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Why have status epilepticus trials failed: Wrong drugs or wrong trials?

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ABSTRACT

Despite burgeoning interest in trials in status epilepticus over the last 20 years, outcomes have yet to improve and a number of high profile studies have failed to deliver for a range of reasons. The range of reasons a trial may fail to meet the intended outcomes are discussed. Recent well designed, adequately powered studies in established status epilepticus failed to meet primary endpoints, but are nonetheless influencing practice, reflecting the importance of interpreting results in the context of broader literature, safety and practical considerations. Studies in refractory and super-refractory status epilepticus have yet to do so, frequently failing to deliver as hoped despite huge financial and human cost. The importance of reviewing regulatory frameworks, and our approach to trial design to address important clinical questions is reviewed, reflecting on lessons from the COVID-19 RECOVERY trials, and other disease areas, together with the potential associated with the use artificial intelligence tools. This paper is based on a presentation made at the 9th London-Innsbruck Colloquium on Status Epilepticus and Acute Seizures in April 2024.

1. Introduction

Interest in improving the treatment of status epilepticus (SE) has been steadily increasing over the last 20 years, with more than 60 registered interventional clinical trials in the last 10 years [1], compared to 11 in the first decade of this century (Fig. 1). Over the same time period the definition of Status Epilepticus has been revised [2], aligning with evidence supporting the need for early intervention to improve outcomes and a better understanding of the underpinning neurobiology. However there is no evidence that outcomes for convulsive status epilepticus have yet improved [3], and a number of high profile much anticipated studies have failed to deliver for range of reasons. This article will consider the reasons a trial may fail to meet the intended outcomes, focussing on a selection of recent SE studies, concluding with some suggestions for the future drawing on the broader literature on trial design.

2. Definitions

Failure is defined as a lack of success or inability to meet an expectation. In the context of interventional clinical trials, studies are typically designed on an estimated outcome of difference – the primary outcome. Any study that failed to meet the primary outcome could thus be defined as a failed trial. However, trials that have technically failed (by this definition), can still influence practice as I will go on to discuss. Arguably there can sometimes be more to learn of value from a study that 'failed', than from some that on paper 'succeed', yet bring little new information to the table, or were poorly designed in the first place. Assessing the value of a 'failed' study requires looking beyond the primary outcome, but also considering the overall aim (typically to find the best treatment, to demonstrate equivalence, or to get a marketing approval), as well as the reasons to for failure (e.g. failure to recruit, halting due to safety concerns, or completion but failure to meet the primary outcome), alongside the broader evidence base about the condition or agents under study.

3. Outcomes from status epilepticus trials

A search using the term "status epilepticus" on the International Clinical Trials Registry Platform yielded 167 studies. Manual review of titles and where available protocols and published outcomes identified 86 which were interventional clinical trials in people with convulsive or non-convulsive status epilepticus, and form the basis of this paper. Phase I and II studies (n = 6), observational and quality improvement studies (n = 43), and those in which cessation of status epilepticus was not a primary outcome (n = 32) were excluded from further review. Where the outcome/current status of any study was not published on the platform, source data was reviewed where available, and additional searching on PubMed and Web of Knowledge undertaken by author name, study title, and study key words (typically status epilepticus and

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therapeutic agent) for additional information. The remaining 86 studies encompassed studies covering paediatric and adult practice, sometimes both, and both convulsive and non-convulsive status epilepticus due to any cause. The author classified studies by status epilepticus stage as defined in Table 1.

As illustrated in Fig. 2, the majority of studies in Initial SE (79 %) were successful in that they met their primary outcome. In contrast only 33 % of studies in super-refractory SE did so, with a clear pattern of diminishing probability of success where the study intervention was later in the treatment pathway (chi squared $p = 0.0075$). In many respects this is not surprising. Later in the patient journey individual centres will have smaller populations, meaning more recruiting centres, and fewer patients/centre which increases both the complexity and cost of any study. It is also well established that the outcome of SE, whilst significantly influenced by age and aetiology, is also worse with longer duration, particularly after the first 1–2 h. A consequence of this is that demonstrating a treatment administered later in the patient journey can improve outcomes, which quite rightly is what most funders, patients and clinicians want to see, is inherently more challenging.

