group 2: patients with super-refractory status epilepticus to whom **ECT will be applied with a continual progressive withdrawal of sedation before the first ECT session onward.**

It is important to clarify that, despite comparing the sedation protocol in this type of intervention, all patients will be receiving other antiepileptic treatments on an individualized basis. It is also important to specify that the dosage of antiepileptic and sedative drugs will be individualized based on the type of drug, as well as the patient's weight and age. The medication reduction schedule in Group 2 will also be implemented on an individualized basis according to the clinical situation of every patient.

### 6.2 STUDY SETTING

Due to the low incidence of SRSE, this project will be multicenter. An initial contact has been made to count on the collaboration of the 13 reference hospitals equipped for electroconvulsive therapy in Catalunya (*Hospital de Sant Pau, Hospital Vall d'Hebron, Hospital Clínic de Barcelona, Hospital del Mar, Hospital de Bellvitge, Hospital Can Ruti, Mútua de Terrassa, Hospital Parc Taulí, Hospital de Sant Boi, Hospital de Martorell, Hospital Josep Trueta, Hospital Joan XXIII and Hospital Arnau de Vilanova*), since they all should have an epilepsy unit and a psychiatry service staffed and accustomed to the use of electroconvulsive therapy. To facilitate patient inclusion, in addition to proposing it to the mentioned hospitals, we will create our multicenter selection through the epilepsy study group of the “Sociedad Española de Neurología” (SEN) and the “Sociedad Española de Epilepsia” (SEEP). We will present our project and choose among the interested centers based on the following criteria:

- To belong to the study group of epilepsy of the SEN or the SEEP.
- To have previous experience on research
- To have hospitalized patients at ICU and neurology department
- To have availability of a portable EEG to use in hospitalization services.
- To have experienced physicians in EEG
- To have availability of ECT and physicians staffed and accustomed to its use.

To establish proper communication among all centers, we will assign a main research team that will act as the principal study coordinator. This team will be composed of members from the epilepsy unit in Girona. At each participating center, a research team will be established with a principal investigator. Linking support investigators from the Girona team will be designated to maintain contact with the principal investigators at each center.

### 6.3 STUDY POPULATION

The study population will consist of patients with superrefractory status epilepticus scheduled to undergo electroconvulsive therapy in the health regions of Spain associated with the centers that agree to participate in the study.

### 6.4 PARTICIPATION CRITERIA

#### Inclusion criteria

- Patients with super-refractory status epilepticus scheduled to undergo ECT
- Adult aged 18 years or older.
- Possibility of conducting a 1-year follow-up after ECT application.
- Patients without cognitive impairment or memory loss prior to the status epilepticus

#### Exclusion criteria

- Patients admitted to the ICU where the reason for intubation and sedation was not status epilepticus.
- Patients with focal status epilepticus without impairment of consciousness.
- Patients with absence type status epilepticus.
- Patients with pheochromocytoma, elevated intracranial pressure with mass effect or any other condition that could compromise ECT.

### Withdrawal criteria:

- Patients who refuse to participate in the study despite meeting the inclusion criteria and none of the exclusion criteria.
- Enrolled patients who withdraw their prior informed consent through the consent withdrawal request document (Annex 11).
- Patients identified with any exclusion criteria during the study, either because it was not detected during enrollment or because it developed subsequently.
- Patients who do not attend follow-up visits, which will be considered study losses.
- Patients who decease, which will also be considered study withdrawals (details of the cause will be required)

All patient losses, regardless of the cause, must be documented along with the reasons for them. The information obtained prior to the withdrawal will be analyzed together with the data from the remaining patients.

## 6.5 SAMPLE SELECTION

The sample selection will be done through a consecutive non-probabilistic sampling, where patients will be selected as they are admitted to the ICUs of participating centers.

## 6.6 SAMPLE SIZE

We calculated the sample size by approximating the efficacy rate of the intermittent interruption sedation protocol based on published cases, assigning it a value of 45%. Additionally, we estimated the efficacy rate of the proposed progressive withdrawal of sedation protocol by the epilepsy unit of Girona, which, by the criteria of the Unit of Epilepsy of Girona's neurologists, was assigned a value of 60%.

Accepting an alpha risk of 0.05 and a beta risk of 0.2 in a bilateral test, 204 participants will be required in each group to detect the statistically significant difference between the two expected success proportions of each protocol.

## 6.7 VARIABLES

### 6.7.1 INDEPENDENT VARIABLE

The independent variable of the study will be “Sedation protocol applied during ECT sessions”. It will be expressed by *Protocol 1/Protocol 2*, with Protocol 1 being the intermittent interruption of sedation and Protocol 2 being the progressive withdrawal of sedation. It is a qualitative dichotomous variable.

### 6.7.2 DEPENDENT VARIABLES

The dependent variables of the study are:

- **Dependent variable of the main objective:** “cessation of status epilepticus”. To evaluate this variable, modified Salzburg consensus criteria for non-convulsive SE (mSCNS) will be used. We will consider the status as ceased if the mSCNS are met for a minimum of 24 hours without requiring an increase in the anesthesia dosage. Since mSCNS are electroencephalographic criteria, to evaluate this variable, a continuous EEG monitoring will be mandatory. The personnel will be blinded during the interpretation of the EEG records. It is a qualitative dichotomous variable that will be expressed by Ceased/Not ceased.
- **Dependent variables of the secondary objectives:**
  - Dependent variable of the changes on epileptic EEG activity: “Electroencephalographic changes”. To assess this variable, the evaluation and comparison of electroencephalographic records before and after each ECT session will be required. Specialized personnel familiar with EEG will be needed for the evaluation of this variable. This personnel will be blinded during the interpretation of the records. It is a qualitative dichotomic variable that will be expressed by Positive changes/*No positive changes*.
  - Dependent variable of the time elapsed between ECT and control of epileptic status: “Time between ECT and achieving status control”. To measure this variable, we will count the days elapsed from the initiation of ECT until the cessation of the status, which will be assessed using the mSCNS as explained earlier. It is a discrete quantitative variable that will be measured in days.
  - Dependent variable of the safety sedation protocol used during ECT: “Adverse Effects”. This variable refers to the potential adverse effects that may occur during sedation and/or ECT. To measure this variable, clinical evaluation, vital signs monitoring, daily



laboratory analyses (complete blood count, electrolytes, blood gas analysis, renal profile, hepatic profile, pancreatic profile and acute phase reactants) and EEG monitoring during and between ECT sessions will be performed to identify possible adverse effects. It is a qualitative nominal variable that will be expressed as one of the followings:

- None
  - Liver disfunction
  - Bradycardia
  - Sedation Tolerance
  - Poor control of clinical seizures
  - Others
  - Cardiorrespiratory depression
  - Renal disfunction
  - Hypotension
  - Sedation dependence
  - Death
- Dependent variable of the neurological sequelae arising from ECT one year post-procedure: “Neurological sequelae”. To measure this variable, it will be necessary to conduct clinical follow-up with comprehensive neurological examinations and perform periodic EEG on patients for 1 year after they emerge from status epilepticus. It is a qualitative nominal variable that will be expressed as one of the followings
    - None
    - Memory loss
    - Focal neurological deficits
    - Cognitive impairment
    - Behavioral problems
    - Secondary epilepsy (on patients who didn’t suffer from it pre-status)

### 6.7.3 COVARIATES

- **Age:** continuous quantitative variable that will be measured in years.
- **Sex:** qualitative dichotomous variable that will be categorized as *Male* or *Female*.
- **Etiology:** since it seems to be the main determinant of outcome and mortality, we will classify it as follows and we will define it as a qualitative nominal variable:
  - Acute symptomatic: SE occurring within 7 days of an acute disease (stroke, encephalitis, metabolic disorders, intoxication, drugs, etc) or 4 weeks of a head trauma.
  - Progressive symptomatic: SE related to progressive diseases (brain tumor, dementias, neurodegenerative diseases, etc)
  - Remote symptomatic: SE in an individual with prior (>7 days) neurological disease (stroke, encephalitis, metabolic disorders, etc), prior (>4weeks) head trauma or other prior systemic disease in absence of acute insult.

- Acute on remote symptomatic: SE occurring in an individual with a previous brain disease due to an acute insult or trigger.
  - Previous epilepsy with acute triggering: SE occurring in a previously epileptic individual with documented low AED levels, AED withdrawal, history of AED noncompliance or change in therapy.
  - Cryptogenic/unknown/idiopathic: SE occurring in patients with no history of seizures and absence of any other neurological diseases.
- **Type of status epilepticus:** to clinically classifies SE. We will define it as a qualitative nominal variable with three different categories: *Convulsive SE/Subtle SE/Focal SE with consciousness impairment*.
  - **Number of ECT sessions performed:** discrete quantitative variable.
  - **Number of times the intensity of ECT had to be increased:** discrete quantitative variable.
  - **Time in status:** duration of SE when starting ECT. We Will define it as a discrete quantitative variable that will be measured in days.
  - **Drugs:** it is significant to consider as multiple different AED can be used in the management of status epilepticus. We will define it as a qualitative nominal variable and their categories will correspond to the AEDs used in each case (phenytoin, levetiracetam, lacosamide, valproic acid, perampanel, etc).
  - **Treatment delay:** early treatment initiation is important to control SE and therefore for a better outcome. We will consider it as a qualitative dichotomic variable: treatment delay of  $\geq 60$  minutes/treatment delay of  $< 60$  minutes.
  - **Structural CNS lesion:** it will be a qualitative dichotomic variable: having or not having a structural CNS lesion.
  - **Epidemiology based Mortality score in SE (EMSE):** clinical score which predicts in-hospital mortality of patients with status epilepticus based on age, etiology, comorbidities and EEG pattern. We will define it as a qualitative dichotomic variable, with a score  $\geq 64$  for bad outcome and  $< 64$  for good outcome. This score can be found in Annexe 5.
  - **Hospital:** qualitative nominal variable.

