Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Kapur J, Elm J, Chamberlain JM, et al. Randomized trial of three anticonvulsant medications for status epilepticus. N Engl J Med 2019;381:2103-13. DOI: 10.1056/NEJMoa1905795

A clinical trial of three anticonvulsant medications for status epilepticus

The Established Status Epilepticus Treatment Trial (ESETT)

Supplementary Appendix - Table of Contents

The Neurological Emergencies Treatment Trials (NETT) and Pediatric Emergency Care Applied Research Network (PECARN) investigators are:

UVA Scientific Coordinating Center
Jaideep Kapur, Emily Gray, Sonya Gunter, Amy Fansler

Clinical Coordinating Center
Robert Silbergleit, William Barsan, Valerie Stevenson, Erin Bengelink, Deneil Harney, Mickie Speers, Joy Black, Natalie Fisher, Donna Harsh, Arthi Ramakrishnan, Lindsey Harris, Nia Bozeman, Aimee Spiteri

Statistical Data Management Center
Yuko Palesch, Jordan Elm, Caitlyn Meinzer, Holly Tillman, Wenle Zhao, Qi Pauls, Chris Arnaud, Catherine R. Dillon, Jodie Riley, Teldon Alford, Cassidy Conner, Ellen Underwood

Pediatric Emergency Care Applied Research Network (PECARN)
James Chamberlain, Kate Shreve, Peter Dayan, Nathan Kuppermann, Kurt Denninghoff, Rachel Stanley, Richard Ruddy, E. Brooke Lerner, J. MIchael Dean, Charles Casper, Lise Nigrovic, Walt Schalick, Doug Nelson, Bobbe Thomas.

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Phenomenology Core
Shlomo Shinnar, Dan Lowenstein, Hannah Cock, Nathan Fountain

Pharmacology Core
James Cloyd, Lisa Coles, Abhi Sathe

National Institutes of Health
Scott Janis, Robin Conwit, Adam Hartman, Brandy Fureman

Other Study Leadership and Advisors (not previously indicated)
Eugen Trinka, David Treiman, Tom Bleck

NETT Hubs and PECARN Sites (ordered by number of subjects enrolled)

Grady Memorial Hospital (36) U10NS059032
Hub Principal Investigator: David Wright
Trial Principal Investigators: Jonathan Ratcliff
Primary Study Coordinators: Alex Hall, Alaina Williams

Children's Medical Center UTSW, PECARN (28)
Trial Principal Investigators: Pamela Okada
Primary Study Coordinators: Amanda Lee, Natasha Truesdale

Children's Healthcare of Atlanta at Egleston (26) U10NS059032
Hub Principal Investigator: David Wright

Trial Principal Investigators: Jonathan Ratcliff, Harold Simon
Primary Study Coordinators: Alex Hall, Nicholas Stanley

Cincinnati Children's Hospital Medical Center, PECARN (23)
Trial Principal Investigators: Lynn Babcock, Steven Chan
Primary Study Coordinators: Mhadhumithaa Naresh, Venita Robinson

Primary Children's Hospital, PECARN (23)
Trial Principal Investigators: Maija Holsti
Primary Study Coordinators: Jieun Hwang, Kristi Carlston, Michael Dela Cruz, Toni Harbour, Reena Karki

University of Kentucky Hospital (23)
Hub Principal Investigator: Roger Humphries
Trial Principal Investigators: Roger Humphries
Primary Study Coordinators: Theresa Mims, Joann Short

Nationwide Children's Hospital, PECARN (22)
Trial Principal Investigators: Daniel M. Cohen
Primary Study Coordinators: Amy Nowakowski, Cindy Lin, Erin Fisher Kenny

Memorial Hermann Texas Medical Center (19) U10NS058930
Hub Principal Investigator: Elizabeth Jones
Trial Principal Investigators: Elizabeth Jones
Primary Study Coordinators: Misty Ottman

Rhode Island Hospital, PECARN (16)
Trial Principal Investigators: Dale Steele, Lisa H. Merck
Primary Study Coordinators: Erin Ryan, Kristin Basso, Lesley (Wasilewski) D'Urso

