Association of guideline publication and delays to treatment in pediatric status epilepticus

Iván Sánchez Fernández, MD, MPH, MBI, Nicholas S. Abend, MD, MSCE, Marta Amengual-Gual, MD, Anne Anderson, MD, Ravindra Arya, MD, DM, Cristina Barcia Aguilar, MD, James Nicholas Brenton, MD, Jessica L. Carpenter, MD, Kevin E. Chapman, MD, Justice Clark, MPH, Raquel Farias-Moeller, MD, William D. Gaillard, MD, Marina Gainza-Lein, MD, Tracy Glauser, MD, Joshua Goldstein, MD, Howard P. Goodkin, MD, PhD, Réjean M. Guerriero, DO, Yi-Chen Lai, MD, Tiffani McDonough, MD, Mohamad A. Mikati, MD, Lindsey A. Morgan, MD, Edward Novotny, Jr., MD, Eric Payne, MD, MPH, Katrina Peariso, MD, PhD, Juan Piantino, MD, Adam Ostendorf, MD, Tristan T. Sands, MD, PhD, Kumar Sannagowdara, MD, Robert C. Tasker, MBBS, MD, Dmitry Tchapyjnikov, MD, Alexis A. Topjian, MD, MSCE, Alejandra Vasquez, MD, Mark S. Wainwright, MD, PhD, Angus Wilfong, MD, Kowryn Williams, MD, PhD, and Tobias Loddenkemper, MD, on behalf of pSERG

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Abstract

Objective
To determine whether publication of evidence on delays in time to treatment shortens time to treatment in pediatric refractory convulsive status epilepticus (rSE), we compared time to treatment before (2011–2014) and after (2015–2019) publication of evidence in treatment of rSE in the Pediatric Status Epilepticus Research Group (pSERG) as assessed by patient interviews and record review.

Methods
We performed a retrospective analysis of a prospectively collected dataset from June 2011 to September 2019 on pediatric patients (1 month–21 years of age) with rSE.

Results
We studied 328 patients (56% male) with median (25th–75th percentile [p25–p75]) age of 3.8 (1.3–9.4) years. There were no differences in the median (p25–p75) time to first benzodiazepine (BZD) (20 [5–52.5] vs 15 [5–38] minutes, \( p = 0.3919 \)), time to first non-BZD antiseizure medication (68 [34.5–163.5] vs 65 [33–142] minutes, \( p = 0.7328 \)), and time to first continuous infusion (186 [124.2–571] vs 160 [89.5–495] minutes, \( p = 0.2236 \)). Among 157 patients with out-of-hospital onset whose time to hospital arrival was available, the proportion who received at least 1 BZD before hospital arrival increased after publication of evidence of delays (41 of 81 [50.6%] vs 57 of 76 [75%], \( p = 0.0018 \), and the odds ratio (OR) was also increased in multivariable logistic regression (OR 4.35 [95% confidence interval 1.96–10.3], \( p = 0.0005 \)).

Conclusion
Publication of evidence on delays in time to treatment was not associated with improvements in time to treatment of rSE, although it was associated with an increase in the proportion of patients who received at least 1 BZD before hospital arrival.

Correspondence
Dr. Loddenkemper
tobias.loddenkemper@
childrens.harvard.edu

From the Division of Epilepsy and Clinical Neurophysiology (I.S.F., MA.-G., C.B.A., J.C., M.G.-L., A.V., T.L.), Department of Neurology and Department of Neurology (R.C.T.), Department of Anesthesiology, Critical Care and Pain Medicine, Boston Children’s Hospital, Harvard Medical School, MA; Department of Child Neurology (I.S.F.), Hospital Sant Joan de Déu, Universitat de Barcelona, Spain; Division of Neurology (N.S.A.), Departments of Neurology and Pediatrics, Children’s Hospital of Philadelphia and University of Pennsylvania; Pediatric Neurology Unit (M.A.-G.), Department of Pediatrics, Hospital Universitari Son Espases, Universitat de les Illes Balears, Palma, Spain; Section of Pediatric Critical Care Medicine (A.A., Y.-C.L.), Department of Pediatrics, Baylor College of Medicine, Houston, TX; Division of Neurology (R.A., T.G., K.P.), Cincinnati Children’s Hospital Medical Center, University of Cincinnati, OH; University of Virginia Health (J.N.B., H.P.G., Charlottesville Center for Neuroscience (J.L.C., W.D.G.), Children’s National Medical Center, George Washington University School of Medicine and Health Sciences, Washington, DC; Departments of Pediatrics and Neurology (K.E.C.), Children’s Hospital Colorado, University of Colorado School of Medicine, Aurora; Department of Pediatric Neurology (R.F.-M., K.S.), Children’s Hospital of Wisconsin, Medical College of Wisconsin, Milwaukee; Instituto de Pediatria (M.G.-L.), Facultad de Medicina, Universidad Austral de Chile, Valdivia, Chile; Servicio de Neuropsiquiatría Infantil (M.G.-L.), Hospital Clínico San Borja Arriarán, Universidad de Chile, Santiago; Ruth D. & Ken M. Davie Pediatric Neurocritical Care Program (E.J., T.M.), Northwestern University Feinberg School of Medicine, Chicago, IL; Division of Pediatric and Developmental Neurology (R.M.G.), Department of Neurology, Washington University School of Medicine, St. Louis, MO; Division of Pediatric Neurology (M.A.M., D.T.), Duke University Medical Center, Duke University, Durham, NC; Department of Pediatrics and Neurology (L.A.M., E.N., M.S.W.), Seattle Children’s Hospital, University of Washington; Center for Integrative Brain Research (L.A.M., E.N., M.S.W.), Seattle Children’s Research Institute, WA; Department of Neurology (E.P.), Mayo Clinic, Mayo Clinic School of Medicine, Rochester, MN; Department of Neurology (P.J.), Doernbecher Children’s Hospital, Oregon Health & Science University, Portland; Department of Neurology (A.O.), Nationwide Children’s Hospital, Ohio State University, Columbus; Division of Child Neurology and Institute for Genomic Medicine (T.T.S.), Columbia University Irving Medical Center, New York Presbyterian Hospital, New York; Division of Critical Care Medicine (A.A.T.), The Children’s Hospital of Philadelphia, Perelman School of Medicine at the University of Pennsylvania; Division of Child and Adolescent Neurology (A.V.), Department of Neurology, Mayo Clinic, Rochester, MN; Barrow Neurological Institute (A.W., K.W.), Phoenix Children’s Hospital; and Department of Pediatrics (A.W., K.W.), University of Arizona School of Medicine, Phoenix.

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Status epilepticus (SE) is one of the most frequent neurologic emergencies in children, with an incidence of 5 to 25 per 100,000.1–4 Longer SE episodes require more invasive and resource-intensive medical care and are associated with higher morbidity and mortality.5 Although long-term outcomes in SE survivors depend largely on etiology,6,7 observational studies showed that delayed treatment is independently associated with worse outcomes8–12 and increased mortality12 in the short term. Therefore, shortening SE duration through timely and effective treatment13–15 may improve short-term outcomes.