Table 8 – Summary of study variables, measurement method and categories

	VARIABLES	DESCRIPTION	MEASUREMENT	CATEGORIES
INDEPENDENT	Sedation protocol during ECT	Qualitative dichotomic	—	Protocol 1 Protocol 2
	DEPENDENT	Cessation of status epilepticus	Qualitative dichotomic	mSCNS electroencephalographic criteria
Electroencephalographic changes		EEG evaluation		Positive changes No positive changes
Time between ECT and achieving status control		Discrete quantitative	Days	—
Adverse effects		Qualitative nominal	Clinical criteria	None, cardiorespiratory depression, liver dysfunction, renal dysfunction, pancreatic dysfunction, hypotension, sedation tolerance, sedation dependance, headache, myalgia, nausea, bradycardia, arrythmia, aspiration, brain edema, poor control of clinical seizures, death, etc.
Neurological sequelae		Qualitative nominal	Clinical criteria	None, cognitive impairment, memory loss, behavioral problems, focal neurological deficits or secondary epilepsy
COVARIATES	Age	Continous quantitative	—	—
	Sex	Qualitative dichotomic		Male / Female
	Etiology	Qualitative nominal	Clinical criteria	Acute symptomatic, Progressive symptomatic, Remote symptomatic, Acute on remote symptomatic, previous epilepsy with acute triggering or cryptogenic

COVARIATES	<b>Type of status epilepticus</b>	Qualitative nominal	Clinical criteria	Convulsive SE Subtle SE Focal SE with consciousness impairment
	<b>Number of ECT sessions performed</b>	Discrete quantitative	Electronic medical history or interview	—
	<b>Number of times the intensity of ECT had to be increased</b>			—
	<b>Time in status</b>		Days	—
	<b>Treatment delay</b>	Qualitative dichotomic	Hours	Treatment delayed $\geq 60'$ Treatment delayed $< 60'$
	<b>Drugs taken</b>	Qualitative nominal	Electronic medical history or interview	Phenytoin, levetiracetam, lacosamide, valproic acid, perampanel, ...
	<b>Structural CNS lesion</b>	Qualitative dichotomic	MRI	Yes/No
	<b>Prognosis</b>		EMSE score	Bad outcome expected ( $\geq 64$ points in EMSE) Good outcome expected ( $< 64$ points in EMSE)
	<b>Hospital</b>	Qualitative nominal	Electronic medical history or interview	—

## 6.8 STUDY INTERVENTION

### 6.8.1 RANDOMIZATION

Once the family and/or caregivers have understood and agreed the study, its stages, the intervention, the follow-up and the possible complications derived from the treatment, the patient will be randomized in a ratio 1:1 into one of the following groups using a randomization computer program:

- Group 1: patients with super-refractory status epilepticus to whom **ECT will be applied with an intermittent interruption of sedation around ECT sessions.**
- Group 2: patients with super-refractory status epilepticus to whom **ECT will be applied with a continual progressive withdrawal of sedation before the first ECT session onward.**

It's important to emphasize that patient information, with details such as name, phone number, address and medical history, will undergo anonymization. In addition, each patient will be assigned a unique identification number for confidentiality purposes.

### 6.8.3 INTERVENTION

All patients participating in the study will undergo ECT under uniform conditions, with the only variation being the sedation protocol.

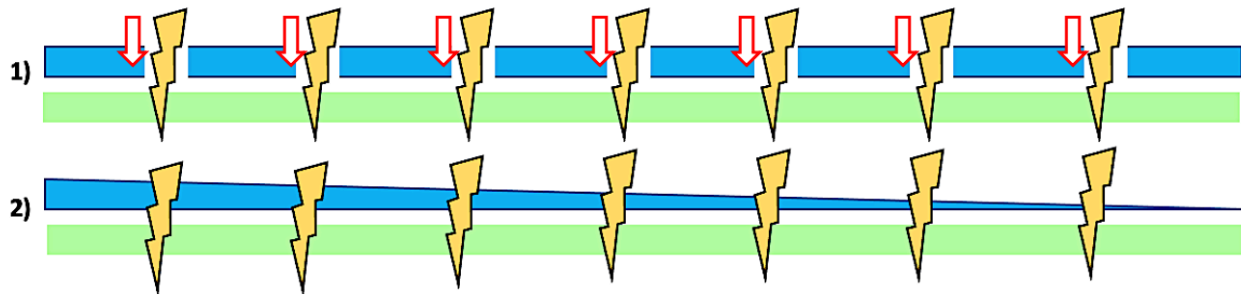
The objective of ECT is to achieve an appropriate seizure, which does not necessarily have to be clinical. Before each session, ischemia will be induced in the distal area of a lower limb, and a muscle relaxant (rocuronium) will be administered to the patient. This approach minimizes the tonic-clonic activity to only one foot, avoiding potential complications and harm to the patient. To the extent possible, the patient will be stimulated during the moments preceding the sessions with the aim of increasing the patient's alertness level. This will be achieved through the use of caffeine, auditory stimuli and/or physical manipulation through postural changes.

In addition to being monitored during the ECT session to determine the optimal generation of the seizure, patients will also be monitored with EEG in between ECT sessions, and the obtained records will be independently assessed by two professionals proficient with the electroencephalographic technique. If there is a discrepancy in the assessment of an EEG record between these two experts, it will be forwarded to the main research team in Girona for reassessment by their specialized neurologists.

Thymatron System IV ECT apparatus will be used for administering ECT, as it is the one most hospitals possess nowadays. The standard initial dose will be around 500mC. Subsequent sessions will see an increase in dosage based on the observed clinical-electric response, reaching a maximum of approximately 1000mC. The number of ECT sessions will be individualized according to each case depending on the results obtained and the clinical situation of each patient. The sedative dose for each patient will be individualized based on weight, height, sex and comorbidities. What will differ in each study group is the sedation protocol.

In **Group 1**, Protocol 1 of sedation will be applied. Protocol 1 consists on the withdrawal of the maximum sedation possible a few hours before the ECT session with the aim of minimizing the amount of sedative in the patient's system during the procedure. Reintroduction of the withdrawn sedation will occur once the session is completed, according to the patient's clinical condition, and so with each ECT session.

In **Group 2**, Protocol 2 of sedation will be applied. Protocol 2 involves a slow, progressive, and individualized withdrawal of the sedation the patient is receiving. Sedation will be maintained during the ECT session, and its administration will never be abruptly interrupted. This way, with each ECT session, the patient will have a lower sedative dose in the system without requiring the abrupt cessation of sedation at any point.



*Figure 4 – Outline of anesthesia medication withdrawal patterns compared in this study. 1) corresponds to protocol 1 and 2) corresponds to protocol 2. The blue bar depicts sedative drugs, the green bar depicts antiepileptic drugs and the lightnings depict ECT sessions. The vertical arrows depict the interruption of sedative drugs.*

## 6.9 DATA COLLECTION

We will obtain all the variables information and perform the different scales or scores with the available information for each patient, obtained through clinical history, scheduled clinical visits and complementary tests, that will be prospectively included in the databases of each hospital as the study progresses. To gather background information, significant medical history, and the patient's current medication, we will conduct an interview with the family members and/or cohabitants and consult the patient's previous medical records.

The electroencephalographic records will be reviewed by specialized and trained personnel, and both the reports and significant records will be digitally added to the patient's medical history.

All relevant clinical data collected from each patient will be documented in a Case Report Form (CRF), which can be found in Annexe 8. As the CRF are being filled, the information will be systematically transferred to a database

### 6.9.1 ENROLLMENT

In the Study Population section (7.3), the population of this study has already been stated. The enrollment process will begin with consecutive patients who attend emergency services of the centers

participating in the study with a prolonged seizure (motor generalized seizure, non-convulsive generalized seizure or prolonged focal seizure with impaired consciousness) that prove to be resistant to benzodiazepines, one or more appropriately prescribed antiepileptic drugs at their correct dosage and sedation after 24 hours. During the initial management of the seizure, it will be important to stabilize and monitor the patient (as explained in Figure 3) and obtain a detailed clinical history and physical examination. A blood analysis should be performed to determine glucose, electrolyte, urea, nitrogen levels, renal and hepatic profiles, complete blood count and other parameters considered. Additionally, a cranial CT scan should be conducted and EEG monitoring initiated.

Once super-refractoriness is established and the patient is stabilized in the ICU, it will be important to perform an MRI and a lumbar puncture to further investigate potential causes of the status. It will also be important to rule out the presence of possible autoimmune diseases such as immune-mediated encephalitis. Additionally, planning potentially useful therapeutic strategies for the patient (detailed in the introduction of this document) will be necessary. The need and timing of the initiation of ECT will depend on the medical judgment of neurologists and intensivists. When the decision to administer ECT to the patient is made, the clinical trial should be explained to the family or caregivers, providing them with the information sheet (Annexe 9). The informed consent form (Annexe 10) should be given and signed by the patient's caregivers to enroll him/her in the study.

