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June 8, 2021

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U.S. Department of Health and Human Services
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Janet Woodcock, M.D.
Acting Commissioner
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U.S. Department of Health and Human Services
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**Re: Project Title: Established Status Epilepticus Treatment Trial
Sponsor: National Institute of Neurological Disorders and Stroke, National
Institutes of Health
Award Number: U01NS088034
ClinicalTrials.gov Identifier: NCT01960075**

Dear Dr. Menikoff and Dr. Woodcock:

Public Citizen, a consumer advocacy organization with more than 500,000 members and supporters nationwide, hereby requests that the Office for Human Research Protections (OHRP) and the Food and Drug Administration (FDA) immediately launch compliance oversight investigations into the already-completed National Institutes of Health (NIH)-funded Established Status Epilepticus Treatment Trial (ESETT) and its review and approval by the responsible institutional review board(s) (IRBs). Based on our review of the protocol and relevant background scientific literature, we are concerned that the trial, as proposed and conducted, failed to (1) materially comply with key requirements of Department of Health and Human Services (HHS) and FDA regulations for the protection of human subjects at 45 C.F.R. Part 46¹ and 21 C.F.R. Parts 50 and 56,² respectively, and (2) satisfy the basic ethical principles upon which those regulations are founded.

¹ All citations of 45 C.F.R. Part 46, Subpart A (also known as the Common Rule) throughout this letter refer to the pre-2018 version of these regulations.

² For the sake of conciseness, only HHS regulatory citations are referenced hereafter when both sets of regulations are applicable.

In ESETT, 462 subjects aged 1 to 94 years who had life-threatening benzodiazepine-refractory status epilepticus were randomly assigned in the emergency rooms of 58 hospitals across the U.S. to receive intravenous levetiracetam, fosphenytoin, or valproate without the informed consent of the subjects (or parental permission for subjects who were children). The goal of the trial was to determine which of these three anticonvulsant drugs would result in better seizure resolution and responsiveness within 60 minutes after initiation of the assigned drug, without additional anticonvulsant medications.^{3,4} All three trial arms potentially exposed some subjects to care that significantly deviated from contemporaneous usual care for status epilepticus patients given the following features of the trial's design:

- The scientific literature cited by the ESETT investigators in their trial protocol,^{5,6,7} as well as a published commentary authored by the ESETT investigators after the trial was completed,⁸ documented that in routine practice, selection of anticonvulsant drug therapy for benzodiazepine-refractory status epilepticus was based on patient-specific factors, including a patient's chronic anticonvulsant drug use and compliance, age, underlying medical conditions, and known responsiveness to a given anticonvulsant drug during prior episodes of status epilepticus. But in ESETT, subjects were randomized to receive any one of the three anticonvulsant drugs being tested irrespective of these individualized usual-care practice considerations.
- The weight-based dosing of the three anticonvulsant drugs tested in the trial was capped at a dose for someone weighing 75 kilograms (kg). As a result, the many enrolled subjects who weighed more than 75 kg were potentially at risk of being underdosed and inadequately treated for their life-threatening status epilepticus.⁹
- The trial protocol considered any unblinding of trial drug assignment before 60 minutes to be a protocol deviation. This was an exceptionally long time to discourage unblinding of treatment assignment in a subject with ongoing status epilepticus and therefore potentially deprived clinicians of valuable information that could have been used to guide further anticonvulsant drug therapy.

These deviations from usual care predictably could have delayed resolution of some subjects' benzodiazepine-refractory status epilepticus and worsened clinical outcomes.

³ Kapur J, Elm J, Chamberlain JM, et al. Randomized trial of three anticonvulsant medications for status epilepticus. *N Engl J Med.* 2019;381(22):2103-2113.

⁴ Chamberlain JM, Kapur J, Shinnar S, et al. Efficacy of levetiracetam, fosphenytoin, and valproate for established status epilepticus by age group (ESETT): a double-blind, responsive-adaptive, randomized controlled trial. *Lancet.* 2020;395(10231):1217-1224.

⁵ Riviello JJ Jr, Ashwal S, Hirtz D, et al. Practice parameter: diagnostic assessment of the child with status epilepticus (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology.* 2006;67(9):1542-1550.

⁶ Brophy GM, Bell R, Claassen J, et al. Guidelines for the evaluation and management of status epilepticus. *Neurocrit Care.* 2012;17(1):3-23.

⁷ Riviello JJ Jr, Claassen J, Laroche SM, et al. Treatment of status epilepticus: An international survey of experts. *Neurocrit.Care.* 2013;18(2):193-200.

⁸ Cock HR, Coles LD, Elm J, et al. Lessons from the Established Status Epilepticus Treatment Trial. *Epilepsy Behav.* 2019 Dec;101(Pt B):106296.

⁹ *Ibid.*

In addition, because none of the three trial groups received management in accordance with contemporaneous usual-care treatment practices, the design of ESETT precluded (1) appropriate monitoring to ensure the safety of enrolled subjects and (2) drawing firm conclusions about whether and how to modify current clinical practices for managing benzodiazepine-refractory status epilepticus.

As a result of these multiple fundamental flaws in the trial's design, it appears that risks to the subjects enrolled in ESETT were not minimized, nor were they reasonable in relation to anticipated benefits, if any, to the subjects and the importance of the knowledge expected to result, as required by HHS human subjects protection regulations at 45 C.F.R. §§ 46.111(a)(1) and (2).

We also are concerned that (1) the information provided to subjects (or to the parents of subjects who were children) after they had already participated in the research without informed consent (or parental permission) failed to describe (a) how management of subjects enrolled in ESETT deviated from contemporaneous usual care for benzodiazepine-refractory status epilepticus and (b) the reasonably foreseeable risks of such deviations; and (2) selection of subjects was not equitable, as required by HHS human subjects protection regulations at 45 C.F.R. §§ 46.111(a)(3), given the disproportionately high enrollment of subjects who were Black compared with the proportion of patients hospitalized in the U.S. for status epilepticus who are Black.

