**Simulation-based sample size calculation for** **randomized controlled trials of EEG-guided anti-seizure treatment in subarachnoid hemorrhage**

Rajesh Amerineni PhD1\*, Haoqi Sun PhD1\*, Harsh Parikh, Kentaro Hoffman, Jin Jing PhD, Wendong Ge PhD, Eric D. Rosenthal MD1, Cynthia Rudin PhD, Alexander Volfovsky PhD, M. Brandon Westover MD PhD1,2\*\*, Sahar F. Zafar MD MSc1\*\*

1Massachusetts General Hospital, Department of Neurology, Boston, MA, USA

2MGH Clinical Data Animation Center (CDAC)

3MGH McCance Center for Brain Health

\*Equally contributed as first authors

\*\*Equally contributed as co-senior authors

**Corresponding Author**

Sahar F. Zafar, MD MSc

Massachusetts General Hospital,

Lunder 6 Neurosciences Intensive Care Unit,

55 Fruit Street,

Boston, MA 02114

Tel: 8572385600

Fax: 8572385601

Email: sfzafar@mgh.harvard.edu

Number of characters in the title:

Number of words in abstract:

Number of words in main text:

Number of references:

Number of figures:

Number of supplemental tables:

**Keywords**:

**Conflicts of Interest and Source of Funding**:

This project received research support from NIH K23NS114201 (SFZ). SFZ: NIH K23NS11420); AES Infrastructure Award. Dr. Zafar is a Clinical Neurophysiologist for Corticare, which played no role in this study. MBW: American Academy of Sleep Medicine Strategic Research Award;  NIH (R01NS102190, R01NS102574, R01NS107291, RF1AG064312, R01AG062989, R01AG073410), NSF (2014431). Dr. Westover is a co-founder of Beacon Biosignals, which played no role in this study.

**Abstract**

**Introduction**: Epileptiform activity (seizures and periodic/rhythmic patterns) are commonly seen during electroencephalograpgy (EEG) monitoring in aneurysmal subarachnoid hemorrhage (aSAH) patients. These patterns are frequently treated with anti-seizure medications (ASMs), despite limited data on whether treatment improves outcomes. Investigating the impact of ASM treatment is challenging given the clinical complexity of aSAH patients and the dynamic nature of epileptiform activity. The objective of this study was to investigate the impact of ASM pharmacodynamics, choice of outcome measures, and timing of treatment on the sample size needed for successful randomized clinical trials (RCT).

**Methods**: We quantified epileptiform activity burden time courses for 48 aSAH patients. We removed the estimated ASM effect using Pharmacokinetic/Pharmacodynamic modeling. We used the “drug free” epileptiform burden time courses to generate RCT simulations comparing ASM treatment to placebo. Our outcome measures were total total epileptiform activity burden, and post-intervention epileptiform burden over 72 and 24 hours. We repeated RCT simulations for increasing duration of treatment delays, varying ASM efficacy and outcome measures. ASM efficacy rates were defined using published RCTs on status epilepticus. Power and sample size calcultions were performed for each simulated RCT.

**Results**: Increasing sample sizes were required with increasing treatment delays from 1 to 70 hours, regardless of ASM efficacy or cEEG outcome measure. The median sample size required for treatment delay of one hour across all ASM efficacies and outcome measures was 49, compared with a median required sample size of 104 required for a treatment delay of 70 hours across all ASM efficacies and outcome measures (1.85 [1.77-2.68] fold intease). With decreasing ASM efficacy, there was a 1.22 [1.08-2.17] fold increase in the sample size.

**Conclusion:** Delays in ASM administration and choice of outcome measures significantly impact the sample size required for successful RCTs. Carefully designing inclusion and exclusion criteria, including stricter enrollment times, and appropriate outcome measures, can increase the success of RCTs investigating treatment of epileptiform activity.