### 6.9.2 FOLLOW-UP

One purpose of this study is to compare the neurological sequelae arising from the application of ECT when performing a gradual sedation reduction protocol versus when using intermittent discontinuation. To achieve this objective, a follow-up will be performed. Patients will attend the center where they underwent ECT, where a blinded neurologist will conduct a clinical visit to assess their condition and identify possible neurological sequelae such as cognitive deficits, memory impairments, behavioral changes, focal neurological deficits or a secondary epilepsy. These visits will also serve as educational measures to review and understand the antiepileptic treatment, if needed. During each visit, an EEG will also be conducted. 3 follow-up visits will be arranged:

- **First visit (first month after ECT):** during this visit, the patient's cognitive state, behavior, and potential neurological deficits will be assessed. Additionally, an EEG will be conducted to compare with future recordings and to adjust medication if deemed necessary.
- **Second and third visits (6 months and 12 months after ECT):** during these follow-up visits, the patient's cognitive state, behavior, and potential neurological deficits will be reassessed, and findings will be compared with previous visits. Additionally, an EEG will be conducted, and its results will be compared with prior records, enabling potential modifications or discontinuation of medication if deemed appropriate

It is important to clarify that, despite the study outlining these follow-up visits, the patient will concurrently be assessed by the neurology service of their reference center as per clinical practice guidelines. Any significant abnormal findings will also be communicated and included in the study

### 6.10 FLOW CHART

The flow chart of our study is shown in Figure 5.

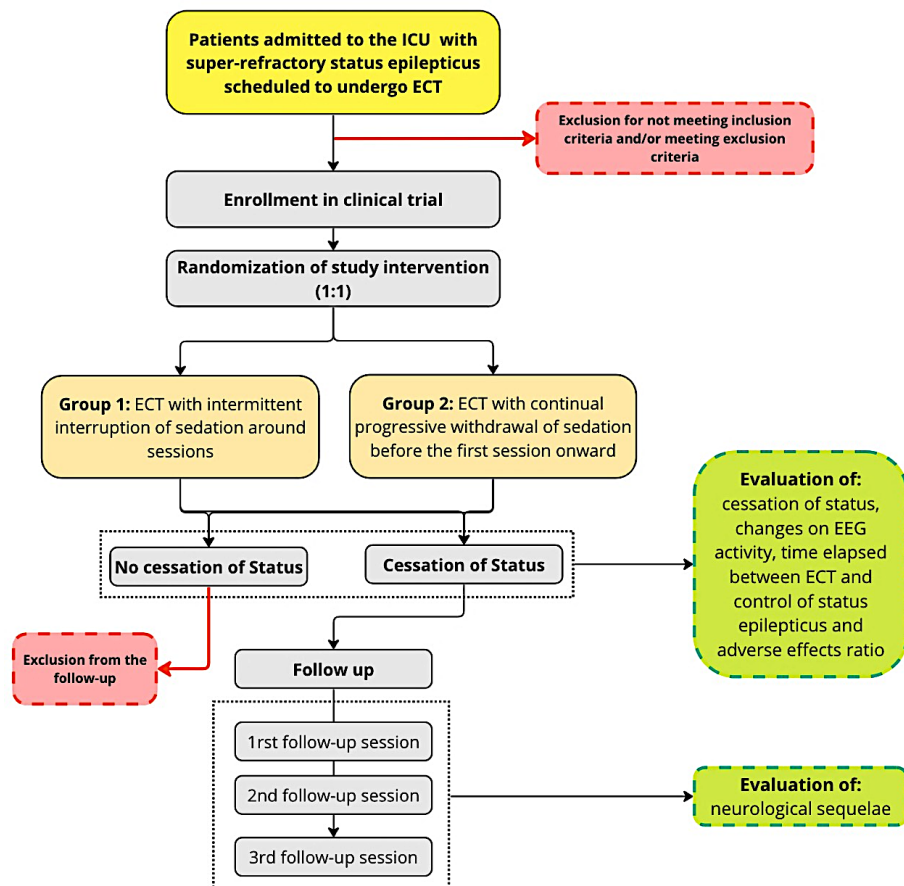


Figure 5 – Flow Chart



## 7. STATISTICAL ANALYSIS

The statistical analysis will be carried out by the statistician through the Statistical Package for Social Sciences (SAPSS) software version 29.0.2. We will establish a  $p < 0,05$  value as statistically significant, defining a 95% confidence interval for all analyses. Analysis will be made by protocol (PP).

### 7.1 DESCRIPTIVE ANALYSES

Qualitative dependent variables (cessation of status, changes in EEG activity, adverse effects and neurological sequelae) will be summarized using proportions.

The time elapsed between ECT and status control (elapsed time hereinafter) will be summarized using medians and interquartile range, because its distribution is asymmetrical.

These analyses will be stratified by the sedation protocol.

In addition, we will stratify by the covariables. Age will be categorized in quartiles.

For the elapsed time we will estimate and draw the Kaplan-Meier curves.

### 7.2 BIVARIATE ANALYSES

The difference of proportions of the qualitative dependent variables between the sedation protocol groups will be tested using chi squared or the Fisher's exact test (if the expected number of cases in a cell will be lower than 5). The difference of medians of the elapsed time between the sedation protocol groups will be tested by the Mann-Whitney's U. The difference of the Kaplan-Meier curves will be tested using the log-rank test.

These analyses will be stratified by the covariables.

### 7.3 MULTIVARIATE ANALYSES

Each one of the adverse effects (cardiorespiratory depression, hypotension, bradycardia, liver disfunction, renal disfunction, sedation tolerance, sedation dependance, poor control of seizures and death) and of the sequelae will be considered dichotomous qualitative variables (for instance death *Yes/No*, etc).

To assess the effect of the sedation protocol on the qualitative dependent variables (cessation of status, changes in EEG activity, each one of the adverse effects and of the neurological sequelae) we will estimate logistic regressions, controlling for the covariables.

In the case of elapsed time, we will estimate a Cox regression controlling for the covariables.

## 8. ETHICAL AND LEGAL CONSIDERATIONS

This study will be submitted to the “Comitè d’ètica d’investigació clínica” (CEIC) of the main investigation center, Hospital Santa Caterina, and it will be optional for each one of the participating centers to present it to their respective CEIC’s. However, the approval of Hospital Santa Caterina’s CEIC will be mandatory to perform this clinical trial. If the CEIC presents some objections or recommendations, the study will be, as far as possible, modified in order to accomplish them.

As the study participants may not be able to do so, their family members or legal guardians should read, understand, and sign the informed consent evaluated by the CEIC (Annexe 9).

This study will be performed according to the human rights and ethical principles established by the World Medical Association in the Helsinki Declaration of Ethical Principles for Medical Research Involving Human Subjects (last reviewed in 2013). The study will also be conducted in accordance with the Principles of Biomedical Ethics from Beauchamp and Childress (last reviewed in 2009), autonomy, non-maleficence, beneficence and justice.

Our project will be developed in accordance to the current Spanish legislation, which is:

- “Real Decreto 1090/2015, de 4 de diciembre, por el que se regulan los ensayos clínicos con medicamentos, los comités de ética de la investigación con medicamentos y el registro español de estudios clínicos”.
- “Ley 14/2007, de 3 de julio, de Investigación biomédica”.
- “Ley 29/2006, de 26 de julio, de garantías y uso racional de los medicamentos y productos sanitarios”
- “Real Decreto Legislativo 1/2015, de 24 de julio, por el que se aprueba el texto refundido de la Ley de Garantías y uso racional de los medicamentos y productos sanitarios”.

Regarding our patient’s privacy and confidentiality, the following legal considerations will be met since all the subject’s data will be anonymized with every patient being given a code number for their identification. These codes will be stored in a database that only researchers and CEIC will have access to as deemed necessary for the investigation:

- “Ley 41/2002, de 14 de noviembre, básica reguladora de la autonomía del paciente y de derechos y obligaciones en materia de información y documentación clínica”.
- “Reglamento (UE) 2016/679 del Parlamento Europeo y del Consejo Europeo, de 27 de abril de 2016, relativo a la protección de personas físicas en lo que respecta al tratamiento de datos personales y a la libre circulación de estos datos.
- “Ley Orgánica 3/2018, de 5 de diciembre, de protección de datos personales y garantía de los derechos digitales”.

Our project will be registered at the “Registro Español de Estudios Clínicos” before its beginning, and its results will be published transparently. All investigators declare not having conflict of interest in any aspect of this research.

## 9. STRENGTHS AND LIMITATIONS

### 9.1 STRENGTHS

**Impact:** our study aims not only to investigate a potential treatment for a condition with high mortality and morbidity but would also be the first clinical trial conducted on therapeutic interventions in super-refractory status epilepticus. Therefore, our research has the potential to have a significant impact on clinical practice, as, if the results are as expected, electroconvulsive therapy could be systematically integrated into therapeutic algorithms.

**Innovation:** our study would be an innovative project, as the available literature on therapeutic strategies for SRSE so far has consisted solely of case series and reviews of case series. To advance in the management of SRSE, it is crucial to initiate studies with designs that allow drawing conclusions with higher evidence, and that is precisely the aim of our work.

**Multicentricity:** the fact that our study is multicenter allows us to encompass populations from different regions and hospitals in Catalonia and potentially other regions of Spain, which enriches the sample.

**Costs:** despite our study being a clinical trial, it would not incur significant costs as both sedation and electroconvulsive therapy, along with subsequent follow-up, are procedures routinely performed in almost all patients in our study. Considering the innovation and potential impact, the relatively low cost is a notable strength.