The following is a more detailed discussion of ESETT and its apparent regulatory and ethical lapses.

A. Overview of ESETT

ESETT was a multicenter, randomized, double-blind, three-arm clinical trial funded by National Institute of Neurological Disorders and Stroke (NINDS) and conducted by the Neurological Emergencies Treatment Trials Network and the Pediatric Emergency Care Applied Research Network (PECARN).^{10,11,12} The trial was conducted with an exception from the informed consent requirements for emergency research under FDA human subjects protection regulations at 21 C.F.R. § 50.24.

From November 2015 to December 2018, ESETT investigators in emergency rooms of 58 participating hospitals across the U.S. enrolled 462 subjects with established status epilepticus that was refractory to benzodiazepine treatment. Subjects were randomly assigned to receive weight-based doses of levetiracetam (175 subjects), fosphenytoin (142 subjects), or valproate (145 subjects) administered intravenously over 10 minutes. Sixteen patients also were enrolled

¹⁰ Kapur J, Elm J, Chamberlain JM, et al. Randomized trial of three anticonvulsant medications for status epilepticus. *N Engl J Med.* 2019;381(22):2103-2113.

¹¹ Chamberlain JM, Kapur J, Shinnar S, et al. Efficacy of levetiracetam, fosphenytoin, and valproate for established status epilepticus by age group (ESETT): a double-blind, responsive-adaptive, randomized controlled trial. *Lancet.* 2020;395(10231):1217-1224.

¹² Study protocol, Established Status Epilepticus Treatment Trial (ESETT); version: 2 Final.

https://www.nejm.org/doi/suppl/10.1056/NEJMoa1905795/suppl_file/nejmoa1905795_protocol.pdf. Accessed June 2, 2021.

for a second episode of status epilepticus, but their second enrollments were excluded from the intention-to-treat analysis.

The dosage of the three study drugs was based on estimated subject weight. Because of the of blinding procedure used for the trial and the fact that the maximum total dose of fosphenytoin that can be administered intravenously safely over 10 minutes is 1,500 milligrams (mg), doses of the three study drugs were capped at the recommended loading dose for a 75 kg patient (for fosphenytoin, 20 mg/kg or 1,500 mg total; for levetiracetam, 60 mg/kg or 4,500 mg total; and for valproate, 40 mg/kg or 3,000 mg total).

The inclusion criteria for ESETT were the following:

- (1) Patient was aged 2 years or older (note that according to the reported trial results, some enrolled subjects were 1 year old).
- (2) Patient had generalized convulsive seizure of greater than five minutes prior to treatment with study drug.
- (3) Patient had received an adequate dose of benzodiazepines.
- (4) Patient continued to have persistent or recurrent convulsions in the emergency department at least five minutes and no more than 30 minutes after the last dose of benzodiazepine.

Exclusion criteria for ESETT included the following, among others:

- (1) Known pregnancy, based solely on history and physical exam;
- (2) Known metabolic disorder, liver disease, or severe kidney impairment based on clinical history; and
- (3) Known allergy or other known contraindication to any of the three study drugs, as per the package inserts.

Notably absent from the exclusion criteria were patients known to have been, or suspected of having been, noncompliant with a specific prescribed chronic anticonvulsant drug prior to onset of their status epilepticus; patients known to have had a prior episode of status epilepticus that was responsive or unresponsive to one of the three study drugs; and patients with a body weight exceeding 75 kg.

The primary outcome of ESETT was clinical cessation of status epilepticus, determined by the absence of clinically apparent seizures and improving responsiveness, within 60 minutes after the start of study-drug infusion, without the use of additional anticonvulsant medication.

The results of ESETT were published in *The New England Journal of Medicine* on November 28, 2019,¹³ and in *Lancet* on April 11, 2020.¹⁴ In accordance with a prespecified stopping rule for futility of finding one drug to be superior or inferior, a planned interim analysis led to the trial being stopped. The primary outcome occurred in 47% of levetiracetam-group subjects (95% credible interval, 39 to 54), 46% of fosphenytoin-group subjects (95% credible interval, 38 to 55), and 49% of valproate-group subjects (95% credible interval, 41 to 57). These response rates were generally lower than those documented in earlier studies of benzodiazepine-refractory status epilepticus.

B. Apparent problems with ESETT protocol design that resulted in a failure to minimize risks to subjects and to ensure that risks were reasonable in relation to anticipated benefits, if any, to the subjects and the importance of the knowledge expected to result

Status epilepticus is a medical emergency and has an estimated mortality rate of approximately 17% according to the ESETT investigators.¹⁵ Importantly, the morbidity and mortality of status epilepticus is determined by the underlying cause of the disorder and **the length of time in status epilepticus**.^{16,17} Benzodiazepines have been well-established as the first-line initial treatment for status epilepticus based on three randomized clinical trials.^{18,19,20}

For benzodiazepine-refractory status epilepticus, the ESETT investigators acknowledged in their protocol the following guidelines and evidence documenting usual-care practices for status epilepticus:

- 2012 Neurocritical Care Society (NCS) guidelines for status epilepticus recommended use of either fosphenytoin or valproate for treatment of benzodiazepine-refractory status epilepticus. (Of note, the NCS guidelines emphasized that (a) selection of anticonvulsant drug therapy for patients who failed initial therapy with a benzodiazepine varied based on the particular patient scenario and (b) valproate was the best option for patients (particularly children) with a history of primary generalized epilepsy.²¹)

¹³ Kapur J, Elm J, Chamberlain JM, et al. Randomized trial of three anticonvulsant medications for status epilepticus. *N Engl J Med*. 2019;381(22):2103-2113.

¹⁴ Chamberlain JM, Kapur J, Shinnar S, et al. Efficacy of levetiracetam, fosphenytoin, and valproate for established status epilepticus by age group (ESETT): a double-blind, responsive-adaptive, randomized controlled trial. *Lancet*. 2020;395(10231):1217-1224.