The American Epilepsy Society guideline recommends initial treatment with benzodiazepine (BZD) within 20 minutes, treatment with non-BZD antiseizure medication (non-BZD ASM) within 40 minutes, and treatment with continuous infusions within 60 minutes,16 but a growing body of literature identified marked delays from these benchmarks.17 Interdisciplinary quality improvement interventions have shown that it is possible to improve time to treatment of electrographic seizures in the intensive care unit (ICU)18 and time to treatment of SE in the hospital.19,20 There are no data on whether publication of evidence on delayed treatment in SE has independently modified time to treatment.

We aimed to address this gap in knowledge by comparing time to treatment before (2011–2014) and after (2015–2019) publication of evidence of delays in time to treatment within the Pediatric Status Epilepticus Research Group (pSERG). Our hypothesis was that published evidence identifying a gap in clinical practice (delayed time to treatment) would lead to improved clinical practice (reduced times to treatment).

**Methods**

**Standard protocol approvals, registrations, and patient consents**

This study was approved by the Institutional Review Board at each institution. Written informed consent was obtained from parents or guardians.

**Study design**

This was a retrospective analysis of prospectively collected data from a multicenter observational study. pSERG is a consortium of pediatric hospitals in the United States and Canada that aims to improve the treatment and, eventually, the prognosis of children with SE.21 pSERG, as an ongoing study, has reported the initial patients in the cohort on different outcomes: on delays in time to treatment,22 use of continuous infusions,23 differences in time to treatment between patients with and without a prior diagnosis of epilepsy,24 factors associated with delays in time to treatment,25 and the association of treatment delays with unfavorable outcomes.12

**Patients**

We studied patients with refractory convulsive SE (rSE). Inclusion criteria were (1) age from 1 month to 21 years; (2) admission to a pSERG hospital between June 1, 2011, and September 1, 2019; and (3) focal or generalized convulsive seizures at onset that continued after administration of at least 2 ASMs, including at least 1 non-BZD ASM or the use of a continuous infusion. Exclusion criteria were (1) nonconvulsive SE detected on EEG lacking convulsive seizures at onset; (2) nonconvulsive SE with motor manifestations limited to infrequent myoclonic jerks; (3) no information on time to administration of the first BZD; (4) no information on time to administration of the first non-BZD ASM; and (5) no information on basic demographic and clinical features such as age, sex, race, time of SE onset, hospital onset, type of SE, or duration of SE. In order not to violate the assumption of independent observations in statistical tests, we included only the first rSE episode for patients who had >1 rSE episode during the study period.

**Variables**

The main outcomes were time to the first BZD, time to the first non-BZD ASM, and time to the first continuous infusion among patients who received any. Secondary outcomes were the proportion of patients who received the first class of each medication (BZD, non-BZD ASM, and continuous infusion) beyond recommended timelines and beyond clinically pre-specified outlier times and, among patients with rSE onset out of the hospital, the proportion of patients who received at least 1 BZD before hospital arrival. The main intervention for all analyses was publication of evidence from pSERG showing delays in time to treatment.22 By the end of 2014, the first article with pSERG data showed that delays in time to treatment of rSE occurred at every step of the treatment pathway, and all pSERG members became aware of delays in time to treatment of rSE because they contributed to the article.22 Therefore, we divided time into the periods June 2011 to December 2014 vs January 2015 to September 2019 as surrogates for pre-awareness and awareness of delays in time to treatment. As more patients were collected, new pSERG analyses in 2016 confirmed the initial results and showed that delays in time to treatment of rSE were common even in patients with a prior diagnosis of epilepsy.24 Further, the American Epilepsy Society evidence-based guideline

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**Glossary**

ASM = antiseizure medication; BZD = benzodiazepine; CI = confidence interval; HR = hazard ratio; ICU = intensive care unit; OR = odds ratio; p25 = 25th percentile; p75 = 75th percentile; pSERG = Pediatric Status Epilepticus Research Group; RMST = restricted mean survival time; rSE = refractory convulsive SE; SE = status epilepticus.
published in 2016 emphasized initial treatment with BZD within 20 minutes, treatment with non-BZD ASM within 40 minutes, and treatment with continuous infusions within 60 minutes.16 Therefore, as a sensitivity analysis, we compared times to treatment defining alternative periods: 2011 to 2016 vs 2017 to 2019. We also evaluated the robustness of our results with an additional sensitivity analysis considering only the hospitals that were part of pSERG since the initial years. We considered as potential confounders the type of SE (continuous or intermittent), hospital onset, SE onset during the day (8 AM–8 PM) or night (8 PM–8 AM), period in the academic year (July–December vs January–June), white race, etiology (structural vs other), history of epilepsy, prior episode of SE, age in years, and sex. The time to medication administration was extracted from families and emergency medical services for out-of-hospital SE onset and from provider documentation and medical records for SE treated in the hospital. Data were collected with a standardized data acquisition tool and then entered into an electronic database hosted by Cincinnati Children’s Hospital Medical Center.21

Statistical analysis and statistical software
Demographic and clinical characteristics were summarized with descriptive statistics. Unless stated otherwise, continuous variables were summarized as median (25th [p25] and 75th [p75] percentile) and categorical variables were summarized as number (percentage). Categorical variables were compared with the Fisher exact test in univariate analysis and with logistic regression with multivariate analysis. We calculated the absolute risk difference and the number needed to treat. We compared time to treatment in univariate analysis with the Peto and Peto modification of the Gehan-Breslow-Wilcoxon test and in multivariate analysis with a Cox proportional hazards regression model. The Peto and Peto26 modification of the Gehan-Breslow-Wilcoxon test is a nonparametric generalized maximum-likelihood estimate of the survival function for interval-censored data that gives more weight to early events and gives less weight to late events, likely outliers in this context. We calculated the differences in time to treatment between groups (before and after publication of evidence of delays) with the difference of the restricted mean survival time (RMST).27,28 The difference of the RMST is an outcome measure that compares the time difference between 2 groups using the areas under the Kaplan-Meier curves up to a clinically meaningful prespecified time.27,28 Considering a clinically meaningful prespecified time of, e.g., 60 minutes for the time to the first BZD, a difference of RMST of, e.g., –3 minutes means that, within the first 60 minutes, patients in the group after publication of evidence received the first BZD a mean of 3 minutes earlier than patients in the group before publication of evidence. For this study, we considered the following clinically meaningful prespecified times: (1) 20, 40, and 60 minutes for the first BZD, which represent the times by which the first-line therapy should be completed, and 20 and 40 minutes after that threshold16; (2) 40, 60, and 120 minutes for the first non-BZD ASM, which represent the times by which the second-line therapy should be completed, and 20 and 80 minutes after that threshold16; and (3) 60, 120, and 240 minutes for the first continuous infusion, which represent the times by which the third-line therapy should be completed, and 60 and 180 minutes after that threshold.16 We considered onset of rSE (in the hospital or out of the hospital) as an effect modifier because time to treatment is likely to be different in these 2 environments. Thus, we stratified the analyses by in-hospital or out-of-hospital rSE onset. We used a conventional 2-sided level of 0.05 for all tests because, even if the expected effect of publication of evidence of delays is to reduce times to treatment, longer times to treatment might have happened due to a secular effect. We adjusted the main results for multiple comparisons with the Benjamini and Hochberg false discovery rate with a q value of 0.05.29 The false discovery rate controls for the expected proportion of false discoveries in order to control for multiple comparisons across multiple tests.29 All statistical analyses were performed with R (version 3.6.0; R Foundation for Statistical Computing, Vienna, Austria), a language and environment for statistical computing30 with RStudio,31 and the packages gdata,32 car,33 lubridate,34 gmodels,35 survival36 and survRM2.37

Data availability
All statistical analyses and results are available in appendix e-1 (github.com/IvanSanchezFernandez/pSERGbeforeafter). The original data are available on request.

