SUPPLEMENTAL MATERIAL:
Comparative Effectiveness and Safety of Seizure Prophylaxis Among Adults after Acute Ischemic Stroke

A. SUPPLEMENTAL TEXT

Get with the Guidelines

The data collected in GWTG included patient sociodemographic, health history, and clinical data detailing the stroke admission (e.g., stroke severity assessment as defined by the validated NIH Stroke Severity Scale, NIHSS).[24, 25] Each patient discharged from the healthcare system with a stroke diagnosis had their data checked for quality and submitted to the GWTG Registry, as required by the Massachusetts Department of Public Health for Primary Stroke Service designation and the Joint Commission Comprehensive Stroke Center program.[21, 23]

Operational Definitions for Measures of Interest

Seizure prophylaxis

We use the term "seizure prophylaxis", instead of "epilepsy treatment", because the diagnosis of epilepsy would require meeting one of the ILAE's operational definition of epilepsy.[57, 58] However, in the acute brain injury phase, it is difficult to determine if a new early seizure is truly unprovoked. For instance, the AIS changes (e.g., metabolic dysfunction of intracellular ions, increased glutamate) and the hospitalization bring several potential provoking factors (e.g., exposure to new drugs, sleep deprivation, hypoxia, sepsis).[48] Because these factors are theoretically transient, one could conservatively argue that every seizure in this acute setting is potentially "provoked" seizure.[59]

Socio-demographic factors

We used data from RPDR to obtain several demographic factors such as age, sex, race, ethnicity, language, and addresses. We obtained a series of clinical factors and then derive some validated summary measures, such as the Charlson Comorbidity Index (CCI,) which can predict a patient's mortality for short and long term by categorizing a range of comorbidities (i.e., a total of 22 conditions such as heart disease). We derived the CCI from the GWTG and RPDR datasets (baseline outpatient and in-hospital data). The CCI is based on the International Classification of Diseases (ICD) diagnosis codes.[60] It is also a good measure of medical morbidity, which may predict seizures (antiseizure drug (ASD) use) and mortality.

Stroke characteristics and severity

Stroke severity is a strong predictor of ASD initiation, seizures, and mortality.[61] Factors of stroke severity include cortical infarction and stroke extension,[62] neuroimaging traits (e.g., infarct volume and location, diffusion-perfusion mismatch, poor collateral blood flow, development of cerebral edema in non-lacunar ischemic stroke), and ischemic stroke mechanism.

We used the validated National Institutes of Health stroke severity score (NIHSS), which is a summary measure of stroke severity and may be associated with seizure risk (and ASD initiation) and mortality. We will obtain NIHSS from the GWTG dataset (in-hospital data). The NIHSS score is defined as the sum of 15 individually evaluated elements, and ranges from 0 to 42. Stroke severity scores can be used as a continuous measure or categorized as no stroke symptoms (0), minor stroke (NIHSS 1-4), moderate stroke (NIHSS 5-15), moderate to severe stroke (NIHSS 16-20), and severe stroke (NIHSS 21-42).[63]

Medication Burden Index

Polypharmacy is a major risk factor for adverse drug reactions and has been associated with mortality.[64] We will use data from the 6 previous months prior to stroke admission to estimate the total daily oral medication other than antiseizure drugs as follows: “Each unique medication identified was classified as a) indicated for at least one of the 21 chronic medical conditions, b) indicated for a diagnosis other than the 21 chronic medical conditions considered, or c) a daily health regimen agent. Several daily oral medications were computed as 1) A+B, and 2) A+B+C. Estimates of numbers of daily medications for the management of co-morbid conditions are presented as the sum of medications potentially indicated for each condition. Estimates of the proportion of daily oral “medication” intake due to daily health regimens were the sum of the number of agents that could not be identified as potentially indicated for a medical condition. To estimate total daily oral medication intake, health regimen agents were combined with the medications for each disease combination and counted in the total”.[64]

Healthcare Utilization

We examined several measures of healthcare utilization, including visit frequency and location and institutionalization (e.g., frequency of ED admissions). We obtained discharge status and length of stay for each stroke admission.

Insurance coverage

Some patients might come to the academic institution but might not follow-up within the hospital MGB system that generates the data at hand (i.e., “leakage” or receiving care elsewhere). Some patients might not be able to come for follow-up care if they are no longer covered by any of the several insurance plans of the MGB system. For all patients, we created a variable named “last service date”, which indicates the date of the last use of the system (could be any trace of medication fill, appointment, phone call, etc.). We then defined loss-to-

follow-up due to loss from the system an observation is censored at either 30 days after their last encounter date in RPDR, or 30 days after Day 0, whichever comes first.

Electroencephalogram (EEG)

Results from EEG can influence the decision to start an ASD. EEG monitoring also questionably improves the probability of survival by diagnosing subclinical seizures or status epilepticus.[6] As discussed in the background section, some patients with certain types of EEG abnormalities would likely benefit from ASDs within hospitalization (e.g., status epilepticus, continuous generalized periodic discharges at a rate greater than 1 Hz, abundant periods of the lateralized rhythmic delta with evolving epileptiform discharges). Others could mostly be harmed by unnecessary ASD initiation (e.g., sporadic epileptic discharges, generalized rhythmic delta activity, multifocal discharges with a triphasic morphology and anterior-posterior gradient). We will create a baseline and time-varying variables for EEG performed, along with the duration of EEG monitoring (e.g., EEG routine vs prolonged 12-24h monitoring).

Specifically, we will obtain a baseline EEG measure with the count of EEGs done during the 6 months prior to stroke admission date. For the time-varying EEG variable, we will create one for each day (t=0 ... t=30). If patient had prolonged EEG monitoring (e.g., 24-48h) the measure will reflect the days of monitoring. If the patient had routine EEG (e.g., <2h), then we will mark that day as one day of EEG surveillance and resume the search for other codes in the subsequent day.

ED visits

An ED visit is a marker of health resource utilization, and time-varying severity (which could represent drug adverse effects, disease complications, decompensated comorbid conditions, etc.). Like EEG, we obtained a baseline ED visit variable with a count of ED visits during the 6 months prior to the stroke admission date. For the time-varying ED visits variable, we will create one indicator variable for each day (t=0 ... t=30), and this will reflect a visit to an ED in the previous 24h of time=t, among those still alive and in the community-dwelling setting.

Methods – Summarized

Ideally, we would address the comparative effectiveness and safety question in this population by randomizing eligible patients at the time of their hospital admission into those assigned ASD for early seizure prophylaxis in the following seven days vs a control group. If this was possible, we could repeat this study with different exposure windows, and we could count death rates in each group at the end of a 30-day follow-up period. However, such trials require a huge sample size, and are currently not feasible in such a vulnerable population (i.e., older patients admitted after AIS are often frail and unable to articulate care needs and preferences).

In this context of arguable indications and exposure windows, we have leveraged multiple new analytical methods to answer whether ASDs for early ("seven days", an arbitrary threshold commonly used)[47, 48, 65] seizure prophylaxis would cause net benefit or harm.

To summarize, in the process of estimating standardized survival curves for the two strategies of interest, we arranged the data with person-time structure, conducted parametric estimation of hazards with pooled logistic regression model with time-varying intercept as a function of time (each day), allowed for time-varying hazard ratio by adding product terms between strategy (initiate vs defer) and time (days), computed survival probabilities using predictions of the conditional survival for each day under each treatment level (initiate vs defer), then estimated inverse probability (IP) weights for censoring (SWC), then estimated IP weights for strategy (SWS), then combined: SWA × SWS. Finally, we used bootstrapping to calculate an approximate 95% confidence interval of the difference of standardized survivals (to address the re-sampling issue introduced by the method).