**Introduction**

Seizures and epileptiform activity (EA) are seen in up to 40% of aneurysmal subarachnoid hemorrhage (aSAH) patients undergoing continuous electroencephalography (cEEG) and are associated with increased mortality and worse functional outcomes1,2. While anti-seizure medications (ASMs) are frequently prescribed in response to EA in aSAH patients, there is no data to showing that treatment improves outcomes1,2. Development of evidence-based treatment guidelines requires randomized controlled trials3. However, designing randomized trials to determine the effectiveness of ASMs in aSAH patients with EA is challenging given the clinical complexity of the disease and the dynamic nature of EA. The timing of medication administration and measurement of electrographic improvement in relation to the onset of EA can be difficult to standardize given the variable, and in some cases self-limiting nature of EA4. Selecting an appropriate outcome measure and sample size are critical to the success of a randomized trial. Large sample sizes increase the power of the study and strengthen the results, but also increase cost and length of the trial. A carefully constructed trial design can improve the power of the trial and reduce the cost to conduct it4.

In this study we evaluated the impact of trial design, including time to drug administration, drug effectiveness, and outcome measure selection, on the estimated required sample size. We developed simulated EEG data based on real aSAH patient EEG data, and performed subsequent randomized clinical trial (RCT) simulations with varying time delays to ASM administration, efficacies of ASMs, and EEG outcome measures to determine their impact on the estimated effect and required RCT sample size4.

**Methods.**

The study was approved by the Institutional Review Board of Mass General Brigham. Informed consent was not required as the EEG recordings, clinical and demographic variables were extracted from a retrospective database of adult (age >18 years) aSAH patients admitted to Massachusetts General Hospital between 2012 and 2017. All patients with high-grade aSAH (>HH3 or >Fisher3) undergo cEEG to monitor for delayed cerebral ischemia and subclinical seizures. Our inclusion criteria was 1) aSAH patients with > 24 hours of cEEG, 2) presence of EA. EA was defined as seizures, generalized and lateralized periodic discharges (GPDs, LPDs) and lateralized rhythmic delta activy (LRDA), as all of these are highly associated with seizures and are frequently treated with anti-seizure medications in clinical practice. Generalized rhythmic delta activity (GRDA) was excluded from our definition of EA as it is a more benign pattern that is not associated with seizures or delayed cerebral ischemia. From the initial cohort of 136 patients, 48 patients met includsion criteria and were selected for analysis. Clinical and demographic variables for the selected patients is shown in Table 1. The data that support the findings of this study are available from the corresponding author (SFZ) upon reasonable request.

*Epileptiform activity burden*

Increased EA burden is associated with worse outcomes not only in aSAH patients, but across a wide spectrum of acute brain injury patients1,2,8. EA burden can therefore serve as a treatment target for randomized trials. We defined the EA burden in aSAH patients to guide generation of simulated EEG data. This process involved several steps. First, a previously developed convolutional neural network (CNN) classifier5,6 was used to classify every consecutive 2-second segment of cEEG data into one of 6 patterns: seizure, GPD, LPD, LRDA, GRDA, or other/normal/artifact. Second, we labeled each 2-second segment as having EA if the CNN detected any seizures, GPD, LPD, or LRDA. Finally, the EA burden was computed as the proportion of 2-second segments having EA in a moving non-overlapping window of 10 minutes.

*Generation of simulated cEEG epileptiform activity data*

The natural course of EA burden was modeled to generate simulated EA burden time courses. As aSAH patients with EA are frequently treated with ASMs, we estimated the EA burden as a function of time that *would have been observed* *had the patient not been treated with ASMs* (EAΦ(t)). The drug-free epileptiform activity EAΦ(t) was modeled using a log-normal function due to the right skewed shape of the natural time course of EA burden4. The reduction in epileptiform burden due to ASM administration was modeled using a one-compartment pharmacokinetics/pharmacodynamics (PK/PD) model. The elimination half life rate constants were based on published population data7. The seven ASMs included in the study along with their elimination half lifes were levetiracetam (8 hours), lacosamide (11 hours), valproic acid (16 hours), midazolam (2.5 hours), phenobarbital (79 hours), pentobarbital (32.5 hours), propofol (20 minutes).

The EA burden simulator is described by Equation 1, and is a log-normal function (the drug-free time course, EAΦ(t)) minus the drug blood concentration from PK model (d(t)), adjusted with a “softplus” function to ensure the EA burden to be positive (the entire model represents the PD part),

, (1)

where , and (t) is the log-normal function

, (2)

where is the peak amplitude, is the mean, and is the standard deviation, which are to be estimated from the data. d(t) is the overall drug blood concentration from PK model

(3)

where is the coefficient for drug *i* that needs to be estimated, is the output of the one-compartment PK model for drug *i,* where \* is convolution operator; is the elimination rate constant for drug *i*, is the infusion rate over time of drug *i*, and the total number of drugs administrated to the patient.