¹⁵ Study protocol, Established Status Epilepticus Treatment Trial (ESETT); version: 2 Final. https://www.nejm.org/doi/suppl/10.1056/NEJMoa1905795/suppl_file/nejmoa1905795_protocol.pdf. Accessed June 2, 2021.

¹⁶ Towne AR, Pellock JM, Ko D, DeLorenzo RJ. Determinants of mortality in status epilepticus. *Epilepsia*. 1994;35(1):27-34.

¹⁷ Neligan A, Shorvon SD. Frequency and prognosis of convulsive status epilepticus of different causes: A systematic review. *Arch Neurol*. 2010;67(8):931-940.

¹⁸ Treiman DM, Meyers PD, Walton NY, et al. A comparison of four treatments for generalized convulsive status epilepticus. *N Engl J Med*. 1998;339(12):792-798.

¹⁹ Alldredge BK, Gelb AM, Isaacs SM, et al. A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus. *N Engl J Med*. 2001;345(9):631-637

²⁰ Silbergleit R, Durkalski V, Lowenstein D, et al. Intramuscular versus intravenous therapy for prehospital status epilepticus. *N Engl J Med*. 2012;366(7):591-600.

²¹ Brophy GM, Bell R, Claassen J, et al. Guidelines for the evaluation and management of status epilepticus. *Neurocrit Care*. 2012;17(1):3-23.

- A medical records survey of 150 patients treated for status epilepticus at critical care units of 15 academic medical centers found that fosphenytoin was the most commonly used second-line anticonvulsant drug (33%), levetiracetam was less commonly used (10%), and valproate was rarely used (<2%).²²
- The NCS Status Epilepticus Guideline Writing Committee reported that among 50 surveyed expert neurointensivists, neurologists, and epileptologists, 80% preferred fosphenytoin (or phenytoin) as treatment for benzodiazepine-refractory status epilepticus, 6% preferred levetiracetam, and 2% preferred valproate. (Of note, these data cited by the ESETT investigators were only for a scenario of an adult patient in good health with no prior seizure history prior to the onset of benzodiazepine-refractory status epilepticus. In contrast, in a scenario of an adolescent patient with a two-year history of juvenile myoclonic epilepsy that was well-controlled on lamotrigine prior to a gastrointestinal illness that resulted in an interruption of her treatment, 62% preferred valproate as treatment for benzodiazepine-refractory status, 16% preferred levetiracetam, and 9% preferred fosphenytoin (or phenytoin). The variation in drug preference across these scenarios highlighted the importance of individual patient-specific factors in selecting anticonvulsant drug therapy for benzodiazepine-refractory status epilepticus.²³
- In a survey of 21 pediatric emergency department directors from PECARN, fosphenytoin was most commonly used for benzodiazepine-refractory status epilepticus in children, followed by levetiracetam, phenobarbital, and valproate.²⁴

Failure of ESETT design to account for patient-specific factors that were considered in usual clinical practice when selecting drug therapy for benzodiazepine-refractory status epilepticus

Levetiracetam, fosphenytoin, and valproate were each used in routine practice for treatment of benzodiazepine-refractory status epilepticus. However, the scientific literature cited by the ESETT investigators themselves in their trial protocol,^{25,26,27} as well as a published commentary authored by the ESETT investigators after the trial was completed,²⁸ documented that in routine practice, selection of anticonvulsant drug therapy for benzodiazepine-refractory status epilepticus was based on patient-specific factors, including a patient's chronic anticonvulsant drug use and compliance, age, underlying medical conditions, and known responsiveness to a given anticonvulsant drug during prior episodes of status epilepticus. But in ESETT, subjects were

²² Cook AM, Castle A, Green A, et al. Practice variations in the management of status epilepticus. *Neurocrit.Care.* 2012;17(1):24-30.

²³ Riviello JJ Jr, Claassen J, Laroche SM, et al. Treatment of status epilepticus: An international survey of experts. *Neurocrit.Care.* 2013;18(2):193-200.

²⁴ Study protocol, Established Status Epilepticus Treatment Trial (ESETT); version: 2 Final. https://www.nejm.org/doi/suppl/10.1056/NEJMoa1905795/suppl_file/nejmoa1905795_protocol.pdf. Accessed June 2, 2021.

²⁵ Riviello JJ Jr, Ashwal S, Hirtz D, et al. Practice parameter: diagnostic assessment of the child with status epilepticus (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology.* 2006;67(9):1542-1550.

²⁶ Brophy GM, Bell R, Claassen J, et al. Guidelines for the evaluation and management of status epilepticus. *Neurocrit Care.* 2012;17(1):3-23.

²⁷ Riviello JJ Jr, Claassen J, Laroche SM, et al. Treatment of status epilepticus: An international survey of experts. *Neurocrit.Care.* 2013;18(2):193-200.

²⁸ Cock HR, Coles LD, Elm J, et al. Lessons from the Established Status Epilepticus Treatment Trial. *Epilepsy Behav.* 2019 Dec;101(Pt B):106296.

randomized to receive any one of the three anticonvulsant drugs being tested irrespective of these individualized usual-care practices.