Statistical Analysis - Detailed

To evaluate the effect of ASD initiation in the first seven days post-AIS on 30-day mortality, we estimated mortality probabilities using model-based predictions of the conditional survival for each day under each treatment strategy.

We first estimated inverse-probability weights by modeling treatment initiation in the original dataset, duplicated the dataset to create "clones," censored the clones as previously described, and assigned them appropriate weights to rebalance the two groups to address both cloning and probability of treatment selection (*cloning-censoring-weighting*).[30] The model for treatment initiation during the grace period was a pooled logistic regression over person-days. It included validated measures of stroke severity and clinical severity (Charlson comorbidity score), all measured at admission, and post-admission measures of the daily prescription count, CMO status, seizures or seizure-like events, and receipt of electroencephalogram, as well as a time-varying intercept (see Table S2 for model parameters for estimating seizure prophylaxis initiation weights).

In the weighted dataset, we fit a time-varying pooled logistic regression model for death as a function of treatment strategy (i.e., an indicator of which method a given clone belonged to) and interaction terms between treatment strategy and time, measured in days from admission until the end of the follow-up to allow for time-varying effects. We predicted mortality probabilities for each day under each treatment strategy from this model.[66] We estimated absolute differences in mean 30-day mortality. To illustrate the magnitude of confounding bias beyond the selection or immortal person-time biases avoided by the clone-censor-weight approach, we repeated the analysis without confounders in the model for treatment initiation

during the grace period, i.e., the model corrected only for the duplications in the pseudo-population of clones. Finally, we obtained 95% confidence intervals for all measures using the bootstrap with 500 replications.

We separately created IPT weights with some variables collected at baseline (i.e., NIHSS, prescription count at baseline, and seizure-like events at baseline) to show the balance (i.e., all SMDs <0.2 after applying IPT weights), please see Supplemental Table S2.

Of note, patients undergoing procedures such as IV injection of tissue plasminogen activator and Endovascular thrombectomy (AIS severity proxies) are at greater risk to develop post-stroke seizures and there could be differential probability of receipt of prophylaxis.

We have included AIS severity (NIHSS scores) in the models (Supplemental Text, page 4, section Emulated Trial Design with Cloning – Methods) to address any additional risk due to procedures used to treat more severe stroke. The selection of variables includes subject matter expertise, appreciation of a directed acyclic diagram based on a specific research question, and examination of the actual distribution of the factors in relation to mortality.[19, 27-30]

Missing Data

We examined patterns of missingness for all pertinent variables to confirm that there was no informative missingness (i.e., variables used in the analysis had negligible missing information).

Pre-planned Stratified Analysis

ASDs may be more harmful to older patients and patients with moderate-to-severe stroke relative to mild stroke. Therefore, we repeated the above analyses stratified by categories of age (65-74 years and ≥75 years) and NIHSS stroke severity (e.g., mild versus moderate).

Technical Section for Addressing Immortal-Person Time

In this study, the trial is about "start treatment within the first seven days after admission" in the same pattern that we would have seen people start treatment in real-life, with everyone starting on day seven if they haven't already done so. In this approach, we first clone the population. Therefore, there is no table 1 to illustrate differences across the two groups; they are identical (one clone is assigned treatment and the other clone is not). Then, we apply censoring weights as they violate one of the protocols. At that time, we use the baseline and time-dependent covariates that affect the change in strategy. In this design, results may be sensitive to when during the seven days people start treatment.

Solving a common methodological problem in observational data with staggered treatment initiation requires aligning the start of follow-up and exposure assignment. Two possible

approaches correspond to two different target trials. First, our proposed target trial, where treatment assignment and follow-up start at baseline (i.e., hospital admission), is the first-time treatment can be initiated. In a randomized trial, the assigned treatment strategy would be known at that time, even if no treatment was initiated that day; in observational studies, assigning patient "clones" to each treatment strategy allows time-zero alignment.[52-55, 67] Second, we could have emulated a trial where patients are randomized each day throughout the first week post-AIS as they become eligible (e.g., a new indication). There would be seven time-zeros when follow-up would start for those assigned to initiating and not initiating on that day in the target trial and, as well as in the observational emulation. Both approaches help avoid selection and immortal time bias by ensuring that the start of follow-up and treatment assignment are aligned, as they would be in a randomized trial.

Alternative traditional approaches to deal with grace periods for exposure initiation have included the following: First, if epilepsy-specific ASD initiators are compared to non-initiators and the day of AIS admission is considered time zero, the start of follow-up would not be aligned with exposure initiation unless treatment initiation occurs exclusively at baseline. This is generally not the case, so patients have already survived several days to be treated. The treated group would therefore have no deaths during the first days of follow-up, a bias that is referred to as an "immortal time bias."[19, 68, 69] More generally, this bias arises in naïve analyses which use post-baseline information to define exposure strategies.[69] Second, an analysis that instead started follow-up for both the treated and untreated groups after the seven-day treatment initiation window would be missing deaths in both groups that occurred during that window. If mortality differed between groups, they would no longer be comparable, even in a randomized trial (with randomization at admission). Excluding the first week of follow-up would miss potential acute effects of epilepsy-specific ASDs and would deplete the sample of the most susceptible patients. Third, starting follow-up of exposed patients on the day of treatment initiation and of unexposed ones on the day of admission would also be biased in the presence of mortality trends during the first days post-AIS since those initiating treatment later would have a different baseline risk.

> ***Cloning and Censoring:*** In the "Initiate Treatment within seven days" dataset, we create a copy of the original dataset but kept data points on clones that started treatment within the grace period and patient clones that were censored at the end of the grace period because they did not begin treatment within the grace period (censor unless it is during the grace period). In the "Do not Initiate Treatment within seven days" dataset, we create a copy of the original dataset but keep data points on clones that never started treatment and clones that started treatment before they started (i.e., they are being censored for starting, censor if start treatment any time during the grace period). Then, we create a cloned dataset consisting of the two combined datasets (i.e., cloned and censored, and now ready to proceed with weighting).

Weighting: In the original data, we fit a weight model among people yet to start treatment (model for treatment initiation). Then, in the cloned dataset, we apply weights [Pr (uncensored at time t | uncensored at time t – 1]. In the treatment arm: the weight contribution is one during the grace period because Pr (uncensored | grace period) = 1 even if the patient does not start treatment.

Patients who have started treatment within the grace period (i.e., protocol compliant) are therefore uncensored at the end of the grace period (e.g., as illustrated in Supplementary Figure S1-C, individual 2), but they need to receive an upweight to account for those who deviated from the protocol (i.e., those who did not start treatment but were supposed to start, based on their assigned strategy – as illustrated in Supplementary Figure S1-C, individual 3). After the grace period (so any other days), the patients cannot be censored because they have already started treatment, so the weight is 1.