### 9.2 LIMITATIONS

**Confounding factors:** our main concern when performing this study is the complexity and individualized nature of managing SRSE. The low incidence of SRSE, the broad spectrum of drugs that can be used, and the multiple etiologies of status epilepticus, among other factors, complicate the formation of homogeneous groups, making it difficult to assert with sufficient evidence that the observed effects in the intervention are 100% attributable to electroconvulsive therapy applied with a specific sedation protocol. However, the sample size and randomization of participants between the intervention groups and the multivariate analysis of the data, while not entirely eliminating, will help mitigate the potential for confounding

**Non-probabilistic sampling method:** the fact that the sampling is consecutive non-probabilistic implies the possibility of selection biases. However, given that our sample is of a substantial size (408) and since the patients will be randomly assigned to both intervention groups, the results could still be considered representative.

**Blinding methods:** the requirement for individualized patient follow-up in both interventions means that the healthcare team cannot be blinded. This may introduce biases such as observer bias. For this reason, it has been decided that both the experts supervising the electroencephalograms and those conducting patient follow-up will be unaware of the sedation protocol each patient received during ECT.

**Multicentricity:** the fact that it is a multicenter study, despite all centers having similar resources and equipment, introduces the potential for inter-observer biases (especially concerning the interpretation of EEG and cognitive and memory deficits) and information biases due to variability in data collection. Systematizing the data collection in this study protocol (identifying which tests should be conducted and when, as it is specified in the Data Collection section (7.9) ) and having two experts independently review the EEG records will help mitigate biases arising from multicentricity

**Loss of patients:** the fact that the study is long-term and requires patients to attend follow-up visits makes it expected that there will be a loss to follow-up within the sample. It is important to consider that patients who recover from status epilepticus already attend follow-up visits, and given the severity of SRSE, most patients are likely to attend their follow-up visits. This is why the patient loss rate is estimated to be low.

## 10. WORK PLAN

### 10.1 RESEARCH TEAM

The clinical trial research team will consist on the following:

- **Director, coordinator and main investigator:** individual whose roles on the research include directing the execution of the project, ensuring proper protocol application, supervising the functioning of all centers, and designing the protocol alongside Bernat Buil. Additionally, they will be responsible for participating in result discussions, drawing conclusions and contributing to dissemination efforts. This role will be carried out by Dr. Cristina Coll, a neurologist from the epilepsy unit in Girona
- **Co-investigators:** includes all the neurologists actively participating in the research at each hospital center.
- **Co-investigator head:** at each participating center, a co-investigator head will be selected from among the co-investigators to ensure compliance with the study protocol, direct the study at their center and maintain communication with the linking support investigators in Girona
- **Linking support investigators:** researchers from the Girona team will be assigned the role of liaising with other centers. Various linking support investigators will be designated (the number of investigators filling this role will depend on the number of hospitals eventually participating in the study), each responsible for specific participating hospitals. Their role will involve maintaining contact with the co-investigator head at each center
- **Health personnel:** includes all personnel necessary to conduct the study without actively participating in it such as anesthesiologists, intensivists, neurologists non participating as investigators, nurses, etc.
- **Other personnel:** statistical analyst and English correctors.

### 10.2 STUDY STAGES

The study will be carried out in 6 stages, which are described below. The total duration of the study will be 3 years (October 2024 – October 2027)

### Stage 0 – Study design

During this stage of the study, the **protocol will be developed**, specifying hypotheses, objectives, design, and methodology through a comprehensive review of the existing literature and publications. In addition, **potential participating hospitals will be contacted**, and the project will be **presented to the Epilepsy Study Group of the SEN and the SEEP** to recruit additional participating centers.

Lead by: Dra. Cristina Coll and Bernat Buil.

Duration: October 2024

### Stage 1 – Ethical evaluation

During this phase of the study, the protocol will be **submitted to the CEIC** of the main research center (Hospital Santa Caterina) and, subsequently, of each participating center for its approval. During this stage the **protocol will also be modified to the extent possible based on the conclusions reached by the CEIC**.

Lead by: Dra. Cristina Coll and members of the CEIC.

Duration: November 2024 – January 2025

### Stage 2 – Initial coordination and training sessions

During this phase of the study, an **initial in-person meeting** will be held between the coordinator and the co-investigator heads from each center. In this meeting, the protocol and all study phases will be reviewed. The roles of each participant in the research will be examined and communication channels will be established. Following this meeting, each co-investigator head will be required to meet with their respective teams to convey the same information. Furthermore, **online training meetings will be conducted to train and standardize the criteria for neurologists** responsible for evaluating EEG records and conducting follow-up. A consensus document will be drafted at the conclusion of these meetings, which all professionals can refer to in case of uncertainty during data collection

Lead by: the whole team

Duration: February 2025 – March 2025

### Stage 3 – Enrollment, Intervention and Data Collection

In this phase of the study, **eligible patients** meeting the inclusion criteria and none of the exclusion criteria (with signed informed consent) **will be recruited**. They will be **randomized** into intervention groups, **undergo ECT with a specified sedation protocol** and undergo a **one-year follow-up**. Throughout

the entire process, **necessary data** for analyzing each variable, as stipulated in the protocol, **will be collected.**

Lead by: the whole team

Duration: March 2025 – March 2027 (we estimate that it will take a year, from March 2025 to March 2026, to collect the sample. We will need to extend this phase until the last recruited patient completes the one-year follow-up, from March 2026 to March 2027).

#### Stage 4 – Statistical Analysis and Data Interpretation

In this phase of the study, a blinded statistician, unaware of which group received each intervention, will conduct the **analysis of the data obtained during the previous phase.** Additionally, **another in-person meeting will be held** between the coordinator and the co-investigator heads of each center. In this meeting, the **results will be presented and interpreted to draft the discussion and conclusions of the study.**

Lead by: statistical analyst and the whole team.

Duration: April 2027 – June 2027

#### Stage 5 – Results publication

In this final phase, the research coordinator will **draft the final dissemination article**, presenting the entire protocol, results, discussion and conclusions of the study. This article will be **submitted to leading epilepsy journals for publication.** **The results**, whether favorable or not, will be **disseminated and discussed** at the national congress of the Spanish Society of Neurology (SEN), the Spanish Society of Epilepsy (SEEP) and/or other relevant international conferences

Lead By: Dra. Cristina Coll

Duration: July 2027 – October 2028



10.3 CHRONOGRAM

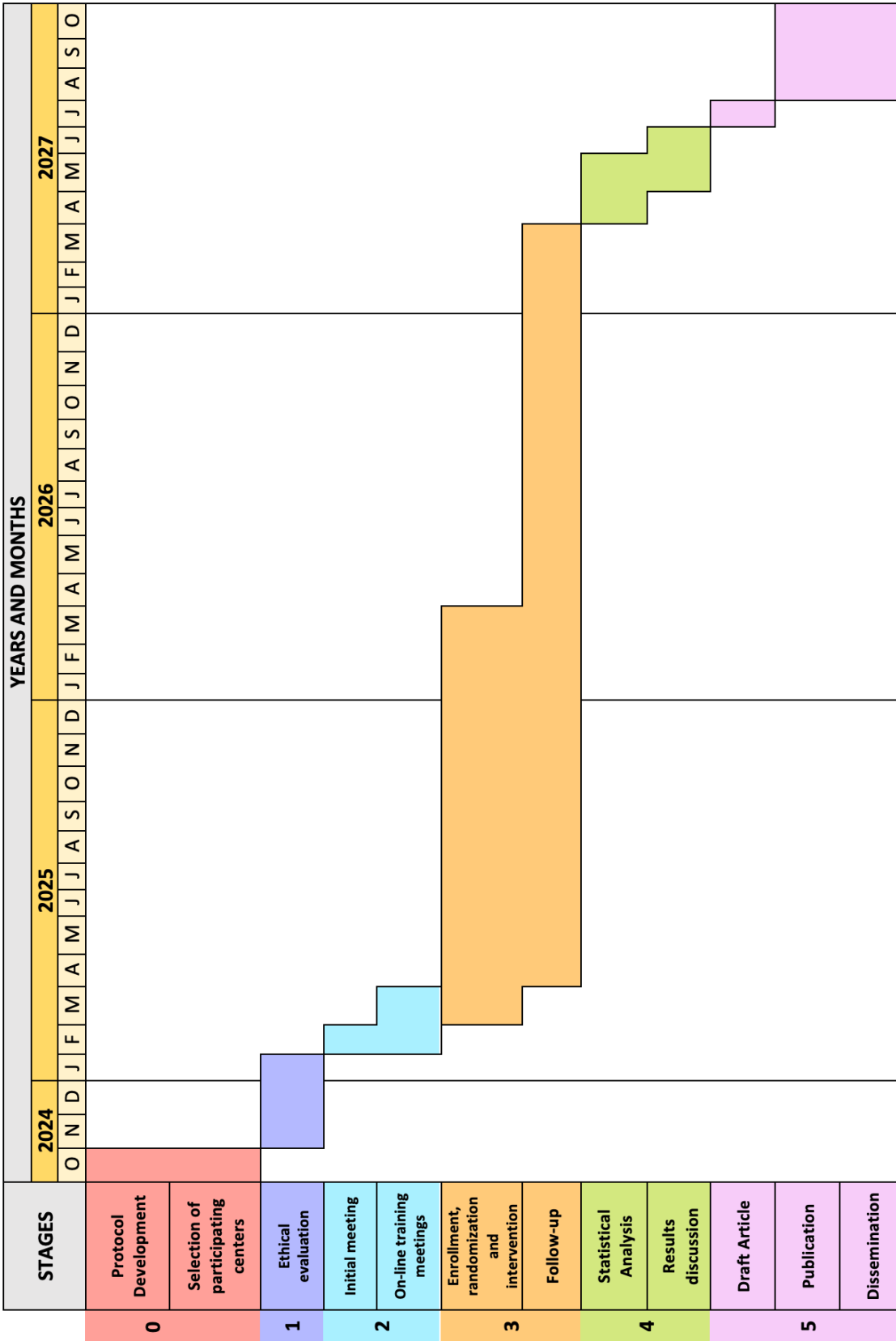


Figure 5 – Chronogram of the study. Months are chronologically ordered: J – January, F – February, M – March, A – April, M – May, J – June, J – July, A – August, S – September, N – November and D – December.