Results

Demographic and clinical characteristics
We evaluated 328 patients (56% male) with a median (p25–p75) age of 3.8 (1.3–9.4) years, 151 (46%) with an rSE episode in the period 2011 to 2014 and 177 (54%) in the period 2015 to 2019. SE started out of hospital in 222 (67.7%) patients and in hospital in 106 (32.3%) patients. The median (p25–p75) length of ICU stay was 4 (2–11) days, and 11 (3.4%) patients died during hospitalization (table 1).

Time to treatment
The median (p25–p75) time to the administration of the first BZD was 17 (5–45) minutes. There was no statistically significant difference between the periods 2011 to 2014 and 2015 to 2019 (20 [5–52.5] vs 15 [5–38] minutes, p = 0.3919) (figure 1A), and it was not significant after adjustment for potential confounders (confounders described in the Methods section) (hazard ratio [HR] 1.01 [95% confidence interval (CI) 0.81–1.27], p = 0.9130) (table e-1, available in GitHub at github.com/IvanSanchezFernandez/pSERGbeforeafter and in zenodo at zenodo.org/badge/latestdoi/230197648). The median (p25–p75) time to the administration of the first non-BZD ASM was 65.5 (33.8–150) minutes. There was no difference between the periods 2011 to 2014 and 2015 to 2019 (68 [34.5–163.5] vs 65 [33–142] minutes, p = 0.7328) (figure 1B), and it was not significant after adjustment for potential confounders (HR 1.01 [95% CI 0.81–1.27], p = 0.9111) (table e-2, available in GitHub and
Among the 152 patients who received at least 1 continuous infusion, the median (p25–p75) time to the administration of the first continuous infusion was 173.5 (113.5–543.2) minutes. There was no statistically significant difference between the periods 2011 to 2014 and 2015 to 2019 (186 [124.2–571] vs 160 [89.5–495] minutes, p =

| Table 1 Demographic and clinical characteristics | 2011–2014 (n = 151) | 2015–2019 (n = 177) | Total (n = 328) |
|--------------------------------------------------|---------------------|---------------------|-----------------|
| **Age, y**                                        | 3.8 (1.2–8.9)       | 4.1 (1.3–9.6)       | 3.8 (1.3–9.4)   |
| **Sex, n (%)**                                    |                     |                     |                 |
| Male                                              | 80 (53)             | 103 (58.2)          | 183 (55.8)      |
| Female                                            | 71 (47)             | 74 (41.8)           | 145 (44.2)      |
| **Race, n (%)**                                   |                     |                     |                 |
| White                                             | 81 (53.6)           | 128 (72.3)          | 209 (63.7)      |
| Black                                             | 38 (25.2)           | 27 (15.3)           | 65 (19.8)       |
| Arabic                                            | 7 (4.6)             | 3 (1.7)             | 10 (3)          |
| Asian                                             | 6 (4)               | 5 (2.8)             | 11 (3.4)        |
| Native American                                   | 1 (0.7)             | 2 (1.1)             | 3 (0.9)         |
| Unknown                                           | 18 (11.9)           | 12 (6.8)            | 30 (9.2)        |
| **Ethnicity, n (%)**                              |                     |                     |                 |
| Not Hispanic                                      | 111 (73.5)          | 136 (76.8)          | 247 (75.3)      |
| Hispanic                                          | 26 (17.2)           | 25 (14.1)           | 51 (15.5)       |
| Unknown                                           | 14 (9.3)            | 16 (9)              | 30 (9.2)        |
| **Medical history, n (%)**                        |                     |                     |                 |
| Developmental delay/intellectual disability       | 76 (50.3)           | 91 (51.4)           | 167 (50.9)      |
| Prior epilepsy                                     | 71 (47)             | 90 (50.8)           | 161 (49.1)      |
| History of SE                                     | 26 (17.2)           | 36 (20.3)           | 62 (18.9)       |
| History of cerebral palsy                         | 13 (8.6)            | 18 (10.2)           | 31 (9.5)        |
| No prior neurologic history                       | 56 (37.1)           | 54 (30.5)           | 110 (33.5)      |
| **Etiology, n (%)**                               |                     |                     |                 |
| Unknown                                           | 47 (31.1)           | 65 (36.7)           | 112 (34.1)      |
| Structural                                        | 44 (29.1)           | 39 (22)             | 83 (25.3)       |
| Genetic                                           | 24 (15.9)           | 38 (21.5)           | 62 (18.9)       |
| Metabolic                                         | 11 (7.3)            | 4 (2.3)             | 15 (4.6)        |
| Other                                             | 25 (16.6)           | 31 (17.5)           | 56 (17.1)       |
| **SE onset, n (%)**                               |                     |                     |                 |
| Out of the hospital                               | 105 (69.5)          | 117 (66.1)          | 222 (67.7)      |
| In the hospital                                   | 46 (30.5)           | 60 (33.9)           | 106 (32.3)      |
| **Convulsive duration (n = 328), min**            | 135 (60–275)        | 120 (60–286)        | 124.5 (60–281.5)|
| **Length of ICU stay (n = 311), d**               | 4.3 (2–11.9)        | 4 (1.7–11)          | 4 (2–11)        |
| **In-hospital mortality (n = 328), n (%)**        | 5 (3.3)             | 6 (3.5)             | 11 (3.4)        |

Abbreviations: ASM = antiseizure medication; BZD = benzodiazepine; SE = status epilepticus. Continuous variables are summarized as median (25th–75th percentiles); categorical variables are summarized as number and percentage. *These conditions are not mutually exclusive; therefore, the percentages can sum to >100%.
0.2236) (figure 1C), and it was not significant after adjustment for potential confounders (HR 1.08 [95% CI 0.77–1.51], p = 0.6428) (table e-3, available in GitHub at and zenodo).

Treatment within clinical recommendations and outliers
Forty-three percent, 27%, and 19% of patients received their first BZD beyond 20, 40, and 60 minutes from seizure onset, respectively. Seventy percent, 54%, and 29% of patients received their first non-BZD ASM beyond 40, 60, and 120 minutes from seizure onset, respectively. Eighty-nine percent, 70%, and 39% of patients received their first continuous infusion beyond 60, 120, and 240 minutes from seizure onset, respectively. These proportions were similar between the periods 2011 to 2014 and 2015 to 2019 (table 2).