In the no treatment arm, patients can get censored during the grace period for starting treatment (e.g., as illustrated in Supplementary Figure S1-D, individuals 2 and 4), then they receive a weight [Pr (no treatment)]. These weights are updated daily [Pr (uncensored at time t | uncensored at time t - 1, history) x Pr (uncensored at time t - 1 | uncensored at time t - 2, history) x, etc.]. These inverse-probability weights allow for adjustment because the same patient does not adhere to both treatment strategies and, therefore must be censored from one of them.[52-55, 67]

Weight creation and Model specifications*:* First, we defined the model for treatment initiation among patients yet to start treatment, and we predict Pr(untreated at time t | untreated at time t - 1): *Numerator: Logit (A/1-A) = B0 + B1*(Age) + B2*(Race)*. *Denominator: Logit (A/1-A) = B0 + B1*(NIHSS) + B2*(Charlson Comorbidity Score) + B3*(CMO Status) + B4*(Seizure-like Event) + B5*(Electroencephalogram) + B6*(Prescription count).* Next, we estimate the weights = 1 / Pr (uncensored at time t | baseline & time-varying baseline variables) and the stabilized weights = (numerator product of treatment weights)/(denominator product of treatment weights). Finally, we define the outcome models (logistic regression), that use stabilized weights in the cloned data and predicts death hazard (int_surv = 1 – haz) within each day: *Logit (Death/1-Death) = B0 + B1*(Date_post_adm) + B2*I(Date_post_adm*Date_post_adm) + B3*(A*Date_post_adm).* Then, we obtain average risk and average survival over each treatment group for the 30 days (i.e., pooled logistic regression, surv = cumprod(int_surv) and risk = 1 – surv). In an additional step with arguable assumptions, we approximate the hazard ratio for the first 30 days with outcome model with constant

treatment effect, that also uses stabilized weights in the cloned data: Logit (D/1-D) = B0 + B1*(Date_post_adm) + B2*I(Date_post_adm*Date_post_adm) + B3*(A).”

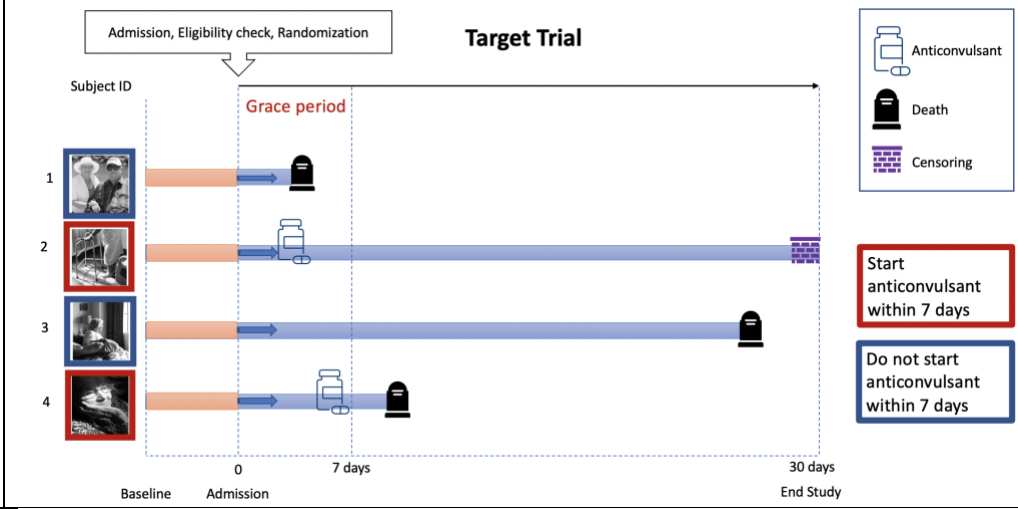
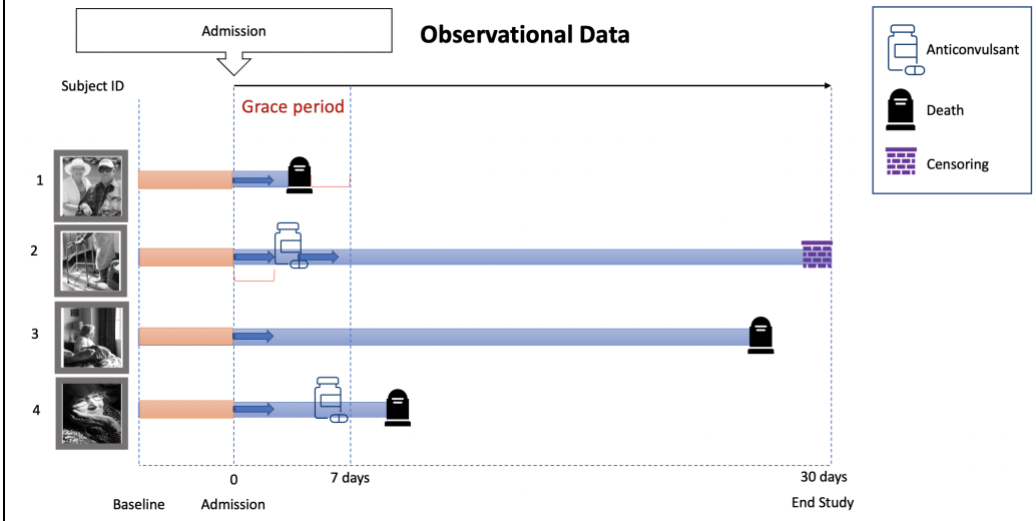
Emulated Trial Design with Cloning