It is not the purpose of this article to critique individual studies, but some other notable observations on review of the data as a whole are worth mentioning. Firstly, of the studies in initial status epilepticus, in all but 5 of the 24, the study agent was a benzodiazepine, often different formulations of the same drug, typically sponsored by the manufacturer. Whilst this is clearly of interest from a marketing perspective, and the advent of non-rectal administration is clearly an improvement, beyond that to what extent this will ultimately drive forward improvements in care is debateable. Secondly, amongst the established status epilepticus studies, comparisons between levetiracetam and older antiseizure medications were particularly common (16 studies in total), but often of dubious quality (for example underpowered, non-randomised), and often using very different definitions of treatment success, meaning pooling of data to try to overcome study limitations would be inherently flawed. All nonetheless incurred costs, took time and effort, and of course involved patients, though to what gain is uncertain. It is also worth stating that, studies that fail to show differences between interventions can also be of value in a descriptive sense, providing some information about the likelihood of success of an intervention, and with respect to other aspects of treatment such as dosing regimens, and timings of treatment.

Table 1
Definitions of status epilepticus type.

Status epilepticus type	Definition applied for classification
Initial	First line treatment by any route
Established	Ongoing or recurring despite 1st line treatment (one or two doses, typically benzodiazepines)
Refractory	Ongoing or recurring despite 1st and 2nd line treatments (typically 1st line benzodiazepines followed by an alternative intravenous antiseizure medication)
Super-refractory	Ongoing or recurring despite 1st and 2nd line treatments and a period of anaesthesia in intensive care

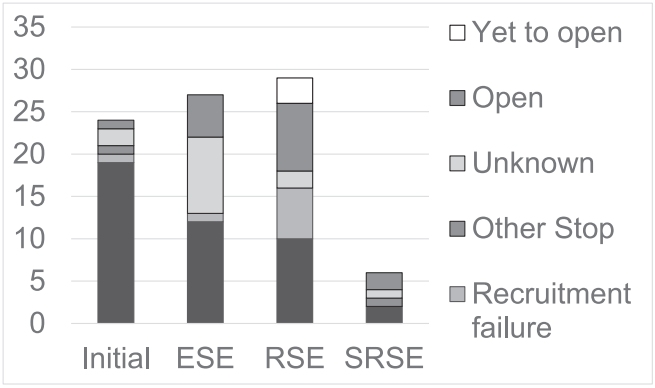

Fig. 2. Outcomes for interventional status epilepticus clinical trials, 1999–2023. Data from the International Clinical Trials Registry Platform (ICTRP) 'status epilepticus', 1999 to 2023, accessed on 20/01/2024. Phase I and II studies, observational and quality improvement studies and those in which cessation of status epilepticus was not a primary outcome were excluded.

4. Contributors to trial failure and impact on practice

There is an extensive literature on why trials fail, particularly in

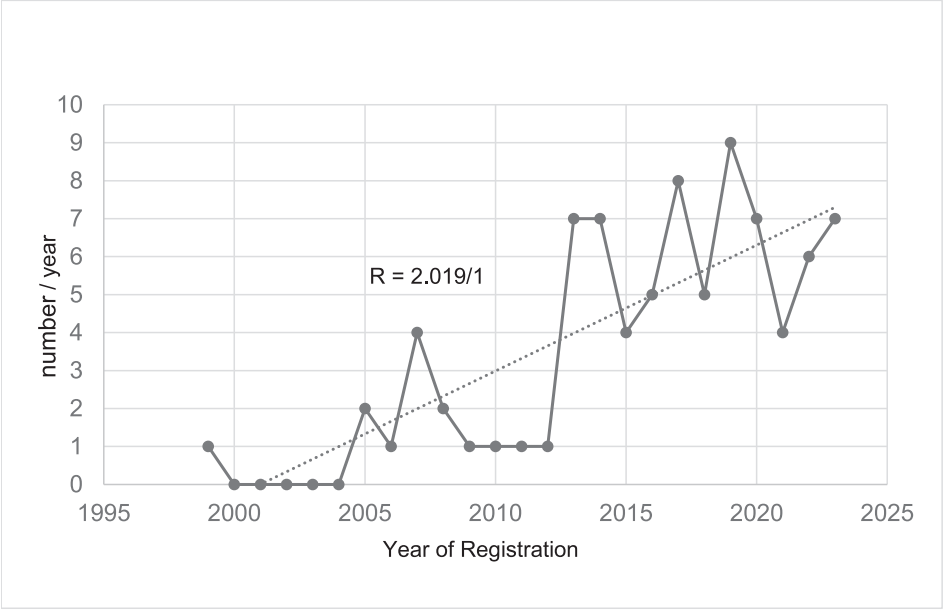

Fig. 1. Interventional status epilepticus clinical trials over time. Data from the International Clinical Trials Registry Platform (ICTRP) search 'status epilepticus', 1999 to 2023, excluding Phase I and II studies, observational and quality improvement studies and those in which cessation of status epilepticus was not a primary outcome.

relation to new drug development where it is estimated that for every 5,000 compounds evaluated in pre-clinical testing, only 5 will enter human clinical trials, and only 1 will lead to a drug approved for human use, taking 12–15 years from initiation at a cost of $2–2.5Billion [4]. With respect to phase III studies and beyond, around 50 % will fail (which of note is exactly the case for the studies presented in section 3). There are many elements in trial design and delivery that may contribute to a study that doesn't meet the intended outcome (Table 2).