Temple University Hospital (16) U10NS059039
Hub Principal Investigator: Nina Gentile
Trial Principal Investigators: Derek Isenberg, Nina Gentile
Primary Study Coordinators: Hannah Reimer, Vernon Sayoc Kalugdan

San Francisco General Hospital (14) U10NS058931
Hub Principal Investigator: Claude Hemphill
Trial Principal Investigators: Claude Hemphill, Debbie Yi Madhok
Primary Study Coordinators: Jeany Duncan, Dominica Randazzo

Children's National Medical Center, PECARN (12)
Trial Principal Investigators: Kathleen Brown
Primary Study Coordinators: Bobbe Thomas, Gina Nauman, Matthew Ledda, Sean Gillen, Vanessa Grant

Stanford University Medical Center (11) U10NS058929
Hub Principal Investigator: James Quinn
Trial Principal Investigators: James Quinn
Primary Study Coordinators: Anita Visweswaran, Rosen Mann

UC Davis Children's Hospital, PECARN (11)
Trial Principal Investigators: Cheryl Vance, Daniel K. Nishijima
Primary Study Coordinators: Kyle Pimenta

University of Michigan University Hospital, PECARN (11)
Trial Principal Investigators: Alexander J. Rogers
Primary Study Coordinators: Noelle Herzog

A.I. duPont Hospital for Children, PECARN (10)
Hub Principal Investigator: Jonathan Bennett
Trial Principal Investigators: Jonathan Bennett
Primary Study Coordinators: Christine Eisenhart

University of Cincinnati Medical Center (10) U10NS058982
Hub Principal Investigator: Opeolu Adeoye
Trial Principal Investigators: Jason McMullan, Brandon Foreman
Primary Study Coordinators: Sara Keegan

Children's Hospital of Wisconsin, PECARN (9)
Trial Principal Investigators: Danny Thomas
Primary Study Coordinators: Duke Wagner

Hennepin County Medical Center, (9) U10NS058994
Hub Principal Investigator: Michelle Biros
Trial Principal Investigators: Brian Driver
Primary Study Coordinators: Audrey Hendrickson, Jamie Stang

Henry Ford Hospital (9) U10NS058974
Hub Principal Investigator: Christopher Lewandowski
Trial Principal Investigators: Christopher Lewandowski, Joseph Miller
Primary Study Coordinators: Kaleem Chaudhry, Shannen Berry

Oregon Health & Science University Hospital (9) U10NS058940
Hub Principal Investigator: Craig Warden
Trial Principal Investigators: Craig Warden
Primary Study Coordinators: Rachel Blake, Jennifer NB Cook

Einstein Medical Center (8) U10NS059039
Hub Principal Investigator: Nina Gentile
Trial Principal Investigators: Erin Sabolick, Nina Gentile
Primary Study Coordinators: Antoine Selman

Crozer-Chester Medical Center (7) U10NS059039
Hub Principal Investigator: Nina Gentile
Trial Principal Investigators: Derek Isenberg, Katrina Kissman
Primary Study Coordinators: Hannah Reimer, Vernon Sayoc Kalugdan

Lyndon B. Johnson General Hospital (7) U10NS058930
Hub Principal Investigator: Elizabeth Jones
Trial Principal Investigators: Elizabeth Jones
Primary Study Coordinators: Misty Ottman, Monica Moore

University of Virginia Medical Center (7) U01NS088034
Trial Principal Investigators: J. Stephen Huff
Primary Study Coordinators: Lea Becker

NYP Columbia University Medical Center (6) U10NS059062
Hub Principal Investigator: Jan Claassen
Trial Principal Investigators: Jan Claassen
Primary Study Coordinators: Angela Velazquez, Cristina Falo

UCSF Medical Center (6) U10NS058931
Hub Principal Investigator: Claude Hemphill
Trial Principal Investigators: Claude Hemphill, Zlatan Coralic, Debbie Yi Madhok
Primary Study Coordinators: Jeany Duncan, Dominica Randazzo

UCSF Benioff Children's Hospital (5) U10NS058931
Hub Principal Investigator: Claude Hemphill
Trial Principal Investigators: Claude Hemphilll, Debbie Yi Madhok, Jackie Grupp-Phelan
Primary Study Coordinators: Jeany Duncan