## 11. BUDGET

### 11.1 PERSONNEL COSTS

The research team members of this clinical trial are employees of the hospital centers where its going to be performed, which means that their activities will be considered as part of their daily clinical practice. Therefore, their activities will not incur additional costs.

### 11.2 SERVICES EXPENSES

- **Statistical Analyst:** it is needed to perform the patient's randomization into intervention groups and to conduct the statistical analysis of the obtained results. We estimate that they will work a total of 60 hours during the one-year patient recruitment period, followed by an additional 50 hours for the final statistical analysis. We have calculated that a total of 110 hours of their work will be required, which will be compensated at a rate of 40€/h. Therefore, the total cost for their services is estimated at €4,400.
- **English editor:** in order to ensure the quality of the article before publication, the services of a high-level editor will be required. We estimate their fees to be €120.

### 11.3 INSURANCE EXPENSES AND TAXES COSTS

This study will be submitted with a low-intervention clinical trial qualification, as the intervention performed is considered valid and safe for clinical practice. Furthermore, the diagnostic and follow-up methods pose no risk to the patient. With the approval of the Ethics Committee for Clinical Investigation (CEIC), all study participants will be covered by the hospital's insurance. Nevertheless, it is important to take into account that clinical insurances usually cost 100€ per participant.

Since the study would be registered as “non-commercial clinical research”, we assume that there would be no tax-related costs

### 11.4 MATERIAL EXPENSES

The intervention and patient follow-up will not require obtaining materials that are not already available in the hospitals. Additionally, since the management and treatment of these patients will not differ from what is provided in normal clinical practice, there will be no additional costs related to the materials and equipment used in the study. The estimated costs for office supplies (such as printing the consent and information sheets) are approximately €150.

### 11.5 TRAVEL EXPENSES

During the study, two in-person meetings will be convened, involving the coordinator and co-investigator heads. These meetings will take place in Girona and will necessitate covering transportation and accommodation expenses for attendees residing outside Girona. We estimate these costs to be approximately €500 per person. We anticipate that the total incurred of these expenses will amount to approximately €10,000.

Additionally, the transportation and accommodation costs for the members of the Epilepsy Unit from Girona for the conference where the study results will be disseminated will need to be covered. These costs are estimated to be around €500 in total.

### 11.6 PUBLICATION AND DIVULGATION COSTS

We will publish the results of the clinical trial in an international Open Access medical journal. We estimate that the editing, formatting, graphic design, review, and final publication will amount to approximately €3,500. Additionally, the study results will be presented at the European Epilepsy Congress (EEC), which will involve covering registration fees for the coordinator and another member of the Epilepsy Unit from Girona. These costs are estimated at approximately €450 per person, totaling around €900.

### 11.7 TOTAL ESTIMATED BUDGET

**Table 9 – Total estimated budget of our clinical trial**

		Quantity (nº)	Price per unit	Total price
Service expenses	Statistical analyst	110 hours	40€/h	4.400€
	Article edition	1 contraction	120€	120€
	Insurance expenses	1 contraction	40.800€	0€ (low intervention)
Material expenses	Office material	—	150€	150€
Travel expenses	Arising from the in-person meetings	20 individuals	500€	10.000€
	Arising from the EEC	2 individuals	250€	500€
Publication and divulgation costs	Publication expenses	1 publication	3.500€	3.500€
	EEC congress	2 inscriptions	450€	900€
				<b>19.570€</b>

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## 13. ANNEXES

### ANNEXE 1 List of etiologies that may cause Status Epilepticus (1)

- 1 Cerebrovascular diseases
  - a Ischemic stroke
  - b Intracerebral bleeding
  - c Subarachnoid bleeding
  - d Subdural hematoma
  - e Epidural hematoma
  - f Sinus venous thrombosis and cortical venous thrombosis
  - g Posterior reversible leukoencephalopathy syndrome
  - h Vascular dementia
- 2 CNS infections
  - a Acute bacterial meningitis
  - b Chronic bacterial meningitis
  - c Acute viral encephalitis (including Japanese B encephalitis, herpes simplex encephalitis, human herpesvirus 6)
  - d Progressive multifocal leukoencephalopathy (PML)
  - e Cerebral toxoplasmosis
  - f Tuberculosis
  - g Neurocysticercosis
  - h Cerebral malaria
  - i Atypical bacterial infections
  - j HIV-related diseases
  - k Prion diseases (Creutzfeldt-Jakob disease, CJD)
  - l Protozoal infections
  - m Fungal diseases
  - n Subacute sclerosing panencephalitis
  - o Progressive Rubella encephalitis
- 3 Neurodegenerative diseases
  - a Alzheimer's disease
  - b Corticobasal degeneration
  - c Frontotemporal dementia
- 4 Intracranial tumors
  - a Glial tumors
  - b Meningioma
  - c Metastases
  - d Lymphoma
  - e Meningeosis neoplastica
  - f Ependymoma
  - g Primitive neuroectodermal tumor (PNET)
- 5 Cortical dysplasias
  - a Focal cortical dysplasia (FCD) II, tuberous sclerosis complex (TSC), hemimegalencephaly, hemimegalencephaly
  - b Ganglioglioma, gangliocytoma, dysembryoplastic neuroepithelial tumor (DNET)
  - c Periventricular nodular heterotopia (PNH) and other nodular heterotopias
  - d Subcortical band heterotopia spectrum
  - e Lissencephaly
  - f Familial and sporadic polymicrogyria
  - g Familial and sporadic schizencephaly
  - h Infratentorial malformations (e.g., dentate dysplasia, mamillary dysplasia, etc.)
- 6 Head trauma
  - a Closed head injury
  - b Open head injury
  - c Penetrating head injury
- 7 Alcohol related
  - a Intoxication
  - b Alcohol withdrawal
  - c Late alcohol encephalopathy with seizures
  - d Wernicke encephalopathy
- 8 Intoxication
  - a Drugs
  - b Neurotoxins
  - c Heavy metals
- 9 Withdrawal of or low levels of antiepileptic drugs
- 10 Cerebral hypoxia or anoxia
- 11 Metabolic disturbances (e.g., electrolyte imbalances, glucose imbalance, organ failure, acidosis, renal failure, hepatic encephalopathy, radiation encephalopathy, etc.)
- 12 Autoimmune disorders causing SE
  - a Multiple sclerosis
  - b Paraneoplastic encephalitis
  - c Hashimoto's encephalopathy
  - d Anti-NMDA (*N*-methyl-D-aspartate) receptor encephalitis
  - e Anti-voltage-gated potassium channel receptor encephalitis (including anti-leucine-rich glioma inactivated 1 encephalitis)
  - f Anti-glutamic acid decarboxylase antibody associated encephalitis
  - g Anti- $\alpha$ -amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor encephalitis
  - h Seronegative autoimmune encephalitis
  - i Rasmussen encephalitis
  - j Cerebral lupus (systemic lupus erythematosus)
  - k CREST (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, telangiectasia) syndrome
  - l Adult-onset Still's disease
  - m Goodpasture syndrome
  - n Thrombotic thrombocytopenic purpura (Moscowitz syndrome, Henoch Schönlein purpura)
- 13 Mitochondrial diseases causing SE
  - a Alpers disease
  - b Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS)
  - c Leigh syndrome
  - d Myoclonic encephalopathy with ragged red fibers (MERRF)
  - e Neuropathy, ataxia, and retinitis pigmentosa (NARP)
- 14 Chromosomal aberrations and genetic anomalies
  - a Ring chromosome 20
  - b Angelman syndrome
  - c Wolf-Hirschhorn syndrome
  - d Fragile X syndrome
  - e X-linked mental retardation syndrome
  - f Ring chromosome 17
  - g Rett syndrome
  - h Down syndrome (trisomy 21)
- 15 Neurocutaneous syndromes
  - a Sturge-Weber syndrome
- 16 Metabolic disorders
  - a Porphyria
  - b Menkes disease
  - c Wilson disease
  - d Adrenoleukodystrophy
  - e Alexander disease
  - f Cobalamin C/D deficiency
  - g Ornithine transcarbamylase deficiency
  - h Hyperprolinemia
  - i Maple syrup urine disease
  - j 3-Methylcrotonyl Coenzyme A carboxylase deficiency
  - k Lysinuric protein intolerance
  - l Hydroxyglutaric aciduria
  - m Metachromatic leukodystrophy
  - n Neuronal ceroid lipofuscinosis (types I, II, III, including Kufs disease)
  - o Lafora disease
  - p Unverricht-Lundborg disease
  - q Sialidosis (type I and II)
  - r Morbus Gaucher
  - s Beta ureidopropionase deficiency
  - t 3-Hydroxyacyl Coenzyme A dehydrogenase deficiency
  - u Carnitine palmitoyltransferase deficiency
  - v Succinic semialdehyde dehydrogenase deficiency
- 17 Others
  - a Familial hemiplegic migraine
  - b Infantile onset spinocerebellar ataxia (SCA)
  - c Wrinkly skin syndrome
  - d Neurocutaneous melanomatosis
  - e Neuroserpin mutation
  - f Wolfram syndrome
  - g Autosomal recessive hyperekplexia
  - h Cockayne syndrome
  - i Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)
  - j Robinow syndrome
  - k Malignant hyperpyrexia