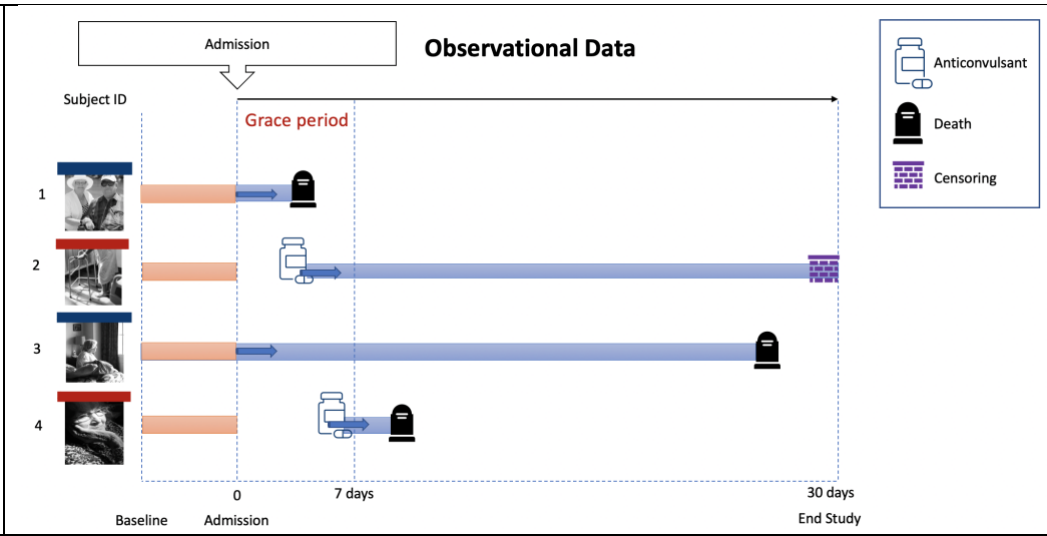
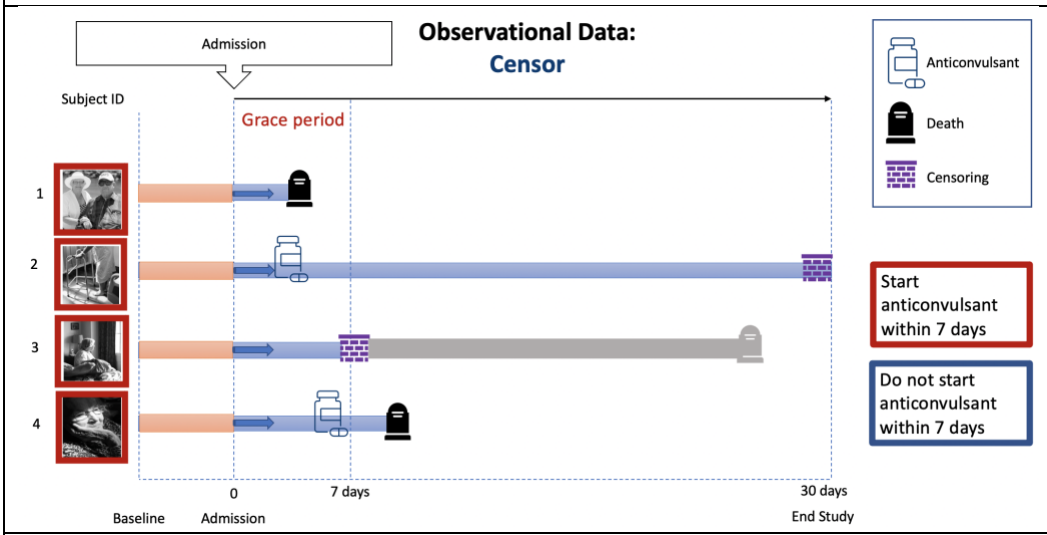
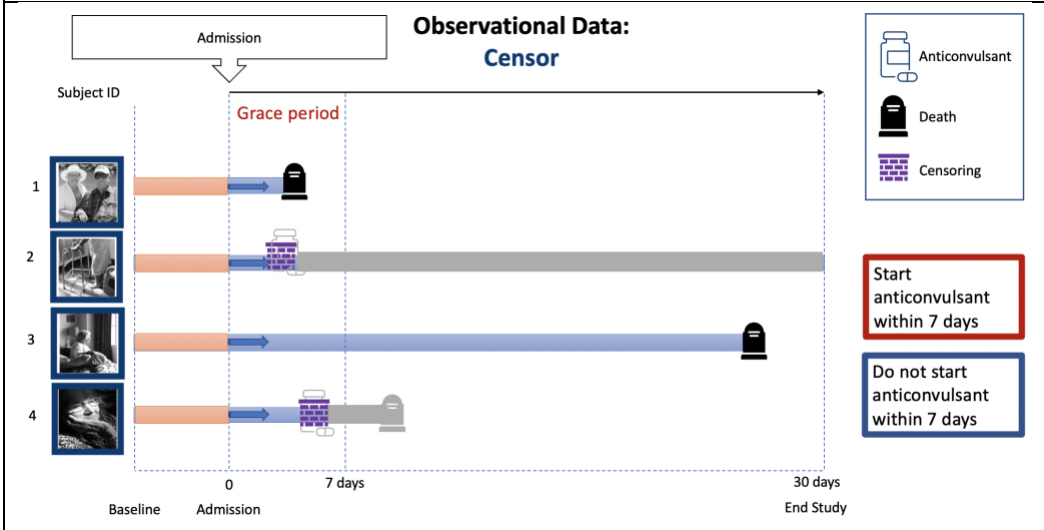
Unlike in a randomized trial, we could not know which treatment strategy the patient had been assigned to until the day of the prescription (for those exposed) or seven days post-AIS (for those unexposed). Therefore, for patients who died within seven days without initiation, we could not know if they would have received treatment had they not died. Thus, for the seven days post-AIS, follow-up days until treatment initiation or death count towards both treatment strategies. To carry out such counting, we duplicated the dataset, creating “clones” of each patient so that each clone would contribute to both treatment strategies until their strategy is known. The follow-up of a clone is censored when its treatment strategy is violated, i.e., clones assigned to no-initiation were censored if they initiated treatment within those seven days, and clones assigned to initiation were censored if they did not initiate by day seven. Thus, only one clone remains in the dataset after the first seven days of follow-up. Lastly, inverse probability weights are applied to the generated pseudo-population of clones for each treatment strategy to address the fact that the same patient does not adhere to both treatment strategies. To mimic randomization, these weights also account for the non-random treatment initiation. This "cloning-censoring-weighting” approach has been used in previous studies and avoids a common methodological problem in observational data with staggered treatment initiation.

In the process of estimating standardized survival curves for the two strategies of interest, we arranged the data with person-time structure, conducted parametric estimation of hazards with pooled logistic regression model with time-varying intercept as a function of time (each day), allowed for time-varying hazard ratio by adding product terms between strategy (initiate vs defer) and time (days), computed survival probabilities using predictions of the conditional survival for each day under each treatment level (initiate vs defer), then estimated inverse probability (IP) weights for censoring (SW^C), then estimated IP weights for strategy (SW^S), then finally combined: $SW^A \times SW^S$. Finally, we used bootstrapping to calculate an approximate 95% confidence interval of the difference of standardized survivals (to address the re-sampling issue introduced by the method).

B. SUPPLEMENTAL FIGURES

Figure S1. Simplistic Representation of the Problem and Solution

	Design	Simplistic illustration of dataset
A.	Target Trial	
B.	Naïve aligned and crude	

C.	**Misaligned** crude	
D.	Cloned, aligned, crude	Initiate Treatment within 7 Days Clone  Initiate Treatment within 7 Days Clone 

Legend: This list of figures illustrates the problem of immortal time bias.

A. Target trial. Such trial does not exist in real life. We illustrated four patients: patients 2 and 4 are randomized to receive epilepsy-specific ASD within 7 days, and we will know that information about randomization at admission. Patients 1 and 3 are randomized to not receive epilepsy-specific ASDs within 7 days. They are then followed from admission until they either die or until the end of the study. Here, they are censored because the study ended at 30 days.

B. Naïve aligned, crude. Depicts crude naïve analysis **including the immortal time**, therefore **introducing immortal time bias**. In patient 4, the follow-up starts at admission, but the person is only exposed starting at day six. In this approach, some of the early deaths are misattributed to the unexposed group (i.e., patient 4 must survive up until day six to be able to receive the exposure and be classified as exposed).

C. Misaligned, crude. Depicts crude or naïve analysis **excluding the immortal time to avoid introducing that bias.** In patient 4, this approach ignores the survival of this person for up to day six and then starts the follow-up at the exposure initiation day, while the unexposed start follow-up continues to be at admission. In this approach, the exposed may be a selective group of patients that are evolving with complications and are about to have highest mortality rate in the subsequent days.

D. Cloned, aligned, crude. First, we create pseudo-observations or 'clones' for each patient, and then assign each of those clones to one of the two treatment strategies at the time of the hospital admission. Next, we proceed to artificially censor those who deviate from the assignment strategy. This is to ensure that clones follow their assigned strategy after the time zero. For instance, patient 2 in the "Initiate Treatment within 7 Days Clone dataset" was assigned to start treatment and started within the period that the patient was supposed to start. However, patient 3 was supposed to start treatment within seven days but deviated from the assigned strategy and needs to be censored. Additional illustrative examples can be found on previously published peer-reviewed publications.[19, 20]