Children's Hospital of Philadelphia (4) U10NS058960
Hub Principal Investigator: Jill Baren
Trial Principal Investigators: Angela Ellison
Primary Study Coordinators: Ashley Woodford, Ima Samba, Marlena Kittick

Children's Hospital of Pittsburgh UPMC, PECARN (4)
Trial Principal Investigators: Robert W. Hickey
Primary Study Coordinators: Rose Azrak

Hahnemann University Hospital (4) U10NS059039
Hub Principal Investigator: Nina Gentile
Trial Principal Investigators: Ralph Riviello
Primary Study Coordinators: John Massey, Lisa Bonacquisti, Vernon Sayoc Kalugdan

Maimonides Medical Center (4) U10NS080377
Hub Principal Investigator: Steven Levine
Trial Principal Investigators: Sergey Motov, Christian Fromm
Primary Study Coordinators: Rukhsana Hossain, Antonios Likourezos, Illya Pushkar,

OSU Wexner Medical Center (4) U10NS080368
Hub Principal Investigator: Thomas Terndrup
Trial Principal Investigators: Thomas Terndrup
Primary Study Coordinators: Salman Khaliqdina, Michael Hill

Regions Hospital (4) U10NS058994
Hub Principal Investigator: Michelle Biros
Trial Principal Investigators: Bjorn Peterson, Michelle Biros
Primary Study Coordinators: Alexia Terwilliger, Joseph Holm, Kyra Wicklund, Sandi Wewerka

Sinai-Grace Hospital (4) U10NS059012
Hub Principal Investigator: Robert Welch
Trial Principal Investigators: Claire Pearson, Vijaya Arun Kumar
Primary Study Coordinators: Farhan Ayaz, Saikat Bhuiyan, Valerie H. Mika

Texas Children's Hospital, PECARN (4)
Trial Principal Investigators: Daniel Rubalcava
Primary Study Coordinators: Juan Mondragon, Victor Gonzalez, Maha Khalil

University Health System University Hospital, San Antonio (4) U10NS058930
Hub Principal Investigator: Elizabeth Jones
Trial Principal Investigators: Lola Morgan
Primary Study Coordinators: Floyd Jones, Lorraine Dishman

University of Minnesota Medical Center Hospital (4) U10NS058994
Hub Principal Investigator: Michelle Biros
Trial Principal Investigators: Thomas Henry (Neuro), Ford Erickson (ED)
Primary Study Coordinators: Abbey Staugaitis, Chloe Lawyer, Kathleen Miller

UPMC Presbyterian Hospital (4) U10NS080371
Hub Principal Investigator: Clif Callaway
Trial Principal Investigators: Alexandra Urban
Primary Study Coordinators: Sara DiFiore, Peter Adams, Brian Baum

Children's Hospital of Michigan, PECARN (3)
Trial Principal Investigators: Claire Pearson, Vijaya Arun Kumar
Primary Study Coordinators: Kristina Hart, Sarah Parker

Christiana Care Health Services (3) U10NS058960
Hub Principal Investigator: Jill Baren
Trial Principal Investigators: Jason Nomura
Primary Study Coordinators: Barbara Davis

Froedtert Memorial Lutheran Hospital (3) U10NS058927
Hub Principal Investigator: Tom Aufderheide
Trial Principal Investigators: Tom Aufderheide
Primary Study Coordinators: Amanda Emmrich, Melissa Mena, Jacob Labinski

Hackensack University Medical Center (3) U10NS059039
Hub Principal Investigator: Nina Gentile
Trial Principal Investigators: Chinwe Ogedegbe,
Primary Study Coordinators: Diana McCarthy, Arelis Villot-Santiago

Massachusetts General Hospital (3) U10NS080369
Hub Principal Investigator: Joshua Goldstein
Trial Principal Investigators: Eric S. Rosenthal
Primary Study Coordinators: Abigail Cohen, Chun Mei Su, Greg Tirrell, Melissa Howell

St. Louis Children's Hospital, PECARN (3)
Trial Principal Investigators: Angela Lumba, Kim Quayle, Sri Chinta
Primary Study Coordinators: Debra Robinson