## ANNEXE 2 Advantages and disadvantages of drugs used in early and established status epilepticus (2).

Drug	Advantages	Disadvantages
<b>Diazepam</b>	Rapid onset of action following IV administration, non-IV formulation available (rectal), long-standing clinical experience in adults and children, efficacy and safety evaluated in randomized controlled trials, relatively inexpensive and widely available	Rapid redistribution responsible for short duration of action; sedation, hypotension, respiratory depression; risk of drug accumulation after repeated doses and infusion; risk of reaction at the injection site
<b>Lorazepam</b>	Rapid onset of action following IV administration, longer effect (>24 hours) after administration compared with diazepam, long-standing clinical experience in adults and children, efficacy and safety evaluated in randomized controlled trials, little risk of drug accumulation	Sedation, hypotension, respiratory depression; risk of reaction at the injection site
<b>Midazolam</b>	Non-IV formulations available (buccal, intranasal, IM), rapid onset of action after administration by any route, efficacy and safety of all formulations evaluated in randomized controlled trials, administration is easy and rapid, better social acceptance than drugs administered rectally, little risk of drug accumulation	Risk of seizure recurrence because of short duration of action; sedation, hypotension, respiratory depression
<b>Clonazepam</b>	Rapid onset of action following IV administration, longer effect after administration compared with diazepam, little risk of drug accumulation	Lack of randomized controlled trials
<b>Phenobarbital</b>	Rapid onset of action following IV administration, long-standing clinical experience in adults and children, efficacy and safety evaluated in randomized controlled trials, inexpensive and widespread availability	Sedation, hypotension, respiratory depression; risk of clinically significant drug interactions; risk of reaction at the injection site
Drug	Advantages	Disadvantages
<b>Phenytoin</b>	Long-standing clinical experience in adults and children, efficacy and safety evaluated in randomized controlled trials, lack of sedation, inexpensive (not fosphenytoin) and widespread availability	Rapid onset of action following IV administration, long-standing clinical experience in adults and children, efficacy and safety evaluated in randomized controlled trials, low incidence of adverse events overall, good cardiovascular and respiratory tolerability, relatively inexpensive and widespread availability
<b>Valproate</b>	Rapid onset of action following IV administration, long-standing clinical experience in adults and children, efficacy and safety evaluated in randomized controlled trials, low incidence of adverse events overall, good cardiovascular and respiratory tolerability, relatively inexpensive and widespread availability	Dizziness, thrombocytopenia, and mild hypotension (uncommon side effects); risk of acute encephalopathy usually associated with hepatic abnormalities or hyperammonemia; risk of pancreatitis and liver failure
<b>Levetiracetam</b>	Long-standing clinical experience in adults and children, lack of drug interactions, low incidence of adverse events overall, good cardiovascular and respiratory tolerability	Somnolence, sedation, agitation, and thrombocytopenia (uncommon side effects); relatively expensive
<b>Lacosamide</b>	Rapid onset of action following IV administration, low incidence of adverse events overall, good cardiovascular and respiratory tolerability	Little clinical experience and lack of randomized controlled trials, risk of cardiac arrhythmias

ANNEXE 3 Patient groups and specific situations where special consideration is needed when initiating treatment for status epilepticus (2).

Patient group/specific situation	Caution
Chronic obstructive pulmonary disease, bronchial asthma	Benzodiazepines may cause hypercapnia and respiratory depression, keep intubation equipment and staff available
Chronic heart failure, children	Rapid administration of antiseizure medication may result in fluid overload and congestive heart failure
Renal failure, hepatic failure	Accumulation of previously administered antiseizure medication could contribute to compromised clinical condition
Mitochondrial disorders in children and adults	Valproic acid contraindicated
Patients with low blood pressure on admission	Risk of further drop in blood pressure with midazolam, phenytoin, propofol, and narcotics
Suspicion of nonconvulsive status epilepticus in comatose patients	Wait for EEG if no clinical hints of nonconvulsive status epilepticus especially in coma (intoxication, eg, with benzodiazepines, may be misinterpreted as nonconvulsive status epilepticus)
No venous access readily available	Consider buccal, nasal, and IM routes of administration; in selected cases, also intraosseous access (special equipment required) should be considered

ANNEXE 4 Common adverse effects of antiepileptic medications (63)

Adverse effect	Class/type of antiepileptic drug most commonly implicated
<b>Neurocognitive</b>	
– Sedation, fatigue, sleepiness	All, but more commonly benzodiazepines, phenobarbital, topiramate, zonisamide, felbamate, rufinamide, pregabalin, tiagabine
– Ataxia, vertigo, diplopia	Carbamazepine, oxcarbazepine, phenytoin, lacosamide
– Tremor	Valproic acid, carbamazepine, oxcarbazepine, phenytoin
– Slow thinking, word-finding problems	Topiramate, zonisamide, phenobarbital, benzodiazepines
– Insomnia	Felbamate, vigabatrin, levetiracetam
– Hyperactivity, inattention	Benzodiazepines, phenobarbital, levetiracetam, valproic acid
– Irritability, behavioral problems	Benzodiazepines, phenobarbital, levetiracetam, vigabatrin
– Mood changes, depression	Levetiracetam, phenobarbital, benzodiazepines, vigabatrin, topiramate, zonisamide
<b>Gastrointestinal</b>	
– Nausea, vomiting	Felbamate, valproic acid, ethosuximide, oxcarbazepine, carbamazepine, lamotrigine, topiramate, zonisamide, rufinamide
– Anorexia	Topiramate, zonisamide, felbamate
– Increased appetite	Valproic acid, clobazam, pregabalin
<b>Headache</b>	Rufinamide, levetiracetam, lamotrigine, oxcarbazepine, lacosamide
<b>Electrolyte disturbances</b>	
– Hyponatremia	Oxcarbazepine, carbamazepine
– Metabolic acidosis	Topiramate, zonisamide
<b>Bone</b>	
– Reduced bone mineral density	Phenobarbital, primidone, phenytoin, carbamazepine, valproate, oxcarbazepine





## ANNEXE 7 Cases of patients with SRSE treated by the Girona Epilepsy Unit using the ECT protocol with progressive reduction of anesthesia

### CASE 1

A 45-year-old woman presented to the intensive care unit with refractory generalized convulsive status epilepticus unresponsive to benzodiazepine and treatment with five antiepileptic drugs (valproate, phenytoin, lacosamide, levetiracetam and perampanel). Past medical history included ocular Sjögren's syndrome and Raynaud's syndrome. She had a recent (<48h) viral illness with fever and myalgias, raising suspicion for Nonconvulsive Refractory Status Epilepticus (NORSE) variant subclinical Febrile Infection-Related Epilepsy Syndrome (FIRES).

Anesthetic induction in the ICU involved propofol, maximum dose isoflurane, maximum dose midazolam, and high-dose ketamine. Treatment included steroids, immunoglobulins, and a ketogenic diet, which was discontinued due to interference with ketogenesis by propofol and corticosteroids. Despite initially negative cerebrospinal fluid PCR, repeat lumbar puncture revealed elevated PMN, necessitating temporary antibiotic therapy despite normal CSF glucose levels. Cranial CT was normal, and blood work showed no abnormalities. Epilepsy protocol MRI demonstrated extensive bilateral supratentorial cortico-subcortical involvement, respecting the basal ganglia, consistent with autoimmune encephalitis in the clinical context. After a few weeks, despite the intracellular and transmembrane onconeural antibodies in serum and CSF being negative, elevated levels of IL-6 and IL-1 in serum ended up supporting the diagnostic suspicion of FIRES.

On the fourteenth day of GCSE, electroconvulsive therapy was initiated. Isoflurane and propofol were progressively reduced during the whole process under continuous vEEG monitoring, with bolus midazolam as rescue medication for any breakthrough seizures. Phenytoin was discontinued, valproate reduced due to steroid induction of metabolism, perampanel increased, and daily anakinra was initiated as etiological immunosuppressive treatment for NORSE, subtype FIRES. Concurrently, ketogenic diet was reintroduced with successful ketosis monitoring urinary ketone bodies and blood glucose every 4 hours. It is worth noting that during their stay in the ICU, they experienced sepsis with multiple complications, which complicated the immunotherapy

Eight ECT sessions were administered over a 2-week period. The first 5 sessions were consecutive days, utilizing a bitemporal montage with increasing intensity from 512mC to 1024mC. The next 3 sessions occurred every 2 days with an intensity of 1060mC. Clinical seizures were induced in all ECT sessions. Rocuronium was administered with distal ischemia in a lower extremity to focus the tonic-clonic activity in the foot and prevent adverse effects of a generalized tonic-clonic seizure.