Figure S2. Patterns of Drug Initiation vs Count of Deaths

	Post-stroke days – count of deaths							
	0	1	2	3	4	5	6	Total count (from yellow only)
Initiate at day 0								
Yes	0/64 = 0%	1/64 = 1.56%	1/63 = 1.59%	4/62 = 6.45%	2/58 = 3.45%	1/56 = 1.79%	1/55 = 1.82%	11/64 = 17.19%
No	1/3107 = 0.03%	26/3106 = 0.84%	33/3080 = 1.07%	40/3047 = 1.31%	47/3007 = 1.56%	29/2960 = 0.98%	38/2931 = 1.3%	242/3107 = 7.79%
Initiate at day 1 (not before)								
Yes	0/55 = 0%	0/55 = 0%	1/55 = 1.82%	1/54 = 1.85%	2/53 = 3.77%	1/51 = 1.96%	2/50 = 4%	8/55 = 14.55%
No	1/3052 = 0.03%	26/3051 = 0.85%	32/3025 = 1.06%	39/2993 = 1.3%	45/2954 = 1.52%	28/2909 = 0.96%	36/2881 = 1.25%	233/3051 = 7.64%
Initiate at day 2 (not before)								
Yes	0/14 = 0%	0/14 = 0%	0/14 = 0%	0/14 = 0%	0/14 = 0%	0/14 = 0%	0/14 = 0%	1/14 = 7.14%
No	1/3038 = 0.03%	26/3037 = 0.86%	32/3011 = 1.06%	39/2979 = 1.31%	45/2940 = 1.53%	28/2895 = 0.97%	36/2867 = 1.26%	206/3011 = 6.84%
Initiate at day 3 (not before)								
Yes	0/5 = 0%	0/5 = 0%	0/5 = 0%	0/5 = 0%	0/5 = 0%	0/5 = 0%	0/5 = 0%	0/5 = 0%
No	1/3033 = 0.03%	26/3032 = 0.86%	32/3006 = 1.06%	39/2974 = 1.31%	45/2935 = 1.53%	28/2890 = 0.97%	36/2862 = 1.26%	174/2974 = 5.85%
Initiate at day 4 (not before)								
Yes	0/3 = 0%	0/3 = 0%	0/3 = 0%	0/3 = 0%	0/3 = 0%	0/3 = 0%	0/3 = 0%	0/3 = 0%
No	1/3030 = 0.03%	26/3029 = 0.86%	32/3003 = 1.07%	39/2971 = 1.31%	45/2932 = 1.53%	28/2887 = 0.97%	36/2859 = 1.26%	135/2932 = 4.6%
Initiate at day 5 (not before)								
Yes	0/6 = 0%	0/6 = 0%	0/6 = 0%	0/6 = 0%	0/6 = 0%	1/6 = 16.67%	0/5 = 0%	1/6 = 16.67%
No	1/3024 = 0.03%	26/3023 = 0.86%	32/2997 = 1.07%	39/2965 = 1.32%	45/2926 = 1.54%	27/2881 = 0.94%	36/2854 = 1.26%	89/2881 = 3.09%
Initiate at day 6 (not before)								
Yes	0/4 = 0%	0/4 = 0%	0/4 = 0%	0/4 = 0%	0/4 = 0%	0/4 = 0%	0/4 = 0%	0/4 = 0%
No	1/3020 = 0.03%	26/3019 = 0.86%	32/2993 = 1.07%	39/2961 = 1.32%	45/2922 = 1.54%	27/2877 = 0.94%	36/2850 = 1.26%	62/2850 = 2.18%

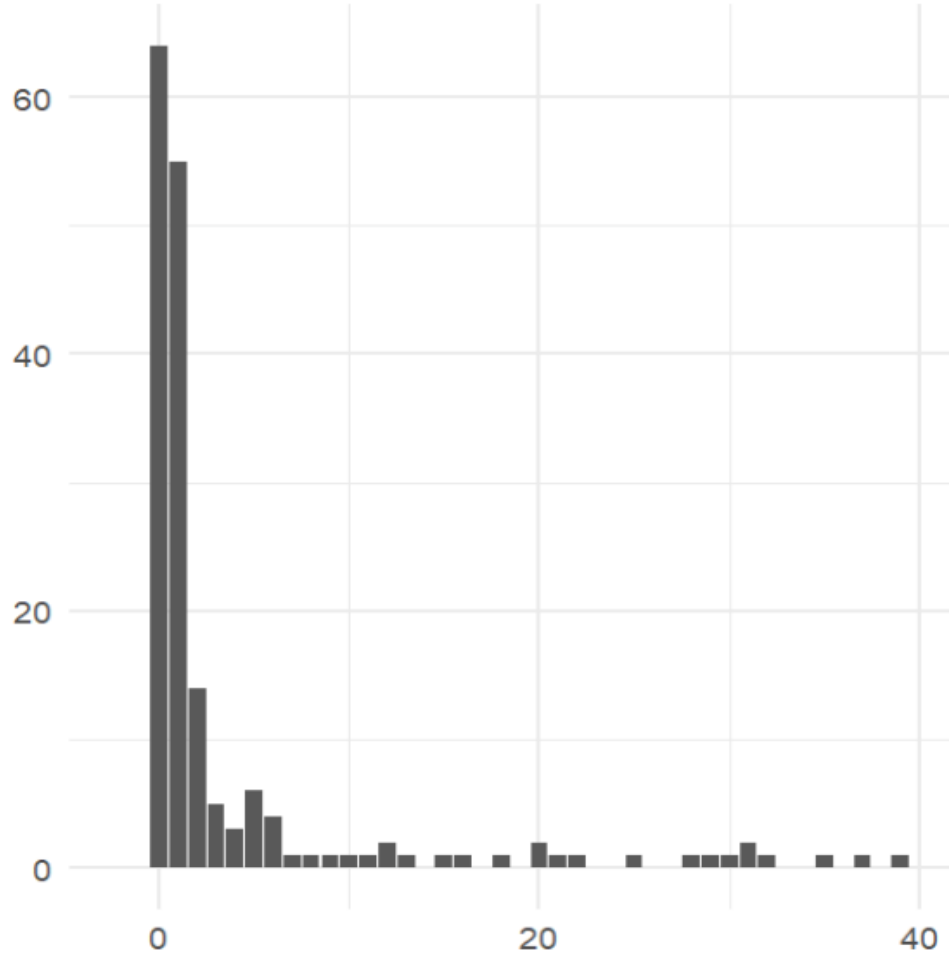
Legend: We provide a breakdown of when the medications of interest were started by post-AIS days within the seven days exposure window (from day zero to day six). In the observational data, 64 patients (42%) received one of the ASDs of interest within the first 24 hours post-AIS admission; Cumulatively, 133 patients (88%) received one of the ASDs of interest within the first 72 hours post-AIS admission. We also note that there was a significant number of deaths in the first 7 days to illustrate the degree of immortal time bias.

Definition for the values in the cells:

Numerator: Among all patients who initiate ASDs of interest on day i post AIS / initiate ASDs of interest after day i (or never initiate ASDs of interest), the count of deaths on day j post AIS.

Denominator: Among all patients who initiate ASDs of interest on day i post stroke / initiate ASDs of interest after day i (or never initiate ASDs of interest), the count of all patients at risk of death on day j post stroke, not including those censored prior to day j.
For the cells under the header “Total count (from yellow only)”:
Numerator: All deaths occurred in the post-AIS period corresponding to the **yellow cells** in that row.
Denominator: All patients at risk of death on the first **yellow cells** in that row (e.g., day 0 post AIS for those initiated ASDs of interest on day 0, day 1 post stroke for those initiated on day 1, and so on).

Figure S3. Patterns of Drug Discontinuation



Legend: We provide a breakdown of when the medications of interest were discontinued. Greater than 60% of the patients initiated on ASDs of interest were discontinued within 24h, and greater than 90% were discontinued within 30 days. Y axis: Patient count. X axis: Last day of ASD dispensation since AIS admission.