Stratification by hospital onset
The proportion of patients receiving their first BZD, first non-BZD ASM, and first continuous infusion beyond recommended time lines and beyond outliers was high in both out-of-hospital onset and in-hospital onset SE and did not change in the period 2015 to 2019 compared with the period 2011 to 2014 (table 2). Among the 157 patients with out-of-hospital onset whose time to hospital arrival was available, 98 (62.4%) received at least 1 BZD before hospital arrival. This proportion increased after publication of evidence of delays (41 of 81 [50.6%] vs 57 of 76 [75%], absolute risk reduction 0.24, number needed to treat 4.1, p = 0.0018 [adjusted p = 0.0036]), and the odds ratio (OR) remained significant in multivariable logistic regression adjusting for potential confounders (confounders described in the Methods section) (OR 4.35 [95% CI 1.96–10.3], p = 0.0005 [adjusted p = 0.0019]). Among the 85 patients with a history of epilepsy whose rSE began out of hospital and whose information on time to hospital arrival was available, 56 (65.9%) received at least 1 BZD before hospital arrival. This proportion increased after publication of evidence of delays (23 of 43 [53.5%] vs 33 of 42 [78.6%], absolute risk reduction 0.25, number needed to treat 40, p = 0.0217 [adjusted p = 0.0220]), and the OR remained significant in multivariable logistic regression with adjustment for potential confounders (OR 3.97 [95% CI 1.28–13.99], p = 0.0220 [adjusted p = 0.0220]). There were no differences between the periods 2011 to 2014 and 2015 to 2019 in time to the first BZD, time to the first non-BZD ASM, and time to the first continuous infusion for out-of-hospital or in-hospital onset (table 3, figure 2, and appendix e-1, github.com/IvanSanchezFernandez/pSERGbeforeafter).

Sensitivity analyses
There was no difference in time to treatment between the periods (1) when considering the alternative periods 2011 to 2016 vs 2017 to 2019 rather than 2011 to 2014 vs 2015 to 2019; (2) when considering only hospitals that had patients enrolled since the initial years of pSERG, using the original periods 2011 to 2014 vs 2015 to 2019; and (3) when considering only hospitals that had patients enrolled since the initial years of pSERG, using the alternative periods 2011 to 2016 vs 2017 to 2019. These sensitivity analyses also confirmed that, among patients with out-of-hospital onset rSE,
| Class of Medication | Global proportion, n/N (%) | 2011–2014, n/N (%) | 2015–2019, n/N (%) | p Value (Fisher exact test) | RMST difference (95% confidence interval), min | p Value (RMST difference) |
|---------------------|-----------------------------|--------------------|--------------------|---------------------------|------------------------------------------|---------------------------|
| Total population    |                             |                    |                    |                           |                                          |                           |
| First BZD >20 min   | 141/328 (43)                | 69/151 (45.7)      | 72/177 (40.7)      | 0.3728                    | −0.3 (−1.9 to 1.2)                       | 0.665                     |
| First BZD >40 min   | 90/328 (27.4)               | 47/151 (31.1)      | 43/177 (24.3)      | 0.1743                    | −1.7 (−4.9 to 1.5)                       | 0.286                     |
| First BZD >60 min   | 62/328 (18.9)               | 34/151 (22.5)      | 28/177 (15.8)      | 0.1568                    | −2.9 (−7.5 to 1.7)                       | 0.214                     |
| First non-BZD ASM >40 min | 231/328 (70.4)     | 106/151 (70.2) | 125/177 (70.6) | 1                         | −0.8 (−2.6 to 1.1)                       | 0.421                     |
| First non-BZD ASM >60 min | 178/328 (54.3)   | 81/151 (53.6) | 97/177 (54.8) | 0.9115                    | −0.6 (−4 to 2.8)                        | 0.722                     |
| First non-BZD ASM >120 min | 95/328 (29)          | 46/151 (30.5) | 49/177 (27.7) | 0.6258                    | −2.1 (−10.1 to 5.9)                      | 0.607                     |
| First CI >60 min    | 135/152 (88.8)             | 62/68 (91.2)       | 73/84 (86.9)       | 0.4493                    | 0.6 (−2.4 to 3.6)                        | 0.698                     |
| First CI >120 min   | 107/152 (70.4)             | 52/68 (76.5)       | 55/84 (65.5)       | 0.1562                    | −5.4 (−14.2 to 3.3)                      | 0.222                     |
| First CI >240 min   | 59/152 (38.8)              | 29/68 (42.6)       | 30/84 (35.7)       | 0.4067                    | −12.7 (−35.8 to 10.4)                    | 0.282                     |
| Out of hospital onset |                             |                    |                    |                           |                                          |                           |
| First BZD >20 min   | 107/222 (48.2)             | 55/105 (52.4)      | 52/117 (44.4)      | 0.2821                    | −0.6 (−2.3 to 1.2)                       | 0.537                     |
| First BZD >40 min   | 71/222 (32)                | 37/105 (35.2)      | 34/117 (29.1)      | 0.3874                    | −1.9 (−5.8 to 2)                         | 0.332                     |
| First BZD >60 min   | 47/222 (21.2)              | 26/105 (24.8)      | 21/117 (17.9)      | 0.2505                    | −2.8 (−8.6 to 3)                         | 0.338                     |
| First non-BZD ASM >40 min | 178/222 (80.2)    | 82/105 (78.1) | 96/117 (82.1) | 0.5025                    | −0.3 (−2.1 to 1.6)                       | 0.797                     |
| First non-BZD ASM >60 min | 142/222 (64)        | 65/105 (61.9) | 77/117 (65.8) | 0.5773                    | 0.9 (−2.7 to 4.5)                        | 0.623                     |
| First non-BZD ASM >120 min | 78/222 (35.1)    | 39/105 (37.1) | 39/117 (33.3) | 0.5757                    | 0.3 (−9.3 to 9.8)                        | 0.956                     |
| First CI >60 min    | 90/101 (89.1)              | 42/45 (93.3)       | 48/56 (85.7)       | 0.3373                    | −0.4 (−2.7 to 1.9)                       | 0.733                     |
| First CI >120 min   | 73/101 (72.3)              | 35/45 (77.8)       | 38/56 (67.9)       | 0.3714                    | −5.4 (−14.8 to 4.1)                      | 0.263                     |
| First CI >240 min   | 41/101 (40.6)              | 19/45 (42.2)       | 22/56 (39.3)       | 0.8395                    | −6 (−32.8 to 20.8)                       | 0.659                     |
| In hospital onset   |                             |                    |                    |                           |                                          |                           |
| First BZD >20 min   | 34/106 (32.1)              | 14/46 (30.4)       | 20/60 (33.3)       | 0.835                     | −0.1 (−2.9 to 2.7)                       | 0.953                     |
| First BZD >40 min   | 19/106 (17.9)              | 10/46 (21.7)       | 9/60 (15)          | 0.4467                    | −1.5 (−6.8 to 3.8)                       | 0.574                     |
| First BZD >60 min   | 15/106 (14.2)              | 8/46 (17.4)        | 7/60 (11.7)        | 0.4158                    | −3.2 (−10.6 to 4.2)                      | 0.400                     |
| First non-BZD ASM >40 min | 53/106 (50)           | 24/46 (52.2) | 29/60 (48.3) | 0.8448                    | −1.6 (−5.5 to 2.2)                       | 0.410                     |
| First non-BZD ASM >60 min | 36/106 (34)            | 16/46 (34.8) | 20/60 (33.3) | 1                         | −3.6 (−10.3 to 3.1)                      | 0.292                     |
| First non-BZD ASM >120 min | 17/106 (16)           | 7/46 (15.2) | 10/60 (16.7) | 1                         | −6.3 (−20.1 to 7.4)                      | 0.365                     |
| First CI >60 min    | 45/51 (88.2)              | 20/23 (87)         | 25/28 (89.3)       | 1                         | 2.9 (−3.9 to 9.7)                        | 0.410                     |
| First CI >120 min   | 34/51 (66.7)              | 17/23 (73.9)       | 17/28 (60.7)       | 0.381                     | −2.8 (−19.3 to 13.7)                     | 0.739                     |
| First CI >240 min   | 18/51 (35.3)              | 10/23 (43.5)       | 8/28 (28.6)        | 0.3784                    | −23.4 (−64.1 to 17.4)                    | 0.260                     |

Abbreviations: ASM = antiseizure medication; BZD = benzodiazepine; CI = continuous infusion; RMST = restricted mean survival time.
the proportion of patients who received at least 1 BZD before hospital arrival increased after publication of evidence on delays (table e-4 and appendix e-1, available in GitHub at github.com/IvanSanchezFernandez/pSERGbeforeafter and in zenodo at zenodo.org/badge/latestdoi/230197648 and ivansanchezfernandez.github.io/pSERGbeforeafter_/Filee1/).