Simulations were generated using a two-step approach. In the first step, we estimated the simulator parameters for each patient from the available data. The parameters to be estimated included , which describes the contribution of the i-th drug on the overall blood concentration, and , , and , which describe the shape of log-normal function. We estimated these parameters by adjusting their values to minimize the mean squared error between actual vs. modeled EA burden. In the second step, we generated simulations using parameters randomly drawn from the multivariate normal distribution approximated from the mean and covariance of the simulator parameters across patients from the first step. Figure 1 shows examples of simulated “drug free” EA burden time courses. Figure 2 shows the observed evolution of EA burden and the estimated / simulated “drug free” burden for all 48 patients.

*Randomized controlled trial (RCT) design*

Several randomized trials of ASM treatment vs. placebo were designed using the simulated cEEG data. For each trial we defined three main variables: treatment delay, ASM efficacy, and outcome measure.

*Treatment delay* was defined as the time from the onset of EA to the time of intervention (ASM vs. placebo), and ranged from 1 to 70 hours. We hypothesized that increasing treatment delay would result in smaller effect sizes and the need for larger sample sizes. This is based on the natural history of EA, which tends to be right skewed. Therefore the difference in EA burden between control and treatment arms will be smaller if intervention is later in the course, and after the peak burden has passed.

*Treatment efficacy* was defined as the percent and rate of reduction in EA burden in response to ASM treatment. We hypothesized that higher efficacy would result in larger effect sizes and therefore smaller sample sizes. We extrapolated ASM efficacies from prior trials and observational studies of ASM treatment for status epilepticus9–11, and also explored hypothetical efficacies of novel therapies that may become available in the future, to determine how these would affect the required sample size. Four different types of ASM efficacy were evaluated:

1. Complete cessation of EA within 60 minutes of ASM administration in 50% of patients in the experimental arm9. The remaining subjects in the experimental arm had a randomly assigned efficacy with variable reduction in EA burden. This efficacy was extrapolated from the randomized trial of levetiracetam, fosphenytoin, and valproate for status epilepticus. In this trial, levetiracetam, fosphenytoin, and valproate each led to seizure cessation by 60 minutes in approximately half the patients with benzodiazepine refractory convulsive status.
2. Complete cessation of EA in 60% of patients within 24 hours of ASM administration in the experimental arm10. The remaining subjects in the experimental arm had a randomly assigned efficacy with variable reduction in EA burden. This efficacy was extrapolated from the randomized trial of lacosamide versus fosphenytoin for nonconvulsive seizures10. 63% of patients in the lacosamide arm achieved seizure control.
3. Complete cessation of EA in 60% of patients within 14 hours of ASM administration in the experimental arm11. The remaining subjects in the experimental arm had a randomly assigned efficacy with variable reduction in EA burden. This efficacy was extrapolated from an observational study of intravenous levetiracetam as an add on treatment in status epilepticus. Levetiracetam was effective in reducing seizures in 57.5% of patients over a mean time of 14 hours.11
4. Complete cessation of EA in 75% patients immediately after ASM administration in the experimental arm. The remaining subjects in the experimental arm had a randomly assigned efficacy with variable reduction in EA burden (hypothetical efficacy).

In the control arm, the cEEG EA burden simulations followed the natural drug free time courses.

Three cEEG outcome measures were evaluated (Figure 3):

a) Total EA burden – cumulative burden from the onset of EA until the end of the recording.

b) Post-intervention 72-hr EA burden – cumulative burden from the time of intervention to 72 hours post intervention (ASM vs. placebo).

c) Post-intervention 24-hr EA burden – cumulative burden from the time of intervention to 24 hours post intervention (ASM vs. placebo).

We hypothesized that outcome measures estimating post-intervention epilepitform activity burden over longer time-windows would result in larger effect sizes and smaller required sample sizes.