C. SUPPLEMENTAL TABLES

Table S1. List of Epilepsy-Specific ASDs

GENERIC	BRAND
Epilepsy-Specific ASD	
Acetazolamide	Diamox
Acetazolamide XR	Diamox Sequels
Brivaracetam	Briviact
Cannabidiol	Epidiolex
Eslicarbazepine	Aptiom
Ethosuximide	Zarontin
Ethotoin	Peganone
Felbamate	Felbatol
Lacosamide	Vimpat
Lamotrigine	Lamictal
Lamotrigine ER	Lamictal XR
Levetiracetam	Keppra, Roweepra, Spritam
Levetiracetam ER	Keppra XR, Roweepra XR, Elepsia XR
Methsuximide	Celontin
Perampanel	Fycompa
Phenobarbital	Solfoton, Luminal
Phenytoin	Epanutin, Dilantin, Phenytek
Retigabine, Ezogabine	Potiga
Rufinamide	Banzel, Inovelon
Tiagabine	Gabitril
Vigabatrin	Sabril, Vigadrone
Not Epilepsy-Specific ASD	
Alprazolam	Xanax, Xanax XR, Alprazolam
Carbamazepine	Epitol, Tegretol, Equetro, Teril
Carbamazepine ER	Carbatrol, Tegretol XR, Epitol ER
Chlordiazepoxide Hydrochloride	Librax
Clobazam	Frisium, Onfi, Sympazan
Clonazepam	Epitril, Klonopin, Rivotril
Clorazepate	Tranxene, Gen-Xene
Diazepam	Diastat, Valium
Divalproex Sodium	Depakote, Depakote sprinkles
Divalproex Sodium ER	Depakote ER
Estazolam	Estazolam
Flumazenil	Flumazenil
Gabapentin	Neurontin, Gralise
Gabapentin ER	Horizant
Lorazepam	Ativan
Midazolam	Midazolam, Seizalam
Oxazepam	Oxazepam
Oxcarbazepine	Trileptal

Oxcarbazepine ER	Oxtellar XR
Pregabalin	Lyrica
Primidone	Mysoline
Temazepam	Temazepam
Topiramate	Topamax
Topiramate ER	Qudexy XR, Trokendi XR
Triazolam	Halcion, Triazolam, Restoril
Valproic acid	Convulex, Depacon, Depakene, Orfiril, Valporal, Valprosid
Zonisamide	Zonegran

Table S2. Characteristics of patients by ASD exposure; standardized IPT weights

	Epilepsy-specific ASD initiator (N=3,171.34)	Epilepsy-specific ASD non-initiator (N=3,170.97)	SMD
Socio-Demographic Characteristics (recorded at admission)			
Age, mean (SD)	76.77 (8.36)	78.09 (8.45)	0.158
Female (%)	1,464.6 (46.2)	1,621.8 (51.1)	0.099
Non-white	400.9 (13.2)	496.3 (16.4)	0.089
Hispanic (%)	29.4 (1.0)	44.3 (1.5)	0.045
Primary insurance Medicare or other government (vs private) (%)	2,461.2 (77.6)	2,563.4 (80.9)	0.081
Baseline Medication Use (recorded during the 90 days before admission)			
Prescription count, Mean (SD)	6.81 (25.06)	7.86 (30.39)	0.038
Categories of medication use (%)			
No prescription recorded**	2,297.9 (72.5)	2,273.4 (71.7)	
1-4 drugs	348.9 (11.0)	347.3 (11.0)	
5-9 drugs	204.9 (6.5)	147.0 (4.6)	
>9 drugs	319.7 (10.1)	403.3 (12.7)	
Baseline Clinical Characteristics (recorded during 12 months before admission)			
Charlson comorbidity score, mean (SD)	0.91 (1.40)	1.15 (1.75)	0.149
Alzheimer's Disease and Related Dementias	90.0 (2.8)	110.0 (3.5)	0.036
Baseline Health-Resource Utilization (recorded during 12 months before admission), %			
Fall-related injury	187.2 (5.9)	342.1 (10.8)	0.177
Seizure-like events	140.3 (4.4)	174.6 (5.5)	0.05
Routine EEG	28.4 (0.9)	25.2 (0.8)	0.011
Long term EEG	3,171.3 (100.0)	3,171.0 (100.0)	<0.001
Acute Ischemic Stroke Severity (recorded at admission), %			
NIHSS (mean (SD))	7.94 (7.69)	7.80 (7.94)	0.018
Mild (0-4)	1,355.0 (42.7)	1,584.6 (50.0)	
Moderate (5-15)	1,175.9 (37.1)	965.3 (30.4)	
Moderate to severe (16-20)	314.8 (9.9)	310.4 (9.8)	
Severe (>20)	325.7 (10.3)	310.6 (9.8)	
In-hospital Measures of Stroke Severity and Complications (recorded during first day of admission)*** (%)			
Observed large vessel occlusion	682.2 (36.3)	634.0 (35.0)	0.029
IV injection of tissue plasminogen activator (tPA)	133.5 (4.2)	233.8 (7.4)	0.136
Endovascular thrombectomy (EVT)	26.0 (0.8)	71.8 (2.3)	0.118
Computed tomography (CT/CAT) Scan	2,102.7 (66.3)	1,950.3 (61.5)	0.1
Magnetic resonance imaging (MRI) of the brain	1,421.8 (44.8)	1,573.1 (49.6)	0.096

Legend: Abbreviations: SD, standard deviation; SMD, standardized mean difference; EEG, electroencephalogram. ** No prescription recorded: the prescription information was a) missing from the MGB structured health system data warehouse, b) the patient was not taking any prescription drug, c) the patient was taking prescription drugs given elsewhere (e.g., over the counter, prescribed and recorded in another healthcare system), d) other unknown reason.

Table S3. Drug Type Count

Drug Type	Count	Percentage (%)
Levetiracetam	142	84.02
Phenytoin	11	6.51
Lamotrigine	8	4.73
Other*	18	4.74

Legend: *Other: Drugs initiated less frequently like Lacosamide and Phenobarbital.

Table S4. Main Results 30-day Risk Differences

Measure	Estimate	95 % CI	
Crude - Naïve comparison of 30-day mortality			
Do not initiate	120 deaths/1000 patients	108 deaths/1000 patients	131 deaths/1000 patients
Initiate	219 deaths/1000 patients	153 deaths/1000 patients	284 deaths/1000 patients
Risk Difference	99 deaths/1000 patients	32 deaths/1000 patients	166 deaths/1000 patients
Standardized (Addressing Selection and Confounding)			
Do not initiate	120 deaths/1000 patients	86 deaths/1000 patients	145 deaths/1000 patients
Initiate	251 deaths/1000 patients	190 deaths/1000 patients	307 deaths/1000 patients
Risk Difference	130 deaths/1000 patients	65 deaths/1000 patients	200 deaths/1000 patients

Table S5. Main Standardized Estimates for Stratified Sample by Stroke Severity

Standardized, Mild Stroke

Measure	Estimate	95 % CI Measure	
Do not initiate	24 deaths/1000 patients	17 deaths/1000 patients	27 deaths/1000 patients
Initiate	75 deaths/1000 patients	34 deaths/1000 patients	92 deaths/1000 patients
Risk Difference	52 deaths/1000 patients	11 deaths/1000 patients	72 deaths/1000 patients

Standardized, Moderate

Measure	Estimate	95 % CI Measure	
Do not initiate	218 deaths/1000 patients	166 deaths/1000 patients	252 deaths/1000 patients
Initiate	356 deaths/1000 patients	280 deaths/1000 patients	421 deaths/1000 patients
Risk Difference	138 deaths/1000 patients	52 deaths/1000 patients	222 deaths/1000 patients

Table S6. Main Standardized Estimates for Stratified Sample by Age Groups

Standardized, < 75 years

Measure	Estimate	95 % CI Measure	
Do not initiate	81 deaths/1000 patients	62 deaths/1000 patients	101 deaths/1000 patients
Initiate	167 deaths/1000 patients	107 deaths/1000 patients	198 deaths/1000 patients
Risk Difference	86 deaths/1000 patients	18 deaths/1000 patients	118 deaths/1000 patients