Discussion

This study demonstrates that, in major pediatric hospitals, publication of evidence showing a gap in clinical practice (delayed treatment in rSE) was not associated with an improvement in clinical practice (sustained reduction in time to treatment for any of the management steps). It was associated, however, with a clinically meaningful improvement: the increase in the proportion of patients with out-of-hospital rSE onset who received at least 1 BZD before hospital arrival. This improvement is probably related to better education of caregivers about seizure action plans, a step that is largely dependent on epileptologists and pediatric neurologists. In turn, the failure of improving time to treatment probably reflects the lack of an implementation policy that includes dissemination of evidence among all stakeholders, modification of standardized treatment plans to emphasize time to treatment, and implementation by multidisciplinary teams.

pSERG is a large multicenter study that includes major pediatric hospitals in the United States and Canada. Evaluation of time to treatment was an open research question within pSERG in the years 2011 to 2014. Existing literature at the time suggested that treatment delay was common in both children and adults with SE, but evidence was sparse and limited to the first treatment steps. A retrospective study in 625 adults and 264 children with SE in the 1989 to 1994 period in Virginia showed that the first ASM (BZD or non-BZD ASM) was given within 30 minutes of seizure onset in only 42% of cases. Similarly, a study of 542 episodes of pediatric SE in the period 2000 to 2004 in Australia and New Zealand showed that the median (p25–p75) time from hospital arrival to administration of a non-BZD ASM was 24 (15–36) minutes. In a study of 263 clinical SE episodes in 225 adult patients in the 2008 to 2011 period in Switzerland showed that initial treatment was delayed for >1 hour in 139 (62%) of patients, including 54 patients with generalized convulsive SE. By the end of 2014, pSERG had collected data that demonstrated delays at every treatment step, and all pSERG members were aware of these delays. Therefore, we compared the periods 2011 to 2014 and 2015 to 2019. Our results remained robust to the alternative comparison of periods 2011 to 2016 and 2017 to 2019 when the evidence for delays was even stronger. Our results were also robust when considering only the hospitals that formed pSERG initially. Our main results remained robust to these sensitivity analyses and together show no major improvements in time to treatment within pSERG after publication of evidence of delays in time to treatment.

Unfortunately, the publication of evidence, even in major scientific journals, is not necessarily sufficient to modify clinical practice. The major stakeholders to reduce time to treatment in SE are the primary caregivers, emergency medical services, emergency department clinicians, general pediatrics and internal medicine clinicians, and adult and child neurologists and epileptologists. Most epileptologists and adult and child neurologists are aware of the importance of early treatment but typically are not the initial responders to prolonged seizures. SE treatment is often initiated by primary caregivers, emergency medical services personnel, and

| Table 3 | Comparison of time to treatment before and after awareness of marked delays in treatment administration for SE |
|----------------|---------------------------------|-----------------|-----------------|
| | 2011–2014 | 2015–2019 | Univariate analysis | Multivariate analysis, HR (95% confidence interval) |
| SE onset out of the hospital (n = 222), n | | | |
| | 105 | 117 | | |
| Time to the first BZD (n = 222), min | 25 (7–60) | 20 (7–50) | 0.2606 | 1.06 (0.81–1.39), p = 0.6829 |
| Time to the first non-BZD ASM (n = 222), min | 82 (45–190) | 80 (55–153) | 0.9441 | 1.02 (0.78–1.35), p = 0.877 |
| Time to the first continuous infusion (n = 101), min | 180 (137–660) | 166 (86.5–586.5) | 0.3165 | 1.27 (0.82–1.97), p = 0.279 |
| | | | |
| SE onset in the hospital (n = 106), n | | | |
| | 46 | 60 | | |
| Time to the first BZD (n = 106), min | 8 (4.3–25.8) | 9.5 (5–24) | 0.6778 | 1 (0.67–1.52), p = 0.974 |
| Time to the first non-BZD ASM (n = 106), min | 44.5 (20.3–86.8) | 36 (23–79.8) | 0.8215 | 1.12 (0.74–1.7), p = 0.5938 |
| Time to the first continuous infusion (n = 91), min | 210 (121–462) | 147.5 (90.8–420) | 0.4022 | 1.14 (0.6–2.16), p = 0.684 |

Abbreviations: ASM = antiseizure medication; BZD = benzodiazepine; HR = hazard ratio; SE = status epilepticus.
emergency department physicians, typically in community hospitals, who may not receive as much training in the importance of time to treatment of SE as in large academic centers. Neurologists and epileptologists need to continue to ensure a timely treatment when directly caring for a patient with active SE, but they may also improve time to treatment by acting as knowledge brokers who transfer the importance of a timely treatment to all initial responders. Educating primary caregivers about individualized seizure action plans and simulating likely SE treatment scenarios to make primary caregivers comfortable administering rescue medications may improve the timeliness and efficacy of the treatment of SE. This transfer of knowledge can occur during routine epilepsy clinic visits; local, regional, and national education; and meetings, directly or through dedicated nursing teams. Support of these education efforts by hospital administrators and

**Figure 2** Kaplan-Meier curves comparing the periods 2011 to 2014 and 2015 to 2019 on time to the administration of the first class of each medication (BZD, non-BZD ASM, and CI) stratified by onset out of the hospital (left) or in the hospital (right).

- **A** Cumulative probability of having received the first BZD in patients with refractory convulsive status epilepticus (rSE) onset out of the hospital. Time axis is truncated at 60 minutes.
- **B** Cumulative probability of having received the first non-BZD ASM in patients with rSE onset out of the hospital. Time axis is truncated at 120 minutes.
- **C** Cumulative probability of having received the first CI (among those patients who received a CI) in patients with rSE onset out of the hospital. Time axis is truncated at 500 minutes.
- **D** Cumulative probability of having received the first BZD in patients with rSE onset in the hospital. Time axis is truncated at 60 minutes.
- **E** Cumulative probability of having received the first non-BZD ASM in patients with rSE onset in the hospital. Time axis is truncated at 120 minutes.
- **F** Cumulative probability of having received the first CI (among those patients who received a CI) in patients with rSE onset in the hospital. Time axis is truncated at 500 minutes.

Time scales are truncated for different medications (time to first benzodiazepine [BZD] truncated at 60 minutes, time to first non-BZD antiseizure medication [ASM] truncated at 120 minutes, and time to first continuous infusion [CI] truncated at 500 minutes).
leadership and recognition by payers are crucial, as are education of and acceptance by patients and caregivers, because implementation ultimately remains a shared responsibility.