For example, it was well-recognized at the time the ESETT trial was designed that low blood levels of anticonvulsant drugs due to inadequate dosing, noncompliance, or withdrawal was one of the most common causes of status epilepticus in both children and adults.^{29,30,31,32,33,34,35} As a result, 2006 clinical guidelines on the diagnostic assessment of status epilepticus in children that were issued by the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society recommended that anticonvulsant drug levels be considered when a child with treated epilepsy develops status epilepticus.³⁶ Likewise, the 2012 NCS guidelines for the evaluation and management of status epilepticus recommended that for status epilepticus patients currently treated with anticonvulsant drugs, a drug level should be checked and history regarding compliance the drugs should be obtained.³⁷ The NCS guidelines further advised that in patients with benzodiazepine-refractory status epilepticus who have known epilepsy and had been taking an anticonvulsant drug before admission, it is reasonable to provide an intravenous bolus of this same anticonvulsant drug, if available, prior to initiating an additional drug. Both sets of guidelines were referenced by ESETT investigators in their protocol. Finally, in a 2019 paper discussing lessons from their trial, the ESETT investigators themselves acknowledged that for subjects already taking any one of the three drugs used in the study for whom there was suspected poor adherence, use of that particular drug for benzodiazepine-refractory status epilepticus may have been preferable.³⁸

Disregarding subjects' chronic anticonvulsant drug use and compliance history and instead randomly picking and administering any one of the three drugs in the ESETT trial exposed some subjects to unusual care that could well have potentially delayed resolution of their benzodiazepine-refractory status epilepticus and worsened clinical outcomes.

²⁹ Towne AR, Pellock JM, Ko D, DeLorenzo RJ. Determinants of mortality in status epilepticus. *Epilepsia*. 1994;35(1):27-34.

³⁰ DeLorenzo RJ, Hauser WA, Towne AR, et al. A prospective, population-based epidemiologic study of status epilepticus in Richmond, Virginia. *Neurology*. 1996;46(4):1029-1035.

³¹ Lowenstein DH, Alldredge BK. Current concepts: Status epilepticus. *N Engl J Med*. 1998;338(14): 970-976.

³² Kelso AR, Cock HR. Status epilepticus. *Pract Neurol*. 2005 Dec;5:322-333.

³³ Riviello JJ Jr, Ashwal S, Hirtz D, et al. Practice parameter: diagnostic assessment of the child with status epilepticus (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology*. 2006;67(9):1542-1550.

³⁴ Brophy GM, Bell R, Claassen J, et al. Guidelines for the evaluation and management of status epilepticus. *Neurocrit Care*. 2012;17(1):3-23.

³⁵ Cook AM, Castle A, Green A, et al. Practice variations in the management of status epilepticus. *Neurocrit Care*. 2012;17(1):24-30.

³⁶ Riviello JJ Jr, Ashwal S, Hirtz D, et al. Practice parameter: diagnostic assessment of the child with status epilepticus (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology*. 2006;67(9):1542-1550.

³⁷ Brophy GM, Bell R, Claassen J, et al. Guidelines for the evaluation and management of status epilepticus. *Neurocrit Care*. 2012;17(1):3-23.

³⁸ Cock HR, Coles LD, Elm J, et al. Lessons from the Established Status Epilepticus Treatment Trial. *Epilepsy Behav*. 2019 Dec;101(Pt B):106296.

Additional examples of how patient-specific factors influenced the selection of initial anticonvulsant drug therapy for benzodiazepine-refractory status epilepticus in routine practice at the time ESETT was conducted include the following:

- For elderly patients on multiple medications for underlying medical conditions, including cardiac disease, selection of fosphenytoin over levetiracetam for benzodiazepine-refractory status epilepticus would have been very unlikely because of the greater risks of hypotension, arrhythmias, and potentially harmful drug-drug interactions. Disregarding subjects' age and underlying medical conditions and randomly picking and administering any one of the three drugs in the ESETT trial could have exposed some subjects to avoidable serious adverse effects of fosphenytoin.
- For patients known to have had a prior episode of benzodiazepine-refractory status epilepticus that was unresponsive to levetiracetam, fosphenytoin, or valproate, selection of the previously ineffective drug typically would have been avoided in the initial treatment of a subsequent episode of benzodiazepine-refractory status epilepticus. On the other hand, for patients known to have had a prior episode of benzodiazepine-refractory status epilepticus that rapidly responded to levetiracetam, fosphenytoin, or valproate, selection of the previously effective drug typically would have been favored in the initial treatment of a subsequent episode of benzodiazepine-refractory status epilepticus. Again, disregarding subjects' prior unresponsiveness or responsiveness to specific anticonvulsant drugs for a prior episode of benzodiazepine-refractory status epilepticus and randomly picking and administering any one of the three drugs in the ESETT trial exposed some subjects to unusual care that could have potentially delayed resolution of their benzodiazepine-refractory status epilepticus and worsened clinical outcomes.

Inadequate treatment due to a cap on weight-based dosing

A 2005 review on status epilepticus that was coauthored by an individual who subsequently became one of the ESETT investigators emphasized the importance of administering sufficient doses of anticonvulsant drugs when treating benzodiazepine-refractory status epilepticus.³⁹ This review cited studies suggesting that initial loading doses of anticonvulsant drugs are frequently inadequate and emphasized that “adequacy of treatment is highly predictive of efficacy.”

Nevertheless, despite being aware of the importance of adequately dosing anticonvulsant drugs when treating patients with benzodiazepine-refractory status epilepticus, the ESETT investigators capped doses of the three study drugs at the recommended loading dose for a 75-kg patient but did not exclude patients weighing greater than 75 kg. As a result, some of the subjects who weighed more than 75 kg, a group that comprised one-third of the people enrolled in ESETT,⁴⁰ likely received sub-therapeutic doses of their assigned anticonvulsant drug, thus potentially delaying resolution of their benzodiazepine-refractory status epilepticus and worsening clinical outcomes.

³⁹ Kelso AR, Cock HR. Status epilepticus. *Pract Neurol*. 2005 Dec;5:322-333.

⁴⁰ Cock HR, Coles LD, Elm J, et al. Lessons from the Established Status Epilepticus Treatment Trial. *Epilepsy Behav*. 2019 Dec;101(Pt B):106296.