Standardized, > 75 years

Measure	Estimate	95 % CI Measure	
Do not initiate	145 deaths/1000 patients	112 deaths/1000 patients	162 deaths/1000 patients
Initiate	301 deaths/1000 patients	206 deaths/1000 patients	354 deaths/1000 patients
Risk Difference	157 deaths/1000 patients	57 deaths/1000 patients	219 deaths/1000 patients

Table S7. Model Parameters for Estimating Epilepsy-specific ASD Initiation Weights

Dataset	Term	Estimate	Standard Error	P value
Model Parameters	Intercept	-7.64	0.17	**0**
	NIHSS	0.08	0.01	**0**
	Charlson Comorbidity Score	0.007	0.04	**0.882**
	CMO Status	-1.32	0.40	**0.001**
	Seizure-like Event	1.72	0.17	**0**
	Electroencephalogram	0.67	0.28	**0.019**
	Prescription Count	0.02	0.01	**0**

Legend: NIHSS, National Institute of Health Stroke Severity; CMO, Comfort Measures Only; SLE, Seizures or Seizure-like Events.

Table S8. The RECORD Statement

Item No.	STROBE items[70]	Location where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract				
1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	(a): Abstract (page 4) (b): Abstract (page 4)	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	1.1: Abstract 1.2: Abstract 1.3 Abstract
Introduction				
Background rationale 2	Explain the scientific background and rationale for the investigation being reported	Introduction		

Objectives	3	State specific objectives, including any prespecified hypotheses	Introduction		
Methods					
Study Design	4	Present key elements of study design early in the paper	Methods		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Methods		
Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	(a): Methods (b) NA	RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was	6.1: Methods 6.2: NA 6.3: NA

		Cross-sectional study - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case		conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of patients with linked data at each stage.	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	Methods	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	Methods
Data sources/ measurement	8	For each variable of interest, give	Methods		Data sources/

		sources of data and details of methods of assessment (measurement) . Describe comparability of assessment methods if there is more than one group.		measurement
Bias	9	Describe any efforts to address potential sources of bias	Methods	Bias
Study size	10	Explain how the study size was arrived at	Methods	Study size
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	Methods	Quantitative variables
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data	(a): Methods (b): Methods (c): Methods (d): Methods (e): Methods	Statistical methods

	were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses		
Data access and cleaning methods		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on	12.1: Methods 12.2: Methods

				the data cleaning methods used in the study.	
Linkage				RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	NA
Results					
Participants	13	(a) Report the numbers of patients at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage.	(a): Results; Figure 1; Table 2; (b): Figure 1 (c): Figure 1	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	13.1 Results; Methods

		(c) Consider use of a flow diagram	
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)	(a): Results (b): Results (c): Results
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report	Results

		numbers of outcome events or summary measures	
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	(a): Results (b): Results: (c): Results
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	Results

Discussion					
Key results	18	Summarise key results with reference to study objectives	Discussion		
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Discussion	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	Discussion
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Discussion		
Generalisability	21	Discuss the generalisability	Discussion		

		(external validity) of the study results			
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Acknowledgments		
Accessibility of protocol, raw data, and programming code				RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Supplemental tables, figures, and text.

D. STATISTICAL CODE

````
---
title: "Lidia Moura - ASD Emulated Trial Design Code"
---

#SETUP
```{r}
library(knitr)
library(dplyr)
library(tidyverse)
library(tidyr)
library(survival)
library(missForest)

# Analysis function

# this is the function used for the analysis
# requires a long, cloned dataset (orig_dat) and the baseline variables
# for standarization (baseline_vars)
analysis_function <- function(orig_dat, baseline_vars, boot = FALSE, trunc_q = 0.975, ...) {

  # sample MRNs if part of the bootstrap
  if (boot) {
    MRNs <- unique(orig_dat$MRN)
    boot_MRNs <- tibble(old_MRN = sample(MRNs, replace = TRUE),
                        MRN = 1:length(MRNs))
    dat <- right_join(boot_MRNs, orig_dat, by = c("old_MRN" = "MRN"))
  } else { # or else just use the original data
    dat <- orig_dat
  }

  #CREATE CLONES
  # these are the people that started treatment within the grace period
  # and those that were censored at the end of the grace period because they didn't
  start_txt <- dat %>%
    # censor unless it's during grace period
    # or if someone started treatment w/in grace period
    filter(Date_post_adm < grace_day | dayA < grace_day) %>%
    # indicator for randomization arm: start treatment within grace period
    mutate(txt = 1)