We observed a clinical relevant improvement in the proportion of patients who received at least 1 BZD before hospital arrival, although this may reflect the growing body of literature suggesting room for improvement in the proportion of caregivers trained in administration of rescue medications for prolonged seizures and in the proportion of patients not treated before hospital arrival. In either case, if the observed improvement is the result of epileptologists and pediatric neurologists better educating families on seizure action plans, it provides a model to educate all the caregivers in the SE treatment chain. Another potential source of delays is that some systemic factors are beyond the control of clinicians. For example, emergency medical services may not be allowed to administer BZD and non-BZD ASM in the out-of-hospital setting, and once in the hospital, the period from ASM order to ASM arrival to the bedside may be long and beyond clinicians’ control, likely requiring further education and dissemination efforts, as well as systematic improvements and policy changes. Despite isolated quality improvement projects, there have not been general policies within pSERG hospitals to formally disseminate information on delays in time to treatment of SE to personnel working in emergency medical services, emergency departments, general pediatrics, pharmacy, nursing, or the ICU. If knowledge is not widely disseminated, improvement based on that knowledge is unlikely to be as large as it could be. Although numbers are not large enough to study each center individually, we did not find any center with improved times after publication of evidence. The time lag from the discovery of a new research finding to its implementation into medical practice varies widely, depending on the research finding, but typically takes several years. Slow tendencies toward improvement may not have been captured in this study, which spans less than a decade. In addition, a tendency for improvement may have been compensated by patients with better treatments not progressing into rSE and therefore not meeting our inclusion and exclusion criteria. Although possible, this is unlikely because we have not seen improvement even in the time to the first BZD. There have been no national or consortium-related formal mechanisms to translate research knowledge into policy changes, and work is in progress to secure funding for further implementation efforts and to amend this crucial aspect. Therefore, the transfer of knowledge between pSERG child neurologists and other stakeholders in hospitals, referring emergency department networks, and the policy changes implemented in the pSERG hospitals have been variable, in part also due to lack of overarching guideline and government input, delay of implementation of clinical findings into health care policies on a regional and national level, and further delays in implementation and monitoring of updated policies. Formal quality improvement projects can improve the efficiency and timeliness of treatment administration. A quality improvement study on the timely detection and treatment of electrographic seizures in the ICU reduced the time from seizure onset to medication administration by half and improved the percentage of seizure termination after the first ASM from 67% to 27%. Its multidisciplinary approach involving all stakeholders and streamlining protocols may be a model to follow in convulsive SE. A quality improvement project on the treatment of convulsive SE reduced the median time to the second-line ASM by half. In a pSERG tertiary care pediatric hospital, implementation of process improvements developed through quality improvement and statistical process control methodology doubled the proportion of patients receiving a first BZD within 10 minutes, thereby resulting in decreases in morbidity, transfer to the ICU, and costs. This study did not only show that multidisciplinary quality improvement projects may reduce time to treatment, but it also showed the magnitude of the downstream consequences: need for ICU transfer was reduced from 39% to 9% of SE cases, reducing hospital charges by $2.1 million in a single hospital. These data highlight the need for pSERG-wide multidisciplinary, systems-focused approaches that include streamlining of communication; formal dissemination of the research findings on the importance of a timely treatment to all stakeholders; policy changes to streamline drug delivery; a standardized education of caregivers, emergency medical services, and emergency room personnel about specific steps to treat SE in a timely manner to avoid unnecessary delays and redundant interventions (table 4); and ultimately financial motivation for payers and health care systems to implement care improvements. Publication of evidence is a first step that may or may not improve practice. Lack of improvement in clinical practice after publication of evidence on a gap in practice may reflect the lack of policy changes to implement this knowledge. Epileptologists and pediatric neurologists who participated in the pSERG research studies became aware of the results. This may have contributed to the improvement in seizure action plans. Yet, there have been no pSERG-wide, regional, or national policy changes to formally disseminate knowledge on delays in time to treatment of SE to all stakeholders, work to emphasize timeliness in treatment protocols, and audit change. Quality improvement methodology does not merely rely on passive diffusion of evidence but adopts the scientific method to, through multiple cycles, identify and implement the strategies that lead to the desired goal of improved practice.

Comparing times to treatment between periods within individual centers was not feasible with the current numbers, although descriptive data showed no improvement in any center. Our sample included patients with rSE and is not necessarily representative of all children with SE. Although pSERG collects cases with nonrefractory SE, this collection began on October 2014 and, therefore, we cannot compare time to treatment before and after publication of evidence of delays in this population. Selection bias resulting from having studied only rSE may limit the generalizability of results, but it would not be expected that time to treatment would have improved only in nonrefractory SE. Members of pSERG are
Table 4 Steps to improve time to treatment

| Potential barriers to timely treatment                                                                 | Proposed actions                                                                                                                                 |
|--------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| Limited awareness of the importance of a timely and well-dosed treatment of SE to improve short-term outcomes | Neurologists and epileptologists act as knowledge brokers disseminating research findings to all involved stakeholders.                        |
| Delayed recognition of seizure by caregivers and teachers                                             | Increase general awareness through education of general public and targeted groups (e.g., teachers, day care providers, etc).                 |
| Delayed recognition of seizures during sleep                                                            | Provide monitoring devices.                                                                                                                                 |
| Limited access to rescue medications and proper seizure action plans for patients with epilepsy        | Improve seizure action plan education.                                                                                                                                 |
| Low proportion of patients with SE treatment by EMS                                                     | Modify regulations to allow EMS to administer appropriate medications in the appropriate circumstances.                                      |
| Delayed, reduced, or redundant ASM treatment in community emergency departments related to low volume of pediatric patients | Educate policy makers and EMS about the importance of a timely treatment.                                                                      |
| Delayed, reduced, or redundant ASM treatment in academic center emergency departments related to provider experience or logistical barriers | Increase collaborations with academic children’s hospitals and community hospitals referring patients.                                        |
| Delayed or reduced ASM treatment in the ICU                                                              | Provide training modules with emergency department professionals. Re-engineer systems to streamline access to rescue medication in the acute treatment of SE. |
| Delayed or reduced ASM treatment in the ICU                                                              | Create pathways standardizing care for SE. Establish communication flow from initial point of epileptologist to endpoint of bedside caregivers. |

Abbreviations: ASM = antiseizure medication; EMS = emergency medical services; ICU = intensive care unit; SE = status epilepticus.

fully aware of marked delays in time to treatment of SE because they all participated in prior pSERG studies and literature review; however, the degree to which physicians in other specialties (e.g., emergency medicine, general pediatrics, critical care medicine) are aware of the delayed time to SE treatment and the association between treatment times and outcomes is unknown. 8–12 We also are not sure to what extent delayed treatment depends on clinicians prescribing it late vs clinicians prescribing it soon but medication administration being delayed by systemic factors beyond clinician control that hinder expeditious administration of medication. Times were assessed based on caregiver and emergency medical services information for out-of-hospital onset and from health care personnel information and hospital records once in the hospital. Information was cross-referenced with caregivers, emergency medical services, nurses, and medication administration records when available to minimize potential information and recall bias. Other studies on the treatment of SE active during this period, such as the SAGE S47 trial for super-refractory SE15 and the established SE treatment trial,16 did not focus on time to treatment and are unlikely to have confounded the perception of treatment delays.