In their 2019 paper discussing lessons from their trial, the ESETT investigators themselves in retrospect acknowledged the risk posed by the cap on study drug dosing when they stated the following:

Given that approximately one-third of the ESETT subjects weighed greater than 75 kg, a significant number of subjects could have received lower than the mg/kg calculation [for drug doses] would have advised. This may be especially important because patients weighing more than 75 kg are likely to have more body fat and, therefore, higher volumes of distribution for the generally lipophilic medications used to treat [established status epilepticus].⁴¹

Note that these higher volumes of distribution would have further increased the likelihood that the anticonvulsant drug doses administered to subjects weighing more than 75 kg were inadequate. Such intentional underdosing of medication represents unusual care.

Emergency unblinding of trial group assignment was explicitly discouraged

The ESETT protocol stated the following regarding emergency unblinding of a subject's trial group assignment:

Emergency unblinding may be required if the treating team feels that subjects' care after the study intervention requires knowledge of what study drug was given. **Emergency unblinding will not be performed within 60 minutes of the start of study drug infusion. The blind should be maintained until after the primary outcome has been collected.**

Emergency unblinding performed prior to 60 minutes or prior to determination of the primary outcome, because of physician judgment that it is necessary for the safety or care of the patient, or because of unanticipated situations is accommodated by calling the hotline **but is a deviation from this protocol.**⁴²

[Emphasis added]

Thus, although the ESETT protocol allowed for emergency unblinding to determine which drug had been administered to a subject who had ongoing status epilepticus in order to guide subsequent treatment, it strongly discouraged such unblinding and required caregivers to call a hotline to find out which study drug the subject had received.

Sixty minutes was an exceptionally long time to discourage unblinding in a patient with unremitting status epilepticus and potentially contributed to a dangerous delay in resolution of status epilepticus in some subjects. As previously noted, the morbidity and mortality of status epilepticus is determined, in part, by the length of time in status epilepticus.

⁴¹ *Ibid.*

⁴² Study protocol, Established Status Epilepticus Treatment Trial (ESETT); version: 2 Final. https://www.nejm.org/doi/suppl/10.1056/NEJMoa1905795/suppl_file/nejmoa1905795_protocol.pdf. Accessed May 19, 2021.

Heightening the concern about the efforts to discourage emergency unblinding was another provision in the ESETT protocol stipulating that rescue therapy was not “indicated” until 20 minutes after the start of the assigned study drug infusion. Rescue therapy appears to have been permitted only after 10 minutes from the end of the study drug infusion, even if subjects had persistent seizures during this period.

These provisions in the protocol too may have exposed some subjects to unusual care that could have contributed to a dangerous delay in resolution of their status epilepticus.

Lack of usual care in any trial group

In ESETT, none of the three trial groups received management in accordance with contemporaneous usual-care treatment practices, which would have involved individualized selection of anticonvulsant drug therapy based on the aforementioned patient-specific factors, appropriate drug dosing for subjects of all weights, and no blinding to which drug(s) had been administered. Instead, in all three trial groups, a subset of subjects received unusual care.

As a result, the design of ESETT precluded (1) appropriate monitoring of the trial by the data and safety monitoring board to ensure the safety of enrolled subjects and (2) drawing firm conclusions about whether and how to modify current clinical practice for managing benzodiazepine-refractory status epilepticus.

Violations of human subjects protection regulations

As a result of these multiple apparent fundamental flaws in the design of ESETT, it appears that the trial failed to satisfy the following criteria required for IRB approval of human subjects research under HHS regulations for the protection of human subjects at 45 C.F.R. §§ 46.111(a)(1) and (2), respectively, which are grounded in the Belmont Report’s basic ethical principle of beneficence:⁴³

- (1) The risks to the subjects are minimized by using procedures that are consistent with sound research design and that do not unnecessarily expose subjects to risk.
- (2) The risks to subjects are reasonable in relation to anticipated benefits, if any, to the subjects and the importance of the knowledge expected to result.

Examples of appropriate steps that could have been taken to minimize risk to subjects in ESETT and ensure that the management provided in each arm of the trial was consistent with usual care for benzodiazepine-refractory status epilepticus include the following:

- (1) The exclusion of patients known to have been, or suspected of having been, noncompliant with a specific prescribed chronic anticonvulsant drug prior to onset of their status epilepticus;

⁴³ National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Ethical principles and guidelines for the protection of human subjects of research. April 18, 1979. <https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/index.html>. Accessed June 2, 2021.

- (2) The exclusion of patients known to have had a prior episode of status epilepticus that was responsive or unresponsive to one of the three study drugs;
- (3) The exclusion of patients with a body weight exceeding 75 kg; and
- (4) The elimination of provisions in the protocol that explicitly discouraged emergency unblinding of subjects' trial group assignment.

Note that this list is not intended to be all-inclusive of the changes that would have been needed to ensure that risks to subjects were minimized and were reasonable in relation to anticipated benefits, if any, to the subjects and the importance of the knowledge that was expected to result.

Given the apparent fundamental flaws in the design of ESETT and the failure to minimize risks to subjects, we are also concerned that the IRBs that reviewed and approved ESETT lacked the professional competence and knowledge among their memberships necessary to ascertain the acceptability of the trial in terms of the standards of professional conduct and practice related to the usual management of patients with benzodiazepine-refractory status epilepticus, as required by HHS regulations at 45 C.F.R. § 46.107(a).

C. Concerns about the informed consent procedures

Enrollment in ESETT occurred under an exception from the informed consent requirements for emergency research under FDA human subjects protection regulations at 21 C.F.R. § 50.24. Under this exception, consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the trial was to be conducted and from which the subjects were to be drawn was required. The protocol also stipulated that subjects or their legally authorized representative were to be notified of enrollment as early as possible and that consent *to continue participation* in the study was to be sought for all subjects. For subjects who wished to discontinue their participation, no further data was to be collected.

If a subject was randomized into ESETT and died before a legally authorized representative or family member could be contacted, a letter was to be sent to the subject's family or legally authorized representative providing basic information about the trial, the subject's inclusion, and contact information so that families could call or write to obtain more information or to get questions answered.