  # these are the people that never started treatment
  # or those that did, before they started (ie they are being censored for starting)
  never_txt <- dat %>%
    # censor if start treatment any time during grace period
    # since once A is 1, is always 1
````
````

```
    filter(A == 0) %>%
    mutate(txt = 0)

  # combine the data
  clones <- bind_rows(start_txt, never_txt)

  # in original data, fit models among people yet to start treatment (Alag = 0)
  # ie model for treatment initiation
  num_mod <- glm(A ~  NIHSS + Charlson_baseline,
                 family = binomial(), data = dat,
                 subset = Alag == 0)
  denom_mod <- glm(A ~  NIHSS + Charlson_baseline + CMO_time_varying + SLE_inhospital
+ EEG_Routine_inhospital + Prescription_Count_inhospital,
                   family = binomial(), data = dat,
                   subset = Alag == 0)

  num_cens <- glm(ltfu ~ Date_post_adm +
                      A*Date_post_adm  ,
                  family = binomial(), data = dat,
                   subset = Date_post_adm < last_day & Death_Status == 0)

  denom_cens <- glm(ltfu ~ Date_post_adm +
                      A*Date_post_adm  ,
                  family = binomial(), data = dat,
                   subset = Date_post_adm < last_day & Death_Status == 0)

  weighted_dat <- clones %>%
    # only use complete cases (because I don't know what else to do with them)
    filter(!if_any(c(NIHSS, Charlson_baseline, CMO_time_varying, SLE_inhospital,
EEG_Routine_inhospital, Prescription_Count_inhospital), is.na)) %>%
    # pr(uncensored at time t | uncensored at time t - 1)
    mutate(pnum = predict(num_mod, newdata = ., type = "response"),
           pdenom = predict(denom_mod, newdata = ., type = "response"),
           pnum_cens = predict(num_cens, newdata = ., type = "response"),
           pdenom_cens = predict(denom_cens, newdata = ., type = "response"),
           numCont = case_when(

             # in the txt arm, weight contribution is 1 during grace period
             # b/c pr(uncensored | grace period) = 1 even if you don't start
             # (in the don't start txt arm, can get censored during grace period for starting txt)
             txt == 1 & Date_post_adm < grace_day ~ 1,

             # at the end of the grace period, these people are UNCENSORED
             # so must upweight them to account for those who didn't start
             # this should ONLY include people who have A = 1
             txt == 1 & Date_post_adm == grace_day ~ pnum,
```

```
        # after the grace period (so any other days),
        # can't be censored because already started
        txt == 1 & Date_post_adm > grace_day ~ 1,

        # in no txt arm, always will be p(no txt)
        # because can always be censored for starting txt
        txt == 0 ~ 1 - pnum
      ),
      # same logic in the denominator
      denomCont = case_when(
        txt == 1 & Date_post_adm < grace_day ~ 1,
        txt == 1 & Date_post_adm == grace_day ~ pdenom,
        txt == 1 & Date_post_adm > grace_day ~ 1,
        txt == 0 ~ 1 - pdenom
      ),

      # censoring weights
      # always probability of not being censored (last day doesn't count)
      numCont_cens = ifelse(Date_post_adm == last_day, 1, 1 - pnum_cens),
      denomCont_cens = ifelse(Date_post_adm == last_day, 1, 1 - pdenom_cens)
  ) %>%
  group_by(MRN,txt) %>%
  # pr(uncensored at time t | uncensored at time t - 1, history) x
  #       pr(uncensored at time t - 1 | uncensored at time t - 2, history) x etc.
  # this only matters for the no txt arm, who keep not taking txt
  mutate(num_prod = cumprod(numCont),
         denom_prod = cumprod(denomCont),
         num_cens_prod = cumprod(numCont_cens),
         denom_cens_prod = cumprod(denomCont_cens),
         # wt = 1 / prob (uncensored at time t | bl & tv vars)

         stabw = (num_prod*num_cens_prod) / (denom_prod*denom_cens_prod))

summary(weighted_dat$stabw)

# truncate weights
tau <- quantile(weighted_dat$stabw, trunc_q, na.rm = TRUE)
weighted_dat$stabw[weighted_dat$stabw > tau] <- tau

# outcome model with stabilized weights
outcome_mod <- glm(event ~ Date_post_adm +
                     txt*Date_post_adm,
                   data = weighted_dat, weights = stabw, family = quasibinomial())

predictions <- bind_rows(baseline_vars,
```

```
                        baseline_vars, .id = "txt") %>%
    # turn txt from 1, 2 to 0, 1
    mutate(txt = as.numeric(txt) - 1) %>%
    # get predicted hazard
    mutate(haz = predict(outcome_mod, newdata = ., type = "response"),
           # and survival within a certain day
           int_surv = 1 - haz) %>%
    group_by(MRN, txt) %>%
    mutate(surv = cumprod(int_surv),
           risk = 1 - surv) %>%
    # only group by treatment to average risk over the treatment group
    ungroup() %>%
    group_by(txt, Date_post_adm) %>%
    # remove some missing values because missing covariates
    # deal with later!
    summarise(average_risk = mean(risk, na.rm = TRUE),
              average_survival = mean(surv, na.rm = TRUE),
              .groups = "drop")

  if (boot) clones <- NULL

  # approximate HR with outcome model with constant treatment effect
  HR_mod <- glm(event ~ Date_post_adm +
                  txt,
                data = weighted_dat, weights = stabw, family = quasibinomial())

  list(predictions = predictions, clones = clones,
       tau = tau,
       denom_mod = broom::tidy(denom_mod),
       HR_mod = broom::tidy(HR_mod))
}
```

```{r}
# Main analysis

main_res <- analysis_function(dat, baseline_vars, boot = FALSE, trunc_q = 0.975)
# save the main results
write_rds(main_res, file = paste0("results/",style, "_", condition,"_",confounders,
"_main_res.rds"))

# survival estimates
predicted_surv <- main_res$predictions
# the cloned data for checking
clones <- main_res$clones
```

```
# the quantile of weights at which they were truncated
tau <- main_res$tau
# the model for the weights
denom_mod <- main_res$denom_mod
# the model for the outcome
HR_mod <- main_res$HR_mod
```

#DATA CHECKING
Now that the main analysis as been run, does the data look as expected?

How many person-days in each arm overall?
```{r}
count(clones, txt) %>% kable()
```

#How many patients in each arm?
```{r}
count(clones, txt, MRN) %>% count(txt) %>% kable()
```

#How many person-days is each person contributing to each treatment arm?
```{r}
person_days <- clones %>%
  group_by(MRN) %>%
  # in either arm did they ever die, get lost to follow-up, or start med
  # (for sanity checking)
  mutate(ever_event = max(event), ever_ltfu = max(ltfu), ever_A = max(A)) %>%
  ungroup() %>%
  count(MRN, txt, ever_event, ever_ltfu, ever_A) %>%
  pivot_wider(names_from = txt, values_from = n,
              names_prefix = "txt_", values_fill = 0)
person_days %>% head %>% kable()
```

What is the median number of person-days contributed to each treatment arm (0; 1)?
```{r}
median(person_days$txt_0); median(person_days$txt_1)
```

```{r}
# Bootstrap
# run the analysis function n_boot times
boot_res <- map(1:n_boot, analysis_function,
  orig_dat = dat, baseline_vars = baseline_vars,
  boot = TRUE, trunc_q = 0.975
```

```
)

# save the bootstrap results
write_rds(boot_res, file = paste0("results/",style, "_", condition,"_",confounders,
"_boot_res.rds"))
```

```{r}
# calculate confidence intervals
boot_res_t <- transpose(boot_res)

boot_predicted_surv <- bind_rows(boot_res_t$predictions, .id = "boot")
boot_tau <- flatten_dbl(boot_res_t$tau)
boot_denom_mod <- bind_rows(boot_res_t$denom_mod, .id = "boot")
boot_HR_mod <- bind_rows(boot_res_t$HR_mod, .id = "boot")

surv_CIs <- boot_predicted_surv %>%
  group_by(txt, Date_post_adm) %>%
  summarise(lci_risk = quantile(average_risk, .025),
            uci_risk = quantile(average_risk, .975),
            lci_survival = quantile(average_survival, .025),
            uci_survival = quantile(average_survival, .975),
            .groups = "drop")

dif_CIs <- boot_predicted_surv %>%
  filter(Date_post_adm == last_day) %>%
  select(-average_survival) %>%
  pivot_wider(names_from = txt,
              values_from = average_risk, names_prefix = "risk_") %>%
  mutate(risk_dif = risk_1 - risk_0) %>%
  summarise(lci_risk_dif = quantile(risk_dif, .025),
            uci_risk_dif = quantile(risk_dif, .975),
            lci_risk_1 = quantile(risk_1, .025),
            lci_risk_0 = quantile(risk_0, .025),
            uci_risk_1 = quantile(risk_1, .975),
            uci_risk_0 = quantile(risk_0, .975))

all_surv <- left_join(predicted_surv, surv_CIs, by = c("txt", "Date_post_adm")) %>%
  rename_with(str_remove, starts_with("average"), "average_")

all_difs <- predicted_surv %>%
  filter(Date_post_adm == last_day) %>%
  select(-average_survival, -Date_post_adm) %>%
  pivot_wider(names_from = txt,
              values_from = average_risk, names_prefix = "risk_") %>%
  mutate(risk_dif = risk_1 - risk_0) %>%
```

```
  bind_cols(dif_CIs)

all_HRs <- boot_HR_mod %>%
  filter(term == "txt") %>%
  summarise(lci_est = quantile(estimate, .025),
            uci_est = quantile(estimate, .975),
            .groups = "drop") %>%
  bind_cols(filter(HR_mod, term == "txt")) %>%
  transmute(HR = exp(estimate),
            lci_HR = exp(lci_est),
            uci_HR = exp(uci_est))
```

```{r}
# 30-day mortality, risk differences, HRs
all_ests <- bind_cols(all_difs, all_HRs)%>%
  rename_with(~ paste0("est_", .x), -starts_with(c("lci", "uci")))%>%
  pivot_longer(everything(),
    names_to = c(".value", "stat"),
   names_pattern = "(.+)_(.+)"
  )

kable(all_ests)

write_csv(all_ests, file = paste0("results/",style, "_", condition,"_",confounders, "_all_ests.csv"))
```

```{r}
# coefficients from the weight model
kable(denom_mod)
write_csv(denom_mod, file = paste0("results/",style, "_", condition,"_",confounders,
"_coeff_weight_model.csv"))
```