In a large multicenter consortium of leading pediatric hospitals, publication of evidence on delays in treatment of rSE among epileptologists and child neurologists did not translate into improvements in time to treatment, although it was associated with an increase in the proportion of patients who received at least 1 BZD before hospital arrival. Because little change has occurred, pSERG will implement interventions to increase public awareness and multidisciplinary care plans to improve time to treatment.

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Farias-Moeller report no disclosures relevant to the manuscript. W. Gaillard is an editor for *Epilepsia* and *Epilepsy Research*. M. Gainza-Lein reports no disclosures relevant to the manuscript. T. Glauser is funded by NIH grants 2U01-NS045911, U10-NS077311, R01-NS053998, R01-NS062756, R01-NS043209, R01-LM011124, and R01-NS065840. He has received consulting fees from Supernus, Sunovion, Eisai, and UCB. He also serves as an expert consultant for the US Department of Justice and has received compensation for work as an expert on medico-legal cases. He receives royalties from a patent license. J. Goldstein, H. Goodkin, R. Guerriero, Y.-C. Lai, T. McDonough, M. Mikati, L. Morgan, E. Novotny, E. Payne, K. Peariso, J. Piantino, A. Ostendorf, T. Sands, K. Sannagowdara, and R. Tasker report no disclosures relevant to the manuscript. D. Tchapyjnikov has received research funding from Children’s Miracle Network Hospitals and Duke Forge. He has also received consultation fees from Gerson Lehrman Group, Guidepoint, IQVIA, and bioStrategies Group. A. Topjian and A. Vasquez report no disclosures relevant to the manuscript. M. Wainwright serves as a scientific consultant and on the clinical advisory board for Sage Pharmaceuticals. A. Wilfong receives research funding from Novartis, Eisai, Pfizer, UCB, Acorda, Lundbeck, GW Pharma, Upsher-Smith, and Zogenix and receives publication royalties from Uptodate. K. Williams reports no disclosures relevant to the manuscript. T. Loddenkemper serves on the Council (and as past president) of the American Clinical Neurophysiology Society, as committee chair at the American Epilepsy Society (Investigator Workshop Committee), as founder and consortium principal investigator of the pSERG, as an associate editor for *Wyllie’s Treatment of Epilepsy*, 6th and 7th editions. He is part of pending patent applications to detect, treat, and predict seizures and to diagnose epilepsy. He receives research support from the NIH, Patient-Centered Outcomes Research Institute, Epilepsy Research Fund, the Epilepsy Foundation of America, the Epilepsy Therapy Project, the Pediatric Epilepsy Research Foundation and received research grants from Lundbeck, Eisai, Upsher-Smith, Mallinckrodt, Sage, and Pfizer. He served in the past as a consultant for Zogenix, UCB, Engage, Amzell, Upsher Smith, Eisai, and Sunovion. He performs video EEG long-term and ICU monitoring, and other electrophysiologic studies at Boston Children’s Hospital and affiliated hospitals and bills for these procedures, and he evaluates pediatric neurology patients and bills for clinical care. He has received speaker honorariums from national societies including the American Academy of Neurology, American Education Services, and American Clinical Neurophysiology Society, and for grand rounds at various academic centers. T.L. is co-inventor of the TriVox Health technology. In the future, it is possible that this technology will be sold commercially. If this were to occur, Dr. Loddenkemper and Boston Children’s Hospital might receive financial benefits in the form of compensation. As in all research studies, the hospital has taken steps designed to ensure that this potential for financial gain does not endanger research participants or undercut the validity and integrity of the information learned by this research. His wife, Dr. Karen Stannard, is a pediatric neurologist. She performs video EEG long-term and ICU monitoring, EEGs, and other electrophysiologic studies and bills for these procedures, and she evaluates pediatric neurology patients and bills for clinical care. Go to Neurology, org/N for full disclosures.

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### Appendix 1 Authors

| Name                     | Location                                    | Contribution                                                                 |
|--------------------------|---------------------------------------------|------------------------------------------------------------------------------|
| Iván Sánchez Fernández, MD, MPH, MBI | Division of Epilepsy and Clinical Neurophysiology, Department of Neurology, Boston Children’s Hospital, Harvard Medical School, Boston, MA | Participated in drafting and revising the manuscript for content, including medical writing, in study concept and design, data acquisition, analysis and interpretation of data, statistical analysis, and study supervision or coordination |
| Nicholas S. Abend, MD, MSCE | Division of Neurology, Departments of Neurology and Pediatrics, Children’s Hospital of Philadelphia and University of Pennsylvania, Philadelphia, PA | Participated in revising the manuscript for content, including medical writing, in study concept and design, data acquisition, and study supervision or coordination |
| Marta Amengual-Gual, MD | Division of Epilepsy and Clinical Neurophysiology, Department of Neurology, Boston Children’s Hospital, Harvard Medical School, Boston, MA | Participated in revising the manuscript for content, including medical writing, in study concept and design, data acquisition, and study supervision or coordination |
| Anne Anderson, MD | Section of Pediatric Critical Care Medicine, Department of Pediatrics, Baylor College of Medicine, Houston, TX | Participated in revising the manuscript for content, including medical writing, in study concept and design, data acquisition, and study supervision or coordination |
| Ravindra Arya, MD, DM | Division of Neurology, Cincinnati Children’s Hospital Medical Center, University of Cincinnati, Cincinnati, OH | Participated in revising the manuscript for content, including medical writing, in study concept and design, data acquisition, and study supervision or coordination |
| Cristina Barcia Aguilar, MD | Division of Epilepsy and Clinical Neurophysiology, Department of Neurology, Boston Children’s Hospital, Harvard Medical School, Boston, MA | Participated in revising the manuscript for content, including medical writing, in study concept and design, data acquisition, and study supervision or coordination |
| James Nicholas Brenton, MD | University of Virginia Health, Charlottesville, VA | Participated in revising the manuscript for content, including medical writing, in study concept and design, data acquisition, and study supervision or coordination |
### Appendix 1 (continued)