*RCT model building and sample size calculation*

Methods for RCT modeling and sample size calculation are summarized in the following steps and shown in Figure 4:

1. 100,000 drug free EA burden time courses were simulated and randomly distributed between the intervention and control group.
2. The total and mean EA burden was calculated for all 100,000 simulations. A two sample t-test of the differences between the mean EA burden was computed to confirm the distribution of drug free EA burden was similar across the control and intervention arms.
3. Multiple RCTs were designed by varying treatment delay, ASM efficacy, and outcome measures. The influence of each of these variables on the required sample size was measured by varying one variable and by keeping the rest constant.
4. The sample size, N, was derived from the effect size and standard deviation of the outcome measures. Effect size was defined as the difference between the means of the outcomes (EA burden) of the intervention and control groups. The following equation was used to calculate the required sample size4:

and are the standard deviation of the outcomes (EA burden) of the control and intervension groups respectively; and are the mean of the outcomes (EA burden) of the control and intervension groups respectively.

1. 1000 rounds of bootsrapping were performed on the entire process (steps 1 to 4) to calculate the median sample and effect sizes along with 95% confidence interval for each RCT design.

**Results**

Tables 2 and 3 summarize the effect sizes and corresponding sample sizes required for RCTs with varying treatment delay, ASM efficacy, and cEEG outcome measures. Increasing sample sizes were required when treatment delays were longer, regardless of ASM efficacy or cEEG outcome measure, with an almost two-fold increase in the sample size required when the delay increased from 1 to 70 hours. The median sample size required for treatment delay of one hour across all ASM efficacies and outcome measures was 49, compared with a median required sample size of 104 required for a treatment delay of 70 hours across all ASM efficacies and outcome measures (1.85 [1.77-2.68] fold increase, p=0.001).

When comparing ASM efficacies, larger sample sizes were required when the EA burden response rate was slower (i.e 60% with complete cessation at 24 hours), compared with a faster response rate ( i.e 60% with complete cessation at 14 hours). The median sample size required for faster EA response rate was 82, compared with the median sample size of 104 required across for a slower EA response rate (1.22 [1.08-2.17] fold increase and p=0.01).

The impact of outcome measure i.e total EA burden 72 or 24 hours post intervention burden, varied with EA burden treatment response rate. With faster response rates i.e rapid reduction of EA burden within an hour of treatment, the smallest sample sizes were required when 24 hour post-intervention burden was used as an outcome measure, regardless of the percent reduction and treatment delay. With slower response rates, i.e gradual reduction of EA burden over 14 and 24 hours regardless of the percent reduction and treatment delay, use of 24-hour post intervention burden as an outcome measure resulted in the largest required sample sizes. This is because slower treatment response rates result in smaller effect sizes when post intervention epileptiform burden was measured wthin narrower time frames.

**Discussion**

Our findings demonstrate the impact of trial design on the sample size needed to detect benefits of ASM treatment in aSAH patients with EA. Delays in administration of treatment, choice of outcome measure, and ASM efficacy all influence the sample size needed. Designing early randomization windows to avoid delays between EA onset and intervention can lower the required sample size. Knowledge of ASM efficacy and EA response rates is also critical in determining the sample size needed.

As demonstrated by the cEEG data from 48 aSAH patients, there was a spontaneous reduction in EA burden over time in our cohort. This natural reduction in EA explains the decreasing effect size between the intervention and control group with increasing treatment delays. Natural reduction in EA burden has also been demonstrated in a similar analysis of neonatal status epilepticus4. Animal models and adult human case reports show a natural evolution of electrographic status epilepticus beginning with discrete seizures, progressing to continuous EA, and ending with periodic patterns and eventually electrocerebral silence12–14. Thus, designing trials that capture EA early in its natural course at the time of randomization could maximize ASM treatment effect sizes and maximize treatment benefits. Early intervention is also relevant from a clinical standpoint given evidence that higher epileptiform burden is associated with worse outcomes in acute brain injury patients (refs).

We selected EA burden as a primary outcome measure in our trial emulations given prior work demonstrating higher burden is associated with worse functional and cognitive outcomes (refs). In a study of aSAH patients, each hour of seizure on cEEG was associated with an odds ratio of 1.10 to 3-month disability and mortality (ref). In our prior work we have demonstrated that increasing peak burden of EA from 0% to 100% of cEEG recording is associated with a 40% increase in the probability of poor functional outcomes (ref). A key step will be determining whether reduction in EA results in improved long-term functional and cognitive outcomes, and reduced risk for developing epilepsy. Given each additional hour of seizures impacts long-term outcomes, the decreasing effect size with treatment delays may also lower the measurable impact of ASM treatment on long-term outcomes.