The patient was continuously monitored with vEEG from the initiation of ECT. Initially, right temporal focal seizures with left temporal propagation were detected lasting one and a half minutes and accompanied by subtle perioral myoclonus and occasional right upper limb myoclonus. After the third ECT session, electroencephalographic improvement was observed, with cessation of seizures but persistent independent bitemporal ictal activity evolving into generalized periodic discharges (GPDs) with variable frequency and modifiers.

During and following ECT, the patient experienced generalized seizures upon attempted sedation withdrawal, prompting transfer to the “Hospital Vall d’Ebron” in Barcelona after 1 month of status. After one and a half months of admission to the said center, despite receiving therapy with tocilizumab, barbiturate coma and other antiepileptic medications, the patient ultimately passed away

In this case, despite mild post-ECT improvements, adjunctive electroconvulsion was insufficient to achieve status control.

## CASE 2

A 62-year-old woman with no known drug allergies and a history of epilepsy treated with levetiracetam 1000mg every 12 hours, phenytoin 100mg every 8 hours, and trunkimazin 0.5mg every night, presented to her local hospital's emergency department with cluster seizures of left oculocervical deviation lasting a few seconds each. During medical evaluation, a generalized tonic-clonic seizure episode was observed and controlled with 10mg of diazepam. Post-seizure observation revealed approximately 10 episodes of disconnection with left oculocervical deviation without regaining consciousness during interictal periods. Suspecting status epilepticus, she was referred to the provincial hospital's emergency service. On arrival, she exhibited a good level of consciousness, fowith normal neurological examination. While in the critical care unit, she experienced an episode similar to those described earlier. An EEG showed critical episodes

of focal onset coinciding with clinical seizures in the left frontal frontocentral region, rapidly propagating to ipsilateral temporal and contralateral frontotemporal regions, with transient improvement following administration of 3mg diazepam and 2000mg lacosamide, which defined the clinical presentation as focal non-convulsive status epilepticus of undetermined etiology. Lumbar puncture revealed no relevant findings, CT scan was normal, and blood analysis was unremarkable.

During her admission, she experienced at least 6 more episodes of disconnection with left oculocervical deviation (some of them witnessed by her daughter). In agreement with the ICU, and given the persistence of seizures with altered consciousness despite intravenous AED treatment, no clinical changes from the status recorded during EEG, and lack of recovery to baseline status, admission to the ICU, orotracheal intubation, and sedation were recommended. Sedation was planned for a minimum of 24-48 hours, followed by an EEG upon awakening to assess status resolution and adjust AED doses. Anticonvulsant treatment (levetiracetam, valproate, lacosamide and phenytoin) was maintained during sedation.

With the gradual withdrawal of sedation, paroxysms observed in the previous EEG reappeared. Clonazepam was added, and the doses of valproate and phenytoin were increased. The following day, sedation withdrawal continued, resulting in EEG alterations that resolved with a propofol bolus. Perampanel was added. Brain MRI showed a slight increase in signal in the head of the left caudate nucleus and parahippocampal gyrus, associated with a mild FLAIR hyperintensity in bilateral parasagittal occipital cortical sulci, findings likely related to postictal changes given the known context of status epilepticus. A new lumbar puncture for the study of onconeural antibodies and surface antibodies was negative. During the ICU stay, the patient developed sepsis secondary to nosocomial pneumonia, requiring antibiotic treatment with ceftazidime and linezolid. A ketogenic diet was also initiated.

After 15 days of admission, due to the persistence of paroxysm-suppression patterns with focal paroxysms in frontal regions of both hemispheres, sedation with ketamine and corticosteroid therapy (later replaced by gamma-globulins) was initiated. After 25 days of admission, given the refractoriness and persistence of ictal activity on EEG despite multiple AEDs and sedation adjustments, ECT was initiated. Five sessions were performed on consecutive days, using a unitemporal montage and

increasing intensity from 506mC to 1064mC. Rocuronium was administered with distal ischemia in a lower extremity to focus the tonic-clonic activity in the foot and prevent adverse effects of a generalized tonic-clonic seizure. Progressive reduction in the duration and quantity of paroxysms was observed during the sessions. Only residual bursts of beta activity lasting 1-3 seconds with left temporal predominance persisted. Activity suggestive of encephalopathy was noted during sessions, later attributed to hyperammonemia as a side effect of valproate, which was subsequently discontinued, leading to encephalopathy resolution. Antiepileptic medication and sedation (isoflurane, midazolam, propofol and ketamine) were gradually reduced during sessions, achieving control of clinical and electrical seizures with lacosamide alone.

After a month and a few days of admission, the patient was without sedation, opened her eyes minimally, and responded to pain. Consciousness gradually returned, and she became aware and oriented, with no neurological focalities beyond mild motor deficit in all four limbs without against gravity claudication. EEG showed signs of diffuse neuronal dysfunction predominantly in frontotemporal regions of both hemispheres but with left predominance, which were considered plausible within the clinical context of the patient. After a month and 10 days of admission, the patient was discharged with outpatient rehabilitation and a pending appointment for neuropsychological assessment. Neuropsychological assessment revealed mild cognitive impairment characterized by executive-attentional dysfunction, anomia, and retrograde amnesia that did not interfere with activities of daily living (non-demanding).

In this case, adjunctive ECT was successful and safe in achieving cessation of the epileptic status.



ANNEXE 8 Case Report Form (Spanish Version)

Investigador: \_\_\_\_\_

Centro: \_\_\_\_\_

**DATOS DE IDENTIFICACIÓN:**

ID del paciente:

Fecha de nacimiento:

Sexo:

- Masculino
- Femenino

**ANTECEDENTES Y ENF. CONCOMITANTES:**

**MEDICACION HABITUAL:**

**DATOS SOBRE EL ESTATUS:**

Fecha de inicio: \_\_/\_\_/\_\_

Hora de inicio: \_\_: \_\_

Tipo de estatus:

- Estatus convulsivo
- Estatus sutil
- Estatus focal con alteración del nivel de consciencia

**Semiología de la crisis:**

**Exploración neurológica durante el periodo ictal (e interictal, si procede):**

**Tiempo de demora entre el inicio de los síntomas y el inicio del tratamiento:**

- <60 min
- ≥60 min

**PRUEBAS COMPLEMENTARIAS:**

(marcar las PPCC realizadas, en qué fecha se realizaron y anotar los hallazgos relevantes en cada una de ellas):

- Análisis sanguíneo** (glucosa, ionograma, urea, perfil renal, perfil hepático, hemograma, etc)

- TC craneal**

**Resonancia magnética craneal**

**Punción lumbar** (parámetros bioquímicos, citología, autoanticuerpos, etc)

**Hallazgos primer registro EEG** (añadir el registro y el informe completo en la base de datos junto con este documento):

**Otras** (en caso de haber realizado más pruebas de las detalladas en el protocolo):

**ETIOLOGÍA:**

*Añadir el registro y el informe completo de todos los registros EEG que se hayan realizado durante el manejo del paciente en la base de datos junto con este documento*

**TRATAMIENTO**

Tratamientos recibidos pre-TEC (durante el episodio actual):

Anotar fecha(s) de administración

- Fenitoína
- Levetiracetam
- Lacosamida
- Ácido Valproico
- Perampanel
- Propofol
- Midazolam
- Ketamina
- Isoflurano
- Infusión de magnesio
- Piridoxina
- Esteroides
- Dieta cetogénica
- Hipotermia
- Drenaje de LCR
- Otros:

**TEC:** rellenar una hoja de TEC (la cual se encuentra al final de este documento) por cada sesión realizada.

**SEGUIMIENTO**

**VISITA 1:** (fecha: \_\_/\_\_/\_\_)

Exploración neurológica:

Alteración de la memoria

- No
- Si. **Detallar:**

Déficits cognitivos

- No
- Si. **Detallar:**

**Hallazgos registro EEG** (añadir el registro y el informe completo en la base de datos junto con este documento):

**VISITA 2:** (fecha: \_\_/\_\_/\_\_)

Exploración neurológica:

Alteración de la memoria

- No
- Si. **Detallar:**

Déficits cognitivos

- No
- Si. **Detallar:**

**Hallazgos registro EEG** (añadir el registro y el informe completo en la base de datos junto con este documento):

**VISITA 3:** (fecha: \_\_/\_\_/\_\_)

Exploración neurológica:

Alteración de la memoria

- No
- Si. **Detallar:**

Déficits cognitivos

- No
- Si. **Detallar:**

**Hallazgos registro EEG** (añadir el registro y el informe completo en la base de datos junto con este documento):

**HOJA DE REGISTRO DE TEC**

**EEG pre-TEC** (añadir el registro y el informe completo en la base de datos junto con este documento):

**¿Qué sedantes y antiepilépticos está recibiendo en este momento y a qué dosis?**

**Intensidad:**

**Montaje:**

**Número de estímulos:**

**Resultado de la TEC:**

- Convulsión generalizada
- No convulsión generalizada

**Efectos adversos:**

- No
- Si:

**Incidencias durante la sesión:**

**Incidencias entre la sesión anterior y la actual:**

**EEG post-TEC** (añadir el registro y el informe completo en la base de datos junto con este documento):

ANNEXE 9 Information sheet of the study (Spanish version)**HOJA DE INFORMACIÓN AL PACIENTE SOBRE EL ESTUDIO**

**Nombre del estudio:** PROGRESSIVE WITHDRAWAL VERSUS INTERMITTENT INTERRUPTION OF SEDATION DURING ELECTROCONVULSIVE THERAPY IN SUPER-REFRACTORY STATUS EPILEPTICUS

**Principal centro investigador:** Hospital Santa Caterina (Girona)

**Investigadora principal:** Dra. Cristina Coll

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Bienvenido/a,

Le invitamos a participar en nuestro estudio, el cual está dirigido por el equipo de neurólogos de la unidad de epilepsia del Hospital Santa Caterina (Girona) y ha sido evaluado y aprobado por el comité ético de este mismo centro.