| Name                        | Location                                                                 | Contribution                                                                                                                                                                                                 |
|-----------------------------|--------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Jessica L. Carpenter, MD    | Center for Neuroscience, Children's National Medical Center, George Washington University School of Medicine and Health Sciences, Washington, DC | Participated in revising the manuscript for content, including medical writing, in study concept and design, data acquisition, and study supervision or coordination                                                   |
| Kevin E. Chapman, MD        | Departments of Pediatrics and Neurology, Children's Hospital Colorado, University of Colorado School of Medicine, Aurora, CO | Participated in revising the manuscript for content, including medical writing, in study concept and design, data acquisition, and study supervision or coordination                                                   |
| Justice Clark, MPH          | Division of Epilepsy and Clinical Neurophysiology, Department of Neurology, Boston Children's Hospital, Harvard Medical School, Boston, MA | Participated in revising the manuscript for content, including medical writing, in study concept and design, data acquisition, and study supervision or coordination                                                   |
| Raquel Farias-Moeller, MD   | Department of Pediatric Neurology, Children's Hospital of Wisconsin, Medical College of Wisconsin, Milwaukee, WI | Participated in revising the manuscript for content, including medical writing, in study concept and design, data acquisition, and study supervision or coordination                                                   |
| William D. Gaillard, MD     | Center for Neuroscience, Children's National Medical Center, George Washington University School of Medicine and Health Sciences, Washington, DC | Participated in revising the manuscript for content, including medical writing, in study concept and design, data acquisition, and study supervision or coordination                                                   |
| Marina Gaínza-Lein, MD      | Division of Epilepsy and Clinical Neurophysiology, Department of Neurology, Boston Children's Hospital, Harvard Medical School, Boston, MA | Participated in drafting and revising the manuscript for content, including medical writing, in study concept and design, data acquisition, and interpretation of data, and study supervision or coordination |
| Tracy Glauser, MD           | Division of Neurology, Cincinnati Children's Hospital Medical Center, University of Cincinnati, Cincinnati, OH | Participated in revising the manuscript for content, including medical writing, in study concept and design, data acquisition, and study supervision or coordination                                                   |
| Joshua Goldstein, MD        | Rush D. & Ken M. Davee Pediatric Neurocritical Care Program, Northwestern University Feinberg School of Medicine, Chicago, IL | Participated in revising the manuscript for content, including medical writing, in study concept and design, data acquisition, and study supervision or coordination                                                   |
| Howard P. Goodkin, MD, PhD  | University of Virginia Hospital, Charlottesville, VA | Participated in revising the manuscript for content, including medical writing, in study concept and design, data acquisition, and study supervision or coordination                                                   |
| Réjean M. Guerrero, DO      | Division of Pediatric and Developmental Neurology, Departments of Neurology, Washington University School of Medicine, St. Louis, MO | Participated in revising the manuscript for content, including medical writing, in study concept and design, data acquisition, and study supervision or coordination                                                   |
| Yi-Chen Lai, MD             | Section of Pediatric Critical Care Medicine, Department of Pediatrics, Baylor College of Medicine, Houston, TX | Participated in revising the manuscript for content, including medical writing, in study concept and design, data acquisition, and study supervision or coordination                                                   |
| Tiffani McDonough, MD       | Ruth D. & Ken M. Davee Pediatric Neurocritical Care Program, Northwestern University Feinberg School of Medicine, Chicago, IL | Participated in revising the manuscript for content, including medical writing, in study concept and design, data acquisition, and study supervision or coordination                                                   |
| Mohamad A. Mikati, MD       | Division of Pediatric Neurology, Duke University Medical Center, Duke University, Durham, NC | Participated in revising the manuscript for content, including medical writing, in study concept and design, data acquisition, and study supervision or coordination                                                   |
| Lindsey A. Morgan, MD       | Department of Pediatrics and Neurology, Seattle Children's Hospital, University of Washington and Center for Integrative Brain Research, Seattle Children's Research Institute, Seattle, WA | Participated in revising the manuscript for content, including medical writing, in study concept and design, data acquisition, and study supervision or coordination                                                   |
| Edward Novotny, Jr., MD     | Department of Pediatrics and Neurology, Seattle Children's Hospital, University of Washington and Center for Integrative Brain Research, Seattle Children's Research Institute, Seattle, WA | Participated in revising the manuscript for content, including medical writing, in study concept and design, data acquisition, and study supervision or coordination                                                   |
| Eric Payne, MD, MPH         | Department of Neurology, Mayo Clinic, Mayo Clinic School of Medicine, Rochester, MN | Participated in revising the manuscript for content, including medical writing, in study concept and design, data acquisition, and study supervision or coordination                                                   |
### Appendix 1 (continued)

| Name                  | Location                                                                 | Contribution                                                                 |
|-----------------------|---------------------------------------------------------------------------|------------------------------------------------------------------------------|
| Katrina Peariso, MD, PhD | Division of Neurology, Cincinnati Children's Hospital Medical Center, University of Cincinnati, Cincinnati, OH | PARTICIPATED IN REVISIONING THE MANUSCRIPT FOR CONTENT, INCLUDING MEDICAL WRITING, IN STUDY CONCEPT AND DESIGN, DATA ACQUISITION, AND STUDY SUPERVISION OR COORDINATION |
| Juan Piantino, MD     | Department of Neurology, Doernbercher Children's Hospital, Oregon Health & Science University, Portland, OR | PARTICIPATED IN REVISIONING THE MANUSCRIPT FOR CONTENT, INCLUDING MEDICAL WRITING, IN STUDY CONCEPT AND DESIGN, DATA ACQUISITION, AND STUDY SUPERVISION OR COORDINATION |
| Adam Ostendorf, MD    | Department of Neurology, Nationwide Children's Hospital, Ohio State University, Columbus, OH | PARTICIPATED IN REVISIONING THE MANUSCRIPT FOR CONTENT, INCLUDING MEDICAL WRITING, IN STUDY CONCEPT AND DESIGN, DATA ACQUISITION, AND STUDY SUPERVISION OR COORDINATION |
| Tristan T. Sands, MD, PhD | Division of Child Neurology & Institute for Genomic Medicine, Columbia University Irving Medical Center, New York Presbyterian Hospital, New York, NY | PARTICIPATED IN REVISIONING THE MANUSCRIPT FOR CONTENT, INCLUDING MEDICAL WRITING, IN STUDY CONCEPT AND DESIGN, DATA ACQUISITION, AND STUDY SUPERVISION OR COORDINATION |
| Kumar Sannagowdara, MD | Department of Pediatric Neurology, Children's Hospital of Wisconsin, Medical College of Wisconsin, Milwaukee, WI | PARTICIPATED IN REVISIONING THE MANUSCRIPT FOR CONTENT, INCLUDING MEDICAL WRITING, IN STUDY CONCEPT AND DESIGN, DATA ACQUISITION, AND STUDY SUPERVISION OR COORDINATION |
| Robert C. Tasker, MBBS, MD | Department of Neurology, Department of Anesthesiology, Critical Care and Pain Medicine, Boston Children's Hospital, Harvard Medical School, Boston, MA | PARTICIPATED IN REVISIONING THE MANUSCRIPT FOR CONTENT, INCLUDING MEDICAL WRITING, IN STUDY CONCEPT AND DESIGN, DATA ACQUISITION, AND STUDY SUPERVISION OR COORDINATION |
| Dimtriy Tchaplyzynov, MD | Division of Pediatric Neurology, Duke University Medical Center, Duke University, Durham, NC | PARTICIPATED IN REVISIONING THE MANUSCRIPT FOR CONTENT, INCLUDING MEDICAL WRITING, IN STUDY CONCEPT AND DESIGN, DATA ACQUISITION, AND STUDY SUPERVISION OR COORDINATION |
| Alexis A. Topjian, MD, MSCE | Division of Critical Care Medicine, The Children's Hospital of Philadelphia, The Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA | PARTICIPATED IN REVISIONING THE MANUSCRIPT FOR CONTENT, INCLUDING MEDICAL WRITING, IN STUDY CONCEPT AND DESIGN, DATA ACQUISITION, AND STUDY SUPERVISION OR COORDINATION |
| Alejandra Vasquez, MD | Division of Epilepsy and Clinical Neurophysiology, Department of Neurology, Boston Children's Hospital, Harvard Medical School, Boston, MA | PARTICIPATED IN REVISIONING THE MANUSCRIPT FOR CONTENT, INCLUDING MEDICAL WRITING, IN STUDY CONCEPT AND DESIGN, DATA ACQUISITION, AND STUDY SUPERVISION OR COORDINATION |

### Appendix 2 Coinvestigators

Coinvestigators are listed at lww.com/WNL/B156

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