While we evaluated EA burden as the primary outcome measure, in future trials, it is essential to also include post ASM treatment improvement in clinical exam as the primary outcome measure. New EA in aSAH patients can also be a harbinger for delayed cerebral ischemia (DCI) (refs). Therefore a combination of ASM treatment with interventions geared towards increasing cerebral blood flow may need to be investigated in randomized trials. Composite outcome measures of EEG findings, clinical exam, and biomarker improvement may therefore be the most appropriate shor-term outcome measures in this patient population.

Limitations of our study include generation of cEEG simulations from EEG data of aSAH patients collected at a single center, limiting generalizability. We extrapolated ASM efficacies from studies of status epilepticus that may not fully translate to EA in aSAH patients. We focused on cEEG outcome measures, whereas clinical outcomes and long-term functional, cognitive, quality of life and epilepsy outcomes are necessary to include in any future randomized trials. Nevertheless, our study demonstrates the necessary prerequisites for designing successful trials assessing the impact of ASM treatment on EA.

In conclusion, time to treatment, outcome measure selection, and ASM efficacy are all critical determinants of the sample size required to conduct successful trials on ASM treatment for EA. Prior to conducting a large scale trial in aSAH patients, further data is needed to more fully define the natural course of EA in a larger cohort of patients, describe the electrographic response of EA to ASMs, and the appropriate therapeutic targets.

**Reference**

1. De Marchis GM, Pugin D, Meyers E, et al. Seizure burden in subarachnoid hemorrhage associated with functional and cognitive outcome. Neurology 2016;86(3):253–260.

2. Zafar SF, Postma EN, Biswal S, et al. Effect of epileptiform abnormality burden on neurologic outcome and antiepileptic drug management after subarachnoid hemorrhageClinical Neurophysiology 2018;129(11):2219–2227.

3. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction—GRADE evidence profiles and summary of findings tables. Journal of clinical epidemiology 2011;64(4):383–394.

4. Stevenson NJ, Boylan GB, Hellström-Westas L, Vanhatalo S. Treatment trials for neonatal seizures: the effect of design on sample size. PloS one 2016;11(11):e0165693.

5. Jing J, d’Angremont E, Zafar S, et al. Rapid annotation of seizures and interictal-ictal continuum eeg patterns. In: 2018 40th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC). IEEE; 2018 p. 3394–3397.

6. Ge W, Jing J, An S, et al. Deep active learning for interictal ictal injury continuum EEG patterns. Journal of neuroscience methods 2021;351:108966.

7. Wishart DS, Feunang YD, Guo AC, et al. DrugBank 5.0: a major update to the DrugBank database for 2018. Nucleic acids research 2018;46(D1):D1074–D1082.

8. Zafar SF, Rosenthal ES, Jing J, et al. Automated Annotation of Epileptiform Burden and Its Association with Outcomes. Annals of neurology 2021;90(2):300–311.

9. Kapur J, Elm J, Chamberlain JM, et al. Randomized trial of three anticonvulsant medications for status epilepticus. New England Journal of Medicine 2019;381(22):2103–2113.

10. Husain AM, Lee JW, Kolls BJ, et al. Randomized trial of lacosamide versus fosphenytoin for nonconvulsive seizures. Annals of neurology 2018;83(6):1174–1185.

11. Aiguabella M, Falip M, Villanueva V, et al. Efficacy of intravenous levetiracetam as an add-on treatment in status epilepticus: a multicentric observational study. Seizure 2011;20(1):60–64.

12. Pender RA, Losey TE. A rapid course through the five electrographic stages of status epilepticus. Epilepsia 2012;53(11):e193–e195.

13. Nowack WJ, Shaikh IA. Progression of electroclinical changes in complex partial status epilepticus: filling in the blanks. Clinical Electroencephalography 1999;30(1):5–8.

14. Treiman DM, Walton NY, Kendrick C. A progressive sequence of electroencephalographic changes during generalized convulsive status epilepticus. Epilepsy research 1990;5(1):49–60.