University of Minnesota Masonic Children's Hospital (3) U10NS058994
Hub Principal Investigator: Michelle Biros
Trial Principal Investigators: Thomas Henry (Neuro), Marissa Hendrickson (ED)Primary Study Coordinators: Chloe Lawyer, Dan Nerheim, Eric Jaton

Detroit Receiving Hospital (2) U10NS059012
Hub Principal Investigator: Robert Welch
Trial Principal Investigators: Claire Pearson, Vijaya Arun Kumar
Primary Study Coordinators: Farhan Ayaz, Saikat Bhuiyan, Valerie H. Mika

Hasbro Children's Hospital, PECARN (2)
Trial Principal Investigators: Dale Steele, Lisa Merck
Primary Study Coordinators: Erin Ryan, Kristin Basso, Lesley (Wasilewski) D'Urso

Hospital of the University of Pennsylvania (2) U10NS058960
Hub Principal Investigator: Jill Baren
Trial Principal Investigators: Jill Baren
Primary Study Coordinators: Barbara Biney, Christopher Gibson, Erica Dahlmeier, Katherine (Lamond) Blackburn, Oluwarotimi (Tim) Vqughan-Ogunlus

Kings County Hospital Center (2) U10NS080377
Hub Principal Investigator: Steven Levine
Trial Principal Investigators: Shahriar Zehtabchi, Richard Sinert
Primary Study Coordinators: Bryce Petty

NYP Morgan Stanley Children's Hospital, PECARN (2)
Trial Principal Investigators: Maria Kwok
Primary Study Coordinators: Brooke Peery, Julie Ochs, Leonor Suarez

Penn Presbyterian Medical Center (2) U10NS058960
Hub Principal Investigator: Jill Baren
Trial Principal Investigators: Jill Baren
Primary Study Coordinators: Barbara Biney, Erica Dahlmeier, Katherine (Lamond) Blackburn, Oluwarotimi (Tim) Vaughan-Ogunlusi

Temple University Hospital Episcopal Campus (2) U10NS059039
Hub Principal Investigator: Nina Gentile
Trial Principal Investigators: Derek Isenberg, Nina Gentile
Primary Study Coordinators: Hannah Reimer, Vernon Sayoc Kalugdan

University of Utah Healthcare (2) U10NS058940
Hub Principal Investigator: Craig Warden
Trial Principal Investigators: Scott Youngquist
Primary Study Coordinators: Margaret Carlson

Pennsylvania Hospital (1) U10NS058960
Hub Principal Investigator: Jill Baren
Trial Principal Investigators: Jill Baren
Primary Study Coordinators: Barbara Biney, Christopher Gibson, Erica Dahlmeier, Oluwarotimi (Tim) Vaughan-Ogunlusi

SUNY Downstate Medical Center (1) U10NS080377
Hub Principal Investigator: Steven Levine
Trial Principal Investigators: Shahriar Zehtabchi
Primary Study Coordinators: Nadege Gilles, Sarah (Zelonis) Weingast

University of Maryland Medical Center (1) U10NS058932
Hub Principal Investigator: Barney Stern
Hub/Trial Principal Investigators: Jennifer Hopp
Primary Study Coordinators: Virginia Ganley