Given the apparent fundamental flaws in the design of ESETT, we are concerned about the adequacy of information that may have been provided (a) to representatives of the communities in which ESETT was to be conducted and from which the subjects were drawn; (b) to enrolled subjects or their legally authorized representatives when their consent to continue participation in the study was sought; and (c) in any letters sent to families or legally authorized representatives of subjects who may have died before a legally authorized representative or family member could be contacted. Specifically, we are concerned that the experimental nature of the trial interventions, the significant deviations from usual care, and the reasonably foreseeable risks of potentially delayed resolution of some subjects' benzodiazepine-refractory status epilepticus and worsened clinical outcomes may not have been described to the community representatives and subjects, their legally authorized representatives, or their families.

In fact, our review of the sample form used to obtain consent (or parental permission) to continue participation in ESETT (copy enclosed), which we obtained under a Freedom of Information Act request submitted to NINDS, revealed that the document totally failed to describe (a) how management of subjects enrolled in ESETT deviated from the usual care for benzodiazepine-refractory status epilepticus, and (b) the reasonably foreseeable risks of such deviations (i.e., the potential dangerous delay in resolution of status epilepticus in some subjects in each trial group). Failure to provide such information violated the Belmont Report's basic ethical principles of respect for persons.

D. Concerns about equitable selection of subjects

The ESETT investigators reported that 193 (42%) of the 462 subjects enrolled in ESETT were Black and 201 (44%) were White.⁴⁴ In contrast, data from the U.S. National Hospital Discharge Survey found that among patients hospitalized for status epilepticus in the U.S. from 2005 to 2010, 27% were Black and 69% were White.⁴⁵ Even accounting for the fact that the incidence of status epilepticus is approximately twofold greater in Blacks than Whites,⁴⁶ these observations appear to indicate that enrollment of subjects who were Black in ESETT was disproportionately high compared with the proportion of patients hospitalized in the U.S. for status epilepticus who are Black.

As a result, we are concerned that the trial, as conducted, failed to satisfy the requirement under HHS regulations for the protection of human subjects at 45 C.F.R. § 46.111(a)(3) that selection of subjects be equitable, which is grounded in the Belmont Report's basic ethical principle of justice.⁴⁷

The apparent lack of equitable selection of subjects is particularly troubling given that the prospective informed consent of the subjects was not obtained prior to their enrollment in ESETT.

E. Conclusions and requested actions

In summary, the apparent regulatory and ethical lapses in the design of ESETT are very troubling and demand the urgent attention of the OHRP and FDA. Public Citizen therefore urges the OHRP and FDA to immediately launch compliance oversight investigations of ESETT and the adequacy of the trial's review and approval by the responsible IRBs. Your investigations must include a careful assessment of the following issues, among others:

- (1) The reviewing IRBs' understanding and assessment of the trial's risks;

⁴⁴ Chamberlain JM, Kapur J, Shinnar S, et al. Efficacy of levetiracetam, fosphenytoin, and valproate for established status epilepticus by age group (ESETT): a double-blind, responsive-adaptive, randomized controlled trial. *Lancet*. 2020;395(10231):1217-1224.

⁴⁵ Dham BS, Hunter K, Rincon F. The epidemiology of status epilepticus in the United States. *Neurocrit Care*. 2014;20(3):476-483.

⁴⁶ *Ibid*.

⁴⁷ National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Ethical principles and guidelines for the protection of human subjects of research. April 18, 1979. <https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/index.html>. Accessed June 2, 2021.

- (2) Whether the reviewing IRBs had the professional competence and knowledge among their memberships necessary to ascertain the acceptability of the trial in terms of the standards of professional conduct and practice related to the usual management of patients with benzodiazepine-refractory status epilepticus;
- (3) The adequacy of information that may have been provided (a) to representatives of the communities in which ESETT was conducted and from which the subjects were drawn; (b) to enrolled subjects or their legally authorized representatives when their consent to continue participation in the study was sought; and (c) in any letters sent to families or legally authorized representatives of subjects who may have died before a legally authorized representative or family member could be contacted; and
- (4) The measures that were taken to ensure that there was equitable selection of subjects across the entire trial.

Finally, the failure to incorporate usual-care clinical practices into the design of randomized clinical trials testing interventions in critically ill patients — resulting in a failure to minimize risks to subjects and deficiencies in informed consent — has been a recurring problem with large multicenter clinical trials funded by the NIH over at least the past two decades. Examples of other trials that were brought to OHRP’s attention because they had regulatory and ethical lapses similar to those seen with ESETT include the following:

- (1) Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) (ClinicalTrials.gov number, NCT00233324);^{48,49}
- (2) Myocardial Ischemia and Transfusion (MINT) Trial, funded by the National Heart, Lung, and Blood Institute (ClinicalTrials.gov number: NCT02981407);⁵⁰ and
- (3) Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis Trial (CLOVERS) (ClinicalTrials.gov number: NCT03434028).⁵¹

Public Citizen therefore urges the OHRP to work with NIH officials to promptly conduct an audit of all ongoing or soon-to-be-initiated NIH-funded clinical trials involving critically ill subjects and assess whether usual-care clinical practices were rigorously characterized and

⁴⁸ Public Citizen. Letter to the Secretary of Health and Human Services regarding the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT). April 10, 2013. <https://www.citizen.org/wp-content/uploads/migration/2111.pdf>. Accessed June 2, 2021.

⁴⁹ Cortes-Puch I, Wesley RA, Carome MA, et al. Usual care and informed consent in clinical trials of oxygen management in extremely premature infants. *PLoS One*. 2016 May 18;11(5):e0155005.

⁵⁰ Office for Human Research Protections and the Veterans Health Administration Office of Research Oversight. Letter to Public Citizen regarding the Myocardial Ischemia and Transfusion (MINT) Trial. June 7, 2018. <https://www.hhs.gov/ohrp/compliance-and-reporting/determination-letters/2018/myocardial-ischemia-and-transfusion-mint-trial-6-7-18/index.html>. Accessed June 2, 2021.