**Figure legends:**

**Figure 1: Example of epileptiform activity burden in a single patient.**

The x-axis is time in hours and y-axis is EA burden in mins/hour. The first panel shows the actual EA burden and superimposed log-normal fit. The second panel shows the EA burden and the superimposed stimulator fit cure including the PK/PD model. The third panel shows the actual drug concentration the patient received over time (y-axis is the normalized drug concentration). The last panel is the final drug free simulated data.

**Figure 2: Epileptiform activity burden across all 48 patients**

1. The natural course of EA burden (log-normal fit) across all patients.
2. The drug free EA burden across all 48 patients.

**Figure 3: cEEG outcome measures**

Three outcome measures were evaluated:

a) Total EA burden – cumulative burden from the onset of EA until the end of the recording.

b) Post-intervention 72-hr EA burden – cumulative burden from the time of intervention to 72 hours post intervention (ASM vs. placebo).

c) Post-intervention 24-hr EA burden – cumulative burden from the time of intervention to 24 hours post intervention (ASM vs. placebo).

**Figure 4: RCT model building and sample size calculation**

100,000 drug free cEEG EA burden time courses were simulated and were randomly distributed between the intervention and control (placebo) group.Multiple RCTs were designed by varying each of the following: Treatment delay, ASM efficacy, and outcome measures. The influence of the each of the variables (treatment delay, ASM efficacy rates, delay in drug response, and outcome measures) on the sample size was measured by varying one variable and by keeping the rest of the variables constant.

\*1000 rounds of bootsrapping were performed on the entire process to calculate the median and 95% confidence interval for sample and effect sizes.

ASM: anti-seizure medication; RCT: randomized control trial; OM: outcome measure; Td: treatment delay

**Table 1. Clinical and Demographic Variables**

|  |  |
| --- | --- |
| Variable |  |
| Age (median, Q1-Q3) | 61 (51-74) |
| Gender, F (N (%)) | 40 (83%) |
| Hunt and Hess Score  1  2  3  4  5 | 6 (12.5%)  7 (14.6%)  12 (25%)  16 (33.3%)  7 (14.6%) |
| Fisher Score  1  2  3  4 | 0 (0.0%)  4 (8.3%)  34 (70.8%)  10 (20.8%) |
| EEG duration, hours (median, Q1-Q3) | 183 (139-230) |
| ASM treatment (N (%)) | 32 (66.7%) |

**Table 2: The effect of trial design on effect size**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **ASM efficacy** | **Outcome** | **Treatment delay (h)** | | | | | | |
| **100% reduction of EA burden in 75% of patients** |  | 1 | 14 | 25 | 40 | 50 | 60 | 70 |
|  | **Effect size (EA burden in minutes)** | | | | | | |
| tEAB | 2370  (1953-2830) | 2182  (1811-2598) | 2023  (1656-2414) | 1801  (1491-2148) | 1689  (1393-2021) | 1570  (1303-1868) | 1467  (1204-1756) |
|  | 928  (773-1100) | 866  (719-1035) | 800  (665-945) | 731  (592-881) | 677  (552-810) | 636  (528-754) | 598  (483-709) |
|  | 350  (282-411) | 341  (281-404) | 313  (261-368) | 284  (230-344) | 262  (213-314) | 245  (203­291) | 229  (185-271) |
| **60% reduction in EA burden over 14 hrs in 60% of patients** | tEAB | 2072  (1745-2473) | 1892  (1568-2258) | 1745  (1460-2093) | 1574  (1301-1891) | 1476  (1227-1764) | 1358  (1122-1650) | 1274  (1047-1556) |
|  | 758  (623-906) | 697  (570-832) | 648  (541-768) | 586  (484-708) | 549  (449-672) | 509  (420-615) | 481  (397-575) |
|  | 232  (190-273) | 215  (178-255) | 200  (163-239) | 179  (144-217) | 166  (137-198) | 155  (130-186) | 145  (120-176) |
| **60% reduction in EA burden over 24 hrs in 60% of patients** | tEAB | 2008  (1672-2380) | 1833  (1505-2165) | 1682  (1395-2004) | 1519  (1262-1838) | 1417  (1185-1688) | 1323  (1090-1584) | 1238  (1009-1474) |
|  | 694  (573-821) | 633  (520-756) | 586  (491-701) | 525  (438-636) | 498  (415-598) | 466  (382-554) | 437  (368-527) |
|  | 162  (135-191) | 151  (126-179) | 140  (115-168) | 124  (103-151) | 117(95-141) | 109(89-129) | 102(84-123) |
| **100% reduction in EA burden over 1hr in 50% of patients** | tEAB | 2035  (1644-2424) | 1870  (1529-2225) | 1716  (1435-2055) | 1540  (1274-1871) | 1424  (1205-1729) | 1339  (1096-1615) | 1252  (1042-1491) |
|  | 792  (655-944) | 737  (614-891) | 685  (562-818) | 617  (509-743) | 578  (475-696) | 539  (443-657) | 507  (424-605) |
|  | 295  (238-350) | 284  (229-334) | 264  (216-312) | 237  (192-281) | 220  (180-261) | 205  (170-247) | 191  (158-231) |
|  |