VCU Medical Center (1) U10NS058966
Hub Principal Investigator: Joseph Ornato

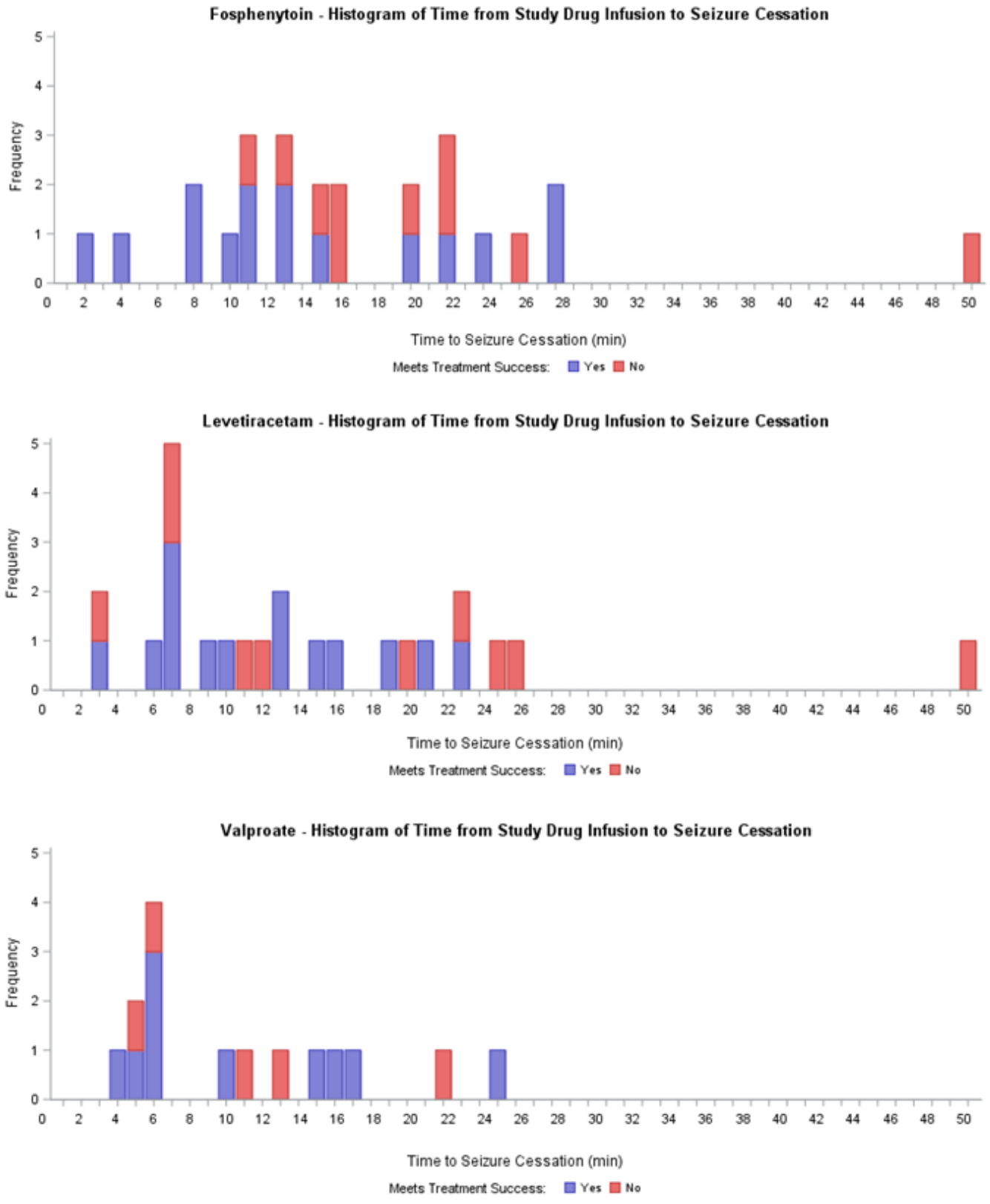

Figure S1. Time from start of study drug infusion to seizure cessation in those with and without success on primary outcome.

This figure shows the number of enrollments that had seizures cessation at each minute within the first hour from the start of study drug infusion. Exact time of seizure cessation was only determined from the subset of enrollments for which clinical teams marked the event in real time on the study voice data logger. (n=64)