⁵¹ Office for Human Research Protections. Letter to Public Citizen regarding the Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis Trial (CLOVERS). September 28, 2020. <https://www.hhs.gov/ohrp/compliance-and-reporting/determination-letters/2020/september-28-2020-crystalloid-liberal-or-vasopressors-early-resuscitation-in-sepsis-trial/index.html>. Accessed June 2, 2021.

appropriately incorporated into the design of these trials. For trials for which usual-care clinical practices were not rigorously characterized and appropriately incorporated into the trial design, subject enrollment should be immediately suspended or delayed.

Please note that the OHRP and FDA may share our complaint letter, with identifiers, with anyone. We will be posting a copy on Public Citizen's website as well.

Thank you for your prompt attention to this important matter regarding the protection of human subjects. We look forward to thorough and careful investigations by the OHRP and FDA into the apparent regulatory and ethical lapses related to ESETT.

Please contact us if you have any questions or need additional information.

Sincerely,



Michael A. Carome, M.D.
Director
Public Citizen's Health Research Group

Enclosure: Sample consent form for continued participation in ESETT

cc: Rachel L. Levine, M.D., Assistant Secretary for Health, HHS
Francis Collins, M.D., Director, NIH
Walter J. Koroshetz, M.D., Director, NINDS, NIH

INFORMED CONSENT

Title of Study: *Established Status Epilepticus Treatment Trial (ESETT): A multicenter, randomized, double-blind, comparative effectiveness study of fosphenytoin, levetiracetam, and valproic acid in subjects with benzodiazepine-refractory status epilepticus*

If you are acting as a representative for another person to participate in this study, “you” throughout this document refers to that person.

INVITATION TO TAKE PART:

You are being invited to take part in a research project called, the *Established Status Epilepticus Treatment Trial (ESETT): A multicenter, randomized, double-blind, comparative effectiveness study of fosphenytoin, levetiracetam, and valproic acid in subjects with benzodiazepine-refractory status epilepticus* conducted by **PI NAME**, MD at **SITE NAME**.

Your decision to take part is voluntary. You may refuse to take part. You may choose to stop taking part at any time. A decision not to take part or to stop being a part of the research project will not change the services that are available to you. You may refuse to answer any written or oral questions you wish.

This research project has been reviewed by the Committee for the Protection of Human Subjects (CPHS) of the **SITE NAME**.

DESCRIPTION OF RESEARCH:

PURPOSE: The purpose of this study is to find out which of three study medicines is safer and more effective at stopping seizures when the seizure hasn't stopped with medications which are initially used to stop seizures. Most seizures stop either without treatment or with medications such as valium. Stopping seizures quickly is important, because longer seizures increase the risk of permanent injuries or even death. When seizures continue longer than 5 minutes, this is called status epilepticus.

The three study medicines are fosphenytoin, levetiracetam and valproic acid.

All three drugs are commonly prescribed by doctors for treating seizures. Levetiracetam and valproic acid are investigational drugs. These drugs have been approved by the Food and Drug Administration (FDA) to prevent seizures in adults and children, but not to stop prolonged seizures as in status epilepticus. Doctors have used both of these drugs “off-label” to safely stop prolonged seizures for years. Fosphenytoin has been approved by the FDA to stop prolonged seizures in adults, but not children. Doctors have also used fosphenytoin to safely stop seizures in children for years.

In this situation, off-label means the medicine's label does not specifically say that it can be used for treating prolonged seizures. Doctors can use their best judgment to prescribe

medicines for any patient, even if the medicines are not FDA-labeled for that particular use.

When a patient comes to the hospital having seizures, the treating doctor usually gives the patient a benzodiazepine (like valium) in a vein. If the seizure does not stop, many patients are treated with fosphenytoin, levetiracetam or valproic acid. It is not known which of these drugs is best at stopping status epilepticus, so doctors use their judgment to choose one of these drugs.

Children and adults who continue to have seizures despite have been treated with a benzodiazepine (such as valium) may be enrolled in this study. Children are included in this study because the treatments being studied are used to treat seizures in both children and adults. About 800 subjects at around 100 institutions across the United States will participate in this study. Enrollment will take place over 5 or more years.

PROCEDURE: Everyone in this study will be treated with a medication for their seizure. Everyone will get a dose of one of the study drugs through an intravenous catheter (a tiny plastic tube directly into a vein, an IV). Initially 1/3 of patients will get fosphenytoin, 1/3 levetiracetam and 1/3 valproic acid. As the study goes on, a higher proportion of patients will be randomized to the drug or drugs performing better. Furthermore, if one drug does not appear to be as effective as the others, it will not be given any more.

Noone will be excluded from participation based on gender, race, color, economic status, or national origin.

Because we could not delay treating your seizures, you already were treated with the study medication. Here is what has happened so far:

A doctor examined you and treated you medically. The doctor determined that you did not have another reason for having a seizure that could be treated easily, like low blood sugar.

After a doctor determined you were eligible for the study, you received one of the three study medicines (either fosphenytoin, levetiracetam or valproic acid). You were randomly assigned (like flipping a coin) ahead of time to one of the three treatment groups, but neither you nor your doctor know which study medicine you received.

The doctor may have given you additional medicine to stop the seizure or prevent additional seizures. As part of your regular medical care, the doctor may have given you one of the three medicines being studied, or a different medicine.

Now, you are being asked to decide whether or not to continue participating in this study.

Continuing in the research does not involve getting any more study medications than you have already been given. Continuing does not involve any more tests or procedures related to this study.

If you decide to continue in the study, we will record medical information about you until you are discharged from the hospital. The information that we have or will collect includes demographics, heart rate, blood pressure, temperature, medical history, seizure

recurrence, ED treatment, adverse events, and the dates of hospital admission and discharge.