Con este documento nuestra intención es informarle sobre los motivos que impulsan este estudio y qué beneficios puede ofrecer participar, para que usted escoja libremente si participar en él o no. Le invitamos a leer con calma este documento y a consultar cualquier duda que le pueda surgir con el equipo de neurólogos que le ha ofrecido la participación.

La participación en este estudio podrá ser revocada en cualquier momento sin sufrir ningún tipo de perjuicio en la asistencia sanitaria a recibir.

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**Descripción y objetivos del estudio:**

Nuestro estudio pretende estudiar estrategias terapéuticas para el estatus epiléptico super-refractario. Esta condición hace referencia a una crisis epiléptica que no remite a pesar de ser tratada con todas las líneas de tratamiento farmacológico disponible.

El estatus epiléptico super-refractario supone una situación clínica de difícil manejo y altas mortalidad y morbilidad. La actividad epiléptica sostenida durante largo periodo de tiempo supone un daño neuronal que puede tener consecuencias potencialmente irreversibles e incluso la muerte. Además de los riesgos inherentes al estatus epiléptico, es sabido que según más se prolonga la estancia hospitalaria (un hecho frecuente en los pacientes en estatus epiléptico super-refractario) mayor es el riesgo de desarrollar complicaciones como infecciones

nosocomiales, úlceras por presión, trombosis, problemas respiratorios o problemas gastrointestinales entre otros. Es por estos motivos que encontrar estrategias para finalizar el estatus epiléptico y para acortar la estancia hospitalaria son de suma importancia.

Existen múltiples herramientas terapéuticas con potencial para ser eficaces en el manejo del estatus epiléptico super-refractario, pero todas ellas requieren ser más estudiadas como para poder incluirlas de forma rutinaria en la práctica clínica. Una de estas herramientas, y el objeto de nuestro estudio, es la terapia electroconvulsiva (TEC de ahora en adelante)

La TEC consiste en aplicar estímulos eléctricos al cerebro de forma controlada y mediante electrodos para causar cambios en la actividad neuronal y, de este modo, influir en la actividad cerebral. Es una terapia ampliamente utilizada en el ámbito de la psiquiatría, especialmente para tratar depresiones resistentes al tratamiento farmacológico. Es una herramienta segura, que ya ha sido utilizada en múltiples ocasiones para tratar estatus epilépticos super-refractarios, pero que no ha sido incluida en estudios que permitan medir en qué grado y circunstancias resulta más eficaz, si es que realmente lo es.

Al referirnos a las circunstancias en la que la TEC es aplicada nos referimos al manejo de la sedación. Los pacientes en estatus epiléptico super-refractario se encuentran por definición bajo sedación. Retirar esta sedación para administrar la TEC, pero cómo hacerlo es todavía un misterio.

Nuestro principal objetivo es medir y comparar la eficacia de la TEC en el control del estatus epiléptico super-refractario usando dos protocolos de sedación diferentes: interrumpirla para administrar cada sesión de TEC y reanudarla posteriormente versus ir disminuyéndola de forma gradual a medida que se vayan realizando sesiones de TEC, sin llegar a interrumpirla de forma brusca en ningún momento.

En este estudio también tenemos otros objetivos secundarios que pretenden evaluar otros aspectos de la TEC y la sedación, como la aparición de efectos adversos, las secuelas neurológicas del estatus epiléptico a largo plazo usando un protocolo de sedación versus el otro al aplicar la TEC, el tiempo que tarda la TEC con cada protocolo de sedación en controlar el estatus epiléptico y la capacidad, sino para controlarlo, para mejorar la crisis epiléptica de un protocolo de sedación versus el otro al aplicar la TEC.



**Metodología e intervención:**

En el estudio participaran un total de 408 pacientes procedentes de diferentes hospitales del territorio español. Estos serán distribuidos de forma aleatoria en uno de los dos grupos de intervención. En el grupo 1 se aplicará la TEC con un patrón de interrupción intermitente de la sedación y en el grupo 2 se aplicará la TEC con un patrón de retirada progresiva de la sedación.

Con cada sesión de TEC se evaluará la respuesta tanto clínica como eléctrica a esta. Una vez finalizado el estatus, si es posible su control, se realizarán 3 visitas de seguimiento durante un periodo de 1 año para evaluar las posibles secuelas neurológicas a largo plazo.

**Beneficios y riesgos del estudio:**

Si el paciente al que representa ha sido seleccionado/ada para entrar en este estudio es porque se encuentra en un punto en el que las opciones terapéuticas son limitadas y, independientemente de su participación en este estudio, se ha decidido que la TEC podría ser útil. Es importante tener claro que recibir la TEC y participar en nuestro estudio pueden ser independientes.

Ambos protocolos de sedación utilizados en este estudio se han llevado a cabo de forma concomitante a la TEC en el pasado, y no se les han asociado efectos adversos, complicaciones o daños significativos. Su uso con la TEC ha sido descrito en revisiones de casos, pero nunca en estudios como el que pretendemos realizar, por lo que la evidencia respecto su eficacia, seguridad y efectos adversos es aun reducida.

El principal beneficio de participar en este estudio es que participar no añade ningún riesgo a los que supone la TEC en si misma. Además, su participación supondría aumentar el conocimiento científico respecto al manejo del estatus epiléptico super-refractario.

Los riesgos a los que se someterá el paciente (secundarios a la TEC y no al estudio en sí) son la cefalea, bradicardia, hipotensión, hipertensión, arritmias, posibles secuelas cognitivas (potencial y parcialmente reversibles), posibles pérdidas de memoria (potencial y parcialmente reversibles) y, aunque el riesgo sea bajo, la muerte.



**Alternativas al procedimiento:**

Dado que recibir o no la TEC es una decisión médica independiente a este estudio, no participar en este no implica no recibir la TEC. Negarse a recibir la TEC implica recibir otras terapias experimentales con menos evidencia que respalde su uso y es incompatible con la participación en este estudio.

**Confidencialidad:**

Los datos personales y sanitarios de los participantes del estudio serán gestionados y almacenados de forma confidencial en nuestra base de datos tal y como estipula la legislación vigente. Cada integrante recibirá un código numérico al que solo tendrán acceso los investigadores del estudio y comité de ética. La información obtenida de los pacientes estará a su disposición en todo momento.

**Participación y compensación económica:**

La participación a este ensayo clínico es voluntaria. Los participantes no recibirán ninguna compensación económica. Tampoco la recibirán los investigadores.

Si desea participar, deberá rellenar la hoja de consentimiento informado que le facilitaremos una vez nos aseguramos que ha comprendido la información proporcionada en este documento.

**Responsabilidad y aseguradora:**

Al tratar-se de un estudio de bajo nivel de intervención, cualquier perjuicio sobre la salud del paciente será cubierto por el seguro de responsabilidad civil de nuestro centro.

**Contacto:**

Ante cualquier duda antes, durante o después de la realización del siguiente estudio, podrá ponerse en contacto con: \_\_\_\_\_

ANNEXE 10 Informed consent form (Spanish version)

**DOCUMENTO DE CONSENTIMIENTO INFORMADO DEL PACIENTE**

Yo, \_\_\_\_\_, con documento de identificación personal (DNI/NIE) \_\_\_\_\_, declaro que:

- He leído y entendido toda la información que se me ha facilitado en la hoja de información del estudio.
- He podido exponer mis dudas y se me han resuelto de forma satisfactoria.
- Entiendo los riesgos y beneficios derivados de participar en este estudio y de las intervenciones que supone.
- No he ocultado ninguna información sobre los antecedentes, las enfermedades ni la medicación que toma el paciente.
- Comprendo que la participación es voluntaria y no remunerada
- Comprendo la gestión que se hará de los datos personales y médicos del paciente.
- Entiendo que puedo solicitar la revocación de este consentimiento informado en cualquier momento.

En consecuencia:

- Doy mi consentimiento para participar en este ensayo clínico y estoy conforme con que la información obtenida se use en futuras investigaciones.
- Acepto que los investigadores puedan contactarme en un futuro si es necesario.

<b>Signatura del paciente o representante:</b>	<b>Signatura del investigador:</b>

Lugar y fecha: \_\_\_\_\_, \_\_\_\_\_ de \_\_\_\_\_ del año \_\_\_\_\_

ANNEXE 11 Request form to withdraw study consent (Spanish version)

**REVOCACIÓN DEL CONSENTIMIENTO INFORMADO**

Yo, \_\_\_\_\_, con documento de identificación personal (DNI/NIE) \_\_\_\_\_, revoco el consentimiento informado firmado previamente para la participación en el estudio *PROGRESSIVE WITHDRAWAL VERSUS INTERMITTENT INTERRUPTION OF SEDATION DURING ELECTROCONVULSIVE THERAPY IN SUPER-REFRACTORY STATUS EPILEPTICUS*

<b>Signatura del paciente o representante:</b>	<b>Signatura del investigador:</b>

Lugar y fecha: \_\_\_\_\_, \_\_\_\_\_ de \_\_\_\_\_ del año \_\_\_\_\_