Table S1. Serious adverse events by MedDRA preferred term

MedDRA preferred term	# EVENTS				# SUBJECTS				% SUBJECTS			
	LEV	FOS	VPA	Total	LEV	FOS	VPA	Total	LEV	FOS	VPA	Total
Total	**98**	**78**	**72**	**248**	**64**	**57**	**46**	**167**	**42.7%**	**45.6%**	**36.8%**	**41.8%**
Convulsion	32	26	23	81	30	25	23	78	20.0%	20.0%	18.4%	19.5%
Depressed level of consciousness	15	12	9	36	15	12	9	36	10.0%	9.6%	7.2%	9.0%
Respiratory depression	10	16	8	34	10	15	8	33	6.7%	12.0%	6.4%	8.3%
Hypotension	4	7	6	17	4	7	6	17	2.7%	5.6%	4.8%	4.3%
Pneumonia	4	2	2	8	4	2	2	8	2.7%	1.6%	1.6%	2.0%
Respiratory failure	1	2	4	7	1	2	4	7	0.7%	1.6%	3.2%	1.8%
Sepsis	1	2	2	5	1	2	2	5	0.7%	1.6%	1.6%	1.3%
Encephalopathy	4	0	1	5	4	0	1	5	2.7%	0.0%	0.8%	1.3%
Cardiac arrest	2	1	0	3	2	1	0	3	1.3%	0.8%	0.0%	0.8%
Rhabdomyolysis	3	0	0	3	3	0	0	3	2.0%	0.0%	0.0%	0.8%
Cerebral infarction	0	2	1	3	0	2	1	3	0.0%	1.6%	0.8%	0.8%
Conversion disorder	2	1	0	3	2	1	0	3	1.3%	0.8%	0.0%	0.8%
Deep vein thrombosis	1	0	2	3	1	0	2	3	0.7%	0.0%	1.6%	0.8%
Atrial fibrillation	0	1	1	2	0	1	1	2	0.0%	0.8%	0.8%	0.5%
Device malfunction	0	0	2	2	0	0	2	2	0.0%	0.0%	1.6%	0.5%
Hypothermia	0	0	2	2	0	0	2	2	0.0%	0.0%	1.6%	0.5%
Septic shock	1	0	1	2	1	0	1	2	0.7%	0.0%	0.8%	0.5%
Hypoglycemia	1	0	1	2	1	0	1	2	0.7%	0.0%	0.8%	0.5%
Intra-cardiac thrombus	0	0	1	1	0	0	1	1	0.0%	0.0%	0.8%	0.3%
Supraventricular tachycardia	1	0	0	1	1	0	0	1	0.7%	0.0%	0.0%	0.3%
Dysphagia	1	0	0	1	1	0	0	1	0.7%	0.0%	0.0%	0.3%
Gastrointestinal hemorrhage	0	1	0	1	0	1	0	1	0.0%	0.8%	0.0%	0.3%
Intestinal ischemia	0	1	0	1	0	1	0	1	0.0%	0.8%	0.0%	0.3%
Retroperitoneal hemorrhage	0	0	1	1	0	0	1	1	0.0%	0.0%	0.8%	0.3%
Small intestinal obstruction	1	0	0	1	1	0	0	1	0.7%	0.0%	0.0%	0.3%
Infusion site extravasation	0	0	1	1	0	0	1	1	0.0%	0.0%	0.8%	0.3%
Hepatic failure	1	0	0	1	1	0	0	1	0.7%	0.0%	0.0%	0.3%
Bacteremia	0	1	0	1	0	1	0	1	0.0%	0.8%	0.0%	0.3%
Clostridium difficile colitis	1	0	0	1	1	0	0	1	0.7%	0.0%	0.0%	0.3%
Endocarditis	0	1	0	1	0	1	0	1	0.0%	0.8%	0.0%	0.3%
Respiratory tract infection	1	0	0	1	1	0	0	1	0.7%	0.0%	0.0%	0.3%
Accidental overdose	0	1	0	1	0	1	0	1	0.0%	0.8%	0.0%	0.3%
Liver function test abnormal	0	0	1	1	0	0	1	1	0.0%	0.0%	0.8%	0.3%
Hypokalemia	1	0	0	1	1	0	0	1	0.7%	0.0%	0.0%	0.3%
Muscle hemorrhage	1	0	0	1	1	0	0	1	0.7%	0.0%	0.0%	0.3%
Cerebrovascular accident	1	0	0	1	1	0	0	1	0.7%	0.0%	0.0%	0.3%