TIME COMMITMENT: None. No time commitment from is required from you if you choose to participate further. Your participation in the study is over when you are discharged from the hospital.

POTENTIAL BENEFITS: Because we do not know which of the study drugs is better, you may benefit from receiving a better medicine, but this is not guaranteed. You may not get any benefit from being in this research study. However, the information that we obtain from this study may benefit people patients (possibly including you) in the future. The information may help us to provide more effective treatments in the future for patients with seizures.

RISKS AND/OR DISCOMFORTS: The study medicines, fosphenytoin, levetiracetam and valproic acid, are all anti-convulsants, but they work in different ways. All the study drugs are commonly used to treat prolonged seizures, but there are risks related to these medicines. The risks of the study medicines are similar to those that you might have experienced if you received treatment for prolonged seizures outside of this study.

The risks of the study medicines include:

Fosphenytoin:

- Low blood pressure
- Excessive sedation (drowsiness)
- Dizziness
- Skin rash
- Pain, discomfort, or inflammation where you got the injection in the vein

Levetiracetam:

- Drowsiness
- Dizziness
- Behavioral changes (nervousness, confusion, aggression)
- Pain, discomfort, or inflammation where you got the injection in the vein

Valproic acid:

- Dizziness
- Excessive sedation (drowsiness)
- Skin rash
- Pain, discomfort, or bruising where you got the shot in the vein

All the medications could cause an allergic reaction. There may be other risks if you are pregnant. Having seizures may cause risk to the fetus. All of these drugs may cause damage to the fetus. There may be other risks of fosphenytoin, levetiracetam and

valproic acid to a pregnant woman or a fetus that are not yet known. We will exclude women who are known to be pregnant, but it will not be possible to obtain the results of a pregnancy test before enrollment. If you are currently pregnant, you should inform the investigator and your doctor.

There is also a risk of breach of confidentiality. We will do our best to keep all of your medical information that we collect confidential. We will keep your study information in a secure location during the course of the study. Only the members of the study team and the persons and entities listed below will have access to your medical information for the study.

You may experience some, all, or none of the risks related to the study medicine that you received and the study device. There may be other unforeseeable risks related to your participation in this study.

ALTERNATIVES: The alternative to continuing to participate is to not continue to take part in the study. If you decide not to continue participating, your decision will not interfere with your current or future medical care.

STUDY WITHDRAWAL: Being in this study is entirely voluntary. You are free to withdraw your consent at any time during the study with no impact on your further care. Your study doctor may decide to stop this study for either medical or other reasons (such as the research is not beneficial, or if it appears to be medically harmful to you, or for administrative reasons).

NEW FINDINGS: You may ask and will receive answers to any questions during the course of the study. You will be informed of any significant new findings that may develop during the course of this research study that may relate to your willingness to continue in this study.

IN CASE OF INJURY: If you suffer any injury as a result of taking part in this research study, please understand that nothing has been arranged to provide free treatment of the injury or any other type of payment. However, all needed facilities, emergency treatment and professional services will be available to you. You should report any injury to **SITE PI, MD** at **SITE NAME, SITE PI PHONE NUMBER** and to the Committee for the Protection of Human Subjects at **CPHS PHONE NUMBER**. You will not be giving up any of your legal rights by signing this consent form.

COSTS, REIMBURSEMENT, AND COMPENSATION: You will not be paid to be in the study. You will not be charged for study activities during the study. The study drug will be provided free of charge.

If you received a bill that you believe is related to your taking part in this research study, please contact **SITE PI, MD PHONE NUMBER**.

CONFIDENTIALITY: To protect your privacy, the information about you collected for this study will be coded with a special study number. Your name and identifying information will not be included with any information in the study database or otherwise used outside of **SITE NAME** and individuals listed here:

- **SITE NAME**
- University of Michigan and affiliates
- University of Virginia and affiliates
- Data Coordination Unit of the Medical University of South Carolina
- National Institutes of Health and affiliates
- Food and Drug Administration
- ESETT Data and Safety Monitoring Board

Identifying information includes your name, address, telephone number, medical record number, and any other information that could directly identify you. A file that links your special study number and your name will be stored in a locked cabinet in a locked office.

Health information about you collected for the study may be stored electronically or on paper. The information stored on the computer is kept in password protected files that are maintained on password protected computers. The information stored on paper is stored in a locked file cabinet in a locked office. Health information about you collected for the study may include copies of part of your chart, which are used to check that information put in the study data base is correct. The study team may keep a copy or have a facsimile sent and kept in a secure location at **SITE NAME**. If sent by fax, a secure number and machine used only for this purpose is required.

Your records will be kept for as long as necessary for purposes of the research study. During that time they will be kept confidential to the extent permitted by law. The results of this study could be published in an article, but would not include any information that would let others know who you are. Study results will be published by group only.

QUESTIONS: If you have further questions concerning matters related to this research, please contact:

Investigator's Name: SITE PI, MD
Telephone Number: PHONE NUMBER
Research Nurse Coordinator: STUDY COORDINATOR
Telephone Number: PHONE NUMBER

SIGNATURES: Sign below only if you understand the information given to you about the research and choose to take part. Make sure that any questions have been answered and that you understand the study. If you have any questions or concerns about your rights as a research subject, call the Committee for the Protection of Human Subjects at (713)500-7942. If you decide to take part in this research study, a copy of this signed consent form will be given to you.

Participant's Name

Signature and Date/Time

OR

Legal Authorized Name

Signature and Date/Time

Person Obtaining Consent Name

Signature and Date/Time

CPHS STATEMENT: THIS STUDY (HSC-_____) has been reviewed by the Committee for the Protection of Human Subjects (CPHS) of the **SITE NAME**. For any questions about research subject's rights, or to report a research-related injury, call the CPHS at **CPHS PHONE NUMBER**

For other questions, please call us at **CPHS PHONE NUMBER**