Median and 95% Confidence Interveal of the effect size (EA burden in minutes) is shown.

tEAB: Total EA burden – cumulative burden from the onset of EA until the end of the recording.

pEAB72 : Post-intervention 72-hr EA burden – cumulative burden from the time of intervention to 72 hours post intervention (ASM vs. placebo).

pEAB24 : Post-intervention 24-hr EA burden – cumulative burden from the time of intervention to 24 hours post intervention (ASM vs. placebo).

**Table 3: The effect of trial design on sample size**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **ASM efficacy** | **Outcome** | **Treatment delay(h)** | | | | | | |
| **100% reduction of EA burden in 75% of patients** |  | 1 | 14 | 25 | 40 | 50 | 60 | 70 |
|  | **Sample size (N)** | | | | | | |
| tEAB | 40  (32-46) | 48  (38-56) | 54  (42-64) | 70  (54-82) | 80  (60-94) | 92  (72-112) | 108  (82-128) |
|  | 28  (22-32) | 34  (26-38) | 38  (30-44) | 42  (32-48) | 44  (36-52) | 48  (38-56) | 50  (40-58) |
|  | 28  (24-34) | 32  (24-36) | 34  (28-40) | 38  (30-44) | 42  (32-48) | 44  (34-52) | 46  (38-54) |
| **60% reduction in EA burden over 14 hrs in 60% of patients** | tEAB | 56  (44-64) | 66  (52-78) | 78  (60-90) | 96  (74-114) | 112  (84-134) | 130  (100-156) | 152  (116-178) |
|  | 44  (34-52) | 54  (42-64) | 60  (48-72) | 68  (52-80) | 72  (56-86) | 78  (62-90) | 82  (66-96) |
|  | 70  (58-82) | 84  (66-98) | 92  (72-108) | 106  (80-124) | 114  (88-132) | 120  (94-142) | 128  (100-150) |
| **60% reduction in EA burden over 24 hrs in 60% of patients** | tEAB | 60  (46-68) | 70  (54-84) | 84  (64-98) | 104  (80-122) | 120  (92-142) | 138  (108-166) | 162  (126-192) |
|  | 54  (42-62) | 66  (50-78) | 74  (56-88) | 84  (64-98) | 88  (70-104) | 94  (72-112) | 100  (80-116) |
|  | 152  (124-176) | 182  (140-216) | 204  (160-244) | 234  (180-280) | 250  (190-302) | 266  (208-322) | 280  (216-336) |
| **100% reduction in EA burden over 1hr in 50% of patients** | tEAB | 60  (48-70) | 70  (56-82) | 82  (64-96) | 104  (78-122) | 120  (92-142) | 138  (106-164) | 160  (124-192) |
|  | 44  (34-50) | 50  (40-58) | 56  (44-66) | 64  (50-76) | 68  (54-80) | 72  (56-84) | 76  (60-90) |
|  | 44  (36-52) | 50  (40-56) | 54  (42-62) | 60  (48-70) | 64  (50-76) | 68  (54-80) | 72  (56-86) |
|  |

Median and 95% Confidence Interval of the samples size is shown.

tEAB: Total EA burden – cumulative burden from the onset of EA until the end of the recording.

pEAB72 : Post-intervention 72-hr EA burden – cumulative burden from the time of intervention to 72 hours post intervention (ASM vs. placebo).

pEAB24 : Post-intervention 24-hr EA burden – cumulative burden from the time of intervention to 24 hours post intervention (ASM vs. placebo).