Cerebrovascular spasm	1	0	0	1	1	0	0	1	0.7%	0.0%	0.0%	0.3%
Hemorrhage intracranial	1	0	0	1	1	0	0	1	0.7%	0.0%	0.0%	0.3%
Hypoxic-ischemic encephalopathy	0	0	1	1	0	0	1	1	0.0%	0.0%	0.8%	0.3%
Agitation	1	0	0	1	1	0	0	1	0.7%	0.0%	0.0%	0.3%
Delirium	1	0	0	1	1	0	0	1	0.7%	0.0%	0.0%	0.3%
Urinary retention	0	0	1	1	0	0	1	1	0.0%	0.0%	0.8%	0.3%
Aspiration	1	0	0	1	1	0	0	1	0.7%	0.0%	0.0%	0.3%
Epistaxis	1	0	0	1	1	0	0	1	0.7%	0.0%	0.0%	0.3%
Hypoxia	1	0	0	1	1	0	0	1	0.7%	0.0%	0.0%	0.3%
Obstructive airways disorder	0	0	1	1	0	0	1	1	0.0%	0.0%	0.8%	0.3%
Pleural effusion	0	1	0	1	0	1	0	1	0.0%	0.8%	0.0%	0.3%
Stridor	1	0	0	1	1	0	0	1	0.7%	0.0%	0.0%	0.3%

LEV is levetiracetam. FOS is fosphenytoin. VPA is valproate

Table S2. Pairwise treatment group differences in the primary outcome

Pairwise Comparison	Absolute Difference in proportion (95% credible intervals)	Probability treatment groups are different
LEV – FOS	1.9% (-10.0%, 13.9%)	Pr(LEV > FOS) = 0.62
VPA - FOS	1.3% (-11.1%, 13.8%)	Pr(VPA > FOS) = 0.58
LEV – VPA	0.06% (-11.3%, 12.5%)	Pr(LEV > VPA) = 0.54

LEV is levetiracetam. FOS is fosphenytoin. VPA is valproate

Table S3. Etiology of established status epilepticus as adjudicated by the phenomenology core

Precipitant of Enrolling Episode, n (%)	Levetiracetam (N=145)	Fosphenytoin (N=118)	Valproate (N=121)	Total
Unprovoked	50 (34.4)	42 (35.5)	34 (28.0)	126 (32.8)
Other *	18 (12.4)	22 (18.6)	21 (17.3)	61 (15.8)
Febrile illness	21 (14.5)	13 (11.0)	25 (20.7)	59 (15.4)
Anti-epileptic drug withdrawal / noncompliance	24 (16.6)	15 (12.7)	16 (13.2)	55 (14.3)
Toxic (alcohol/drug withdrawal, poisoning, etc.)	12 (8.3)	8 (6.8)	8 (6.6)	28 (7.3)
Insufficient information to determine - idiopathic	7 (4.8)	3 (2.5)	9 (7.4)	19 (4.9)
Acute stroke / hemorrhage	6 (4.1)	8 (6.8)	3 (2.5)	17 (4.4)
CNS tumor	2 (1.4)	4 (3.4)	2 (1.7)	8 (2.1)
CNS infection	3 (2.1)	1 (0.8)	2 (1.7)	6 (1.6)
Metabolic (hypoglycemia, hyponatremia, etc.)	2 (1.4)	2 (1.7)	1 (0.8)	5 (1.3)

* “Other” most frequently included afebrile and non-CNS infections, combinations of etiology, subacute stroke or hemorrhage, vasculitis, other encephalopathy, ventricular-peritoneal shunt failure, or sleep deprivation

Table S4. Analysis of primary outcome and interaction with baseline covariates

Covariate	p-value for test of all interactions*	p-value for test that random effect is 0
Sex (Male or Female)	0.76	N/A
Race (White, Black, Other)	0.98	N/A
Ethnicity (Hispanic, Not Hispanic)	0.92	N/A
Time from Onset (minutes)	0.33	N/A
Etiology (Non-epileptic spell, Seizure/Status epilepticus, Unable to determine)	0.60	N/A
Site (random effect)	N/A	1

Baseline covariates were evaluated individually in logistic regression models of the primary outcome that included treatment group indicators, the main effect of the covariate, and interaction terms with treatment. Site was handled as a random effect in a generalized linear mixed model with logit link with two indicators for treatment groups.

*Joint test of all interaction terms with treatment groups is a 2 degrees of freedom chi-squared test except for etiology and race which are 4 degree of freedom tests.