From New England Journal of Medicine, Pocock & Stone, The primary outcome fails – what next? 375:9, page 862, copyright © (2016) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society [5].

Amongst the studies in established status epilepticus, 3 in particular [6–8] were adequately powered, well designed by multidisciplinary teams, and recruited to targets. These are summarized in Table 3. None reached significance for the primary outcome, whether analysed as per protocol, by subgroup analysis, or where applicable by adjudicated outcomes/excluding protocol deviations. Serious adverse reactions (unexpected or otherwise) rates were low, and there were also no differences in safety parameters between the study agents in any of the studies. So in terms of primary endpoint, all of these studies "failed", despite arguably good trial design reflecting on the questions posed in Table 2.

However, such studies, specifically including ESETT have also been cited as amongst the twelve historical landmarks in the treatment of Status Epilepticus [9], and Levetiracetam and Valproate are now recognized as effective treatments for CSE internationally, appearing in national guidelines, including in some the statement that "levetiracetam may be quicker to administer and have fewer adverse events" [10]. Levetiracetam use was anyway increasing prior to these publications, for example in German and Swiss centres being used in just over 60 % cases by 2016 [11]. However, a more recent (2022) German study [12] demonstrating levetiracetam was the choice after benzodiazepines in 91 % of cases, together supports that practice has changed, despite that neither levetiracetam nor valproate are licensed for status epilepticus. This likely reflects a clear trend in favour of Levetiracetam and/or valproate in the broader literature, including on pooled data fewer adverse events [13,14]. Also that phenytoin has largely fallen out of favour as a maintenance agent with newer better tolerated alternatives having been available for decades, together with practical advantages in terms of ease of administration with both levetiracetam and valproate. This highlights the importance of also asking the last questions from Table 2, in which case arguably none of these studies should be considered a failure, nor the wrong trials. Of note, there was much debate at the point of pre-trial design [15] about which drugs to include, with emerging interest in lacosamide but insufficient data at that time to justify randomisation under exception to informed consent, as required for SE research [16], as well as concerns that it might not be effective in generalized epilepsies has still not been established. Inclusion of Phenobarbitone was also considered, but consensus was that this was unlikely to become accepted at least in the developed world reflecting poor tolerability as a maintenance agent.

Table 3
Multicentre Established Status Epilepticus Trials, published 2019.

Trial	Agents (mg/kg)	Design	Population	Primary Outcome	Results
ESETT	LEV (60) VPA (40) fosPHT (20PE)	DB RCT (USA) Bayesian Adaptive allocation 58 sites	2y+ 3 age stratifications N = 384	60 min clinical seizure cessation without other ASM/ ICU	LEV 47 % fosPHT 45 % VPA 46 % (NS) NS Safety/ ARs
EcLIPSE	LEV (40) PHT (20)	Open RCT (UK) 30 sites	6 m> <18y N = 286	Time to clinical cessation CSE	LEV 35mins, PHT 45mins (NS) NS Safety/ ARs
ConSEPT	LEV(40) PHT (20)	Open RCT (NZ& AUS) 13 sites	3 m>< 16y 2 age stratifications N = 223	Clinical cessation CSE 5mins after infusion	LEV 60 % PHT 50 % (NS) NS Safety/ ARs

Rates of Serious adverse reactions and serious unexpected adverse reactions were low.
ESETT = Established Status Epilepticus Treatment Trial [6]; EcLIPSE = Emergency treatment with Levetiracetam or Phenytoin in convulsive Status Epilepticus in children [7]; ConCEPT = Convulsive Status Epilepticus Paediatric Trial [8]; LEV = levetiracetam; VPA = valproate; PHT = Phenytoin; PE = Phenytoin Equivalents; DB = double blind; RCT = Randomized controlled trial; ASM = Antiseizure medication; ITU = Intensive Care Unit; CSE = convulsive status epilepticus; NS = non significant differences; mins = minutes; ARs = Adverse Reactions.

5. What could we do differently?

That is not to say we couldn't do things differently. Particularly in relation to refractory and super-refractory status epilepticus, that trials in these conditions are challenging and costly is evident from both the relatively small number of studies in these populations, as well as the proportion which have failed to recruit, as shown in Fig. 2, and summarized in Table 4. Data from the ESETT study demonstrated that even in the presence of carefully designed protocols and extensive training, implementation can vary considerably between and within sites [20] hampering study delivery. The relative rarity of RSE and SRSE means even more centres are required to achieve meaningful numbers, in which context implementation challenges are likely to be exacerbated. There is also less consensus on meaningful clinical outcomes than in

Table 2
Questions to ask when the primary outcome fails.