Table S5, Criteria for determination of primary outcome						
Treatment	Additional anticonvulsant medications (including intubations)?,		Clinically apparent seizures at 60 minute assessment?,		Improving responsiveness at 60 minute assessment?,	
Levetiracetam n=145	Y	52**	Y	14	Y	4
					N	10
			N	37	Y	15
					N	22
	N	93	Y	6	Y	1
					N	5
			N	87	Y	68
					N	19
Fosphenytoin n=118	Y	46	Y	6	Y	1
					N	5
			N	40	Y	13
					N	27
	N	72	Y	2	Y	0
					N	2
			N	70	Y	53
					N	17
Valproate n=121	Y	46	Y	8	Y	3
					N	5
			N	38	Y	15
					N	23
	N	75	Y	3	Y	1
					N	2
			N	72	Y	56
					N	16

Y = yes, N = no, **One subject receiving levetiracetam received additional anticonvulsant medications prior to 60 minutes, and the clinically apparent seizures and improving responsiveness at 60 minutes assessment was marked as “Unknown”. Blue background indicates treatment success on primary outcome.

Table S6. Computations of the futility analysis

Look	Predictive probability that an arm is identified as best / worst at maximum sample size*			Predictive probability that any arm Wins**
	Levetiracetam	Fosphenytoin	Valproate	
Analysis after 400th Enrollment (N=384 unique subjects)	.0013 / .0008	.002 / .0027	.0022 / .0013	0.01

* Maximum sample size was assumed to be 720 unique subjects for calculation of the predictive probabilities.

** This represents the sum of the predictive probabilities arm is best/worst at the maximum sample size for each of the 3 groups. If this sum is < 5%, the trial stops for futility.

Table S7. Post hoc analysis of time to seizure cessation by adjudication and real time response to query

	Levetiracetam	Fosphenytoin	Valproate
Seizure cessation within 20 minutes of trial drug initiation among patients with treatment success, n (%)*	53 (77.9%) n=68	43 (81.1%) n=53	43 (78.2%) n=55*

* Seizure cessation within 20 minutes was unable to be determined for 1 patient

Summary Description of Statistical Methods for Primary Analysis

The primary objective of ESETT was to identify the most effective and/or the least effective treatment among three commonly used second-line therapies for status epilepticus within an emergency department setting. A Bayesian approach was used to estimate the probability that each treatment is the best or worst, with a prior assumption that all three treatments were equally likely to be the best. We chose this approach, rather than a Bayes factor or a frequentist testing approach, because it allowed us to directly answer the question of clinical interest for this comparative effectiveness trial: Which treatment is best? Or, if there is no single best treatment, is there a worst treatment?

Prior to observing study data all three treatments were considered to be equally likely to be the most effective or least effective treatment. Each of the three treatment arms is modeled independently. Using Bayes theorem, the prior, likelihood, and data, we found a posterior distribution for each treatment arm. We assumed a noninformative Uniform(0,1) prior, (i.e. Beta(1,1)) and updated based upon the observed binomial data using a conjugate beta-binomial model. From these three posterior distributions, the probability that each treatment is the most effective (least effective) treatment was calculated. In brief, we randomly drew from the three posteriors, repeatedly (106 iterations), and counted the number of times a treatment was better than the other two, out of all the iterations, to calculate the probability that a given treatment was the best. The same approach was taken to calculate the probability that a given treatment was the worst. To control the false positive rate, we pre-specified criteria for trial success. Specifically, the probability that a treatment was the best (or worst) had to be greater than 0.975, in order to claim we have identified the best (or worst).

The threshold of 0.975 was chosen by convention (analogous to alpha of 0.025 one-sided comparison), and because an extensive simulation study demonstrated that, with this threshold and study design, the overall probability of a Type I error for identifying a best or worst treatment was less than 5%. The type I error probability (false positive rate) of this trial is the probability of incorrectly identifying a most effective treatment and/or incorrectly identifying a least effective treatment. In the simulations we empirically determined the type I error rate for this design by the number of times that one treatment was identified as the best and/or one treatment was identified as the worst (i.e. the probability that a treatment was the best (worst) was > 0.975) when in fact it was not the best/worst treatment, divided by the total number of iterations. Unlike a study in which a success can be achieved in numerous different ways (e.g. multiple doses versus a control or primary multiple endpoints), here one and only one treatment could be identified as best and it cannot also simultaneously be identified as the worst treatment. However, the multiple interim analyses would lead to multiplicity. Starting adaptive randomization prior to the possibility of early stopping likely may have decreased the probability of a Type I error.