Is there some indication of potential benefit?
Was the trial underpowered?
Was the primary outcome appropriate (or accurately defined)?
Was the population appropriate?
Was the treatment regimen appropriate?
Were there deficiencies in trial conduct?
Is a claim of non-inferiority of value?
Do subgroup findings elicit positive signals?
Do secondary outcomes relevel positive findings?
Can alternative analysis help?
Does more positive external evidence exist?
Is there a strong biologic rationale that favours the treatment?

Table 4
Published Refractory and Super-refractory Status Epilepticus Trials.

Trial	Agents (SE Type)	Design	Population (number of sites)	Primary Outcome	Results
Rossetti [17]	Propofol Barbituates (RSE)	SB RCT	16+ N = 150 (5)	RSE control on wean after 36–48 h burst suppression	Terminated 3y (n = 24)
STATUS	Brexanolone Placebo (SRSE)	DBRCT	2y+ N = 132 (122)	Anaesthetic wean <6 days and 24 h free of SE	Brenaxolone 43.9 % Placebo 42.4 % (NS)
RAISE**	Ganaxolone Placebo (RSE)	DBRCT	12+ N = 124 (74)	SE Cessation <30mins No progression to Anaesthesia within 36 h	ACTIVE (no longer recruiting)

STATUS = a study with SAGE-547 for super-refractory status epilepticus [18]; RAISE = Randomised therapy in Status Epilepticus [19]; RSE = refractory status epilepticus; SRSE = super refractory status epilepticus; DBRCT = double blind randomized controlled trial; SE = status epilepticus; mins = minutes.

earlier stages of treatment. The regulatory environment for randomised trials comes with numerous hurdles and expense, potentially distorting the research agenda, and driving the focus towards compliance with rules, rather than innovation in trial design. Additionally, for clinicians and academics, there is more tangible reward for grants and publications, than for recruitment to studies and improving patient care. Yet we also know that trials don't need to be complicated to inform management, and clinicians will actively contribute patients where this is made sufficiently practical and efficient. Many trials will fail by design. Nowhere was this more evident than in the context of Covid-19 and the recovery trials. Of registered trials during covid-19, only 5 % of almost 3000 comparisons were adequately powered, and of over half a million participants recruited in the first few months of the pandemic, only 26 % were in an adequately powered trial [21]. In the face of a major public health crisis, with a high mortality, lots of opinions and candidate drugs, it was recognized that large scale randomisation was required to identify effective treatments, leading to the UK lead Recovery Trials [22]. These "took the trial to the patient", involved simple randomisation, inclusion and exclusion criteria with a 1 page case report form and extensive linkage to National health datasets, evaluating 14 different treatments, and had recruited almost 40,000 patients in the first year alone. Four effective treatments, and importantly 6 ineffective were identified. The benefits of streamlined point of care trial designs hasn't been unnoticed internationally [23], and could surely be applied to SE. Other tools that could be usefully incorporated into SE trials include DOOR (desirability of outcome ranking, which combines multiple outcomes and competing risks into a single ordinal scale), with the potential addition of "tie-breaker" components to ensure important outcomes (e.g. mortality, or Intubation) aren't under-emphasised [24,25]. The role that artificial intelligence tools might play not only in EEG analysis [26] but also more broadly in trial design has also yet to be explored [27].

6. Conclusions

SE Trials, both successful and those that have "failed" by standard definitions have definitively changed practice, for example earlier use of benzodiazepines including pre-hospital, and the use of safer and quicker to administer 2nd line agents, both of which are associated with are clearly associated with improved outcomes [28]. Yet there is much to be learnt from taking a broader look at how we design and conduct them. One particularly pertinent question that should strike a chord with any clinician managing status epilepticus, or indeed epilepsy in other contexts is "*why is it easier to prescribe an unproven medication as part of standard care than to randomise the patient into a trial to learn whether the same medication is safe and effective*" (personal communication, Richard Haynes, Professor of Renal Medicine and Trial design, University of Oxford). As outlined in recent reviews "*Trial regulations need to be rewritten to be fit for purpose….. good intentions are not enough……regulatory practice must change. Those responsible for designing trials must also adapt…..designing trials that align with care pathways and cause minimal disruption to participants is key to success*" [29]. Indications are that some authorities and funders at least are listening [30].

CRediT authorship contribution statement

Hannah Cock: Writing – review & editing, Writing – original draft, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Hannah Cock reports a relationship with London-Innsbruck Colloquium on Status Epilepticus and Acute Seizures that includes: travel reimbursement. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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