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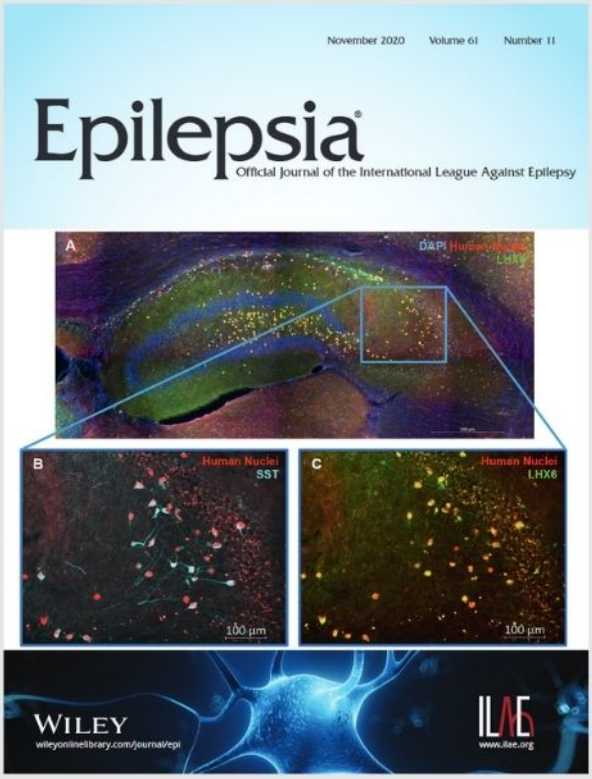

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RESEARCH ARTICLE

Quantifying and controlling the impact of regression to the mean on randomized controlled trials in epilepsy

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Abstract

Objective: Randomized controlled trials (RCTs) in epilepsy for drug treatments are plagued by high costs. One potential remedy is to reduce placebo response via better control over regression to the mean (RTM). Here, RTM represents an initial observed seizure rate higher than the long-term average, which gradually settles closer to the average, resulting in apparent response to treatment. This study used simulation to clarify the relationship between eligibility criteria and RTM.

Methods: Using a statistically realistic seizure diary simulator, the impact of RTM on placebo response and trial efficacy was explored by varying eligibility criteria for a traditional treatment phase II/III RCT for drug-resistant epilepsy.

Results: When the baseline period was included in the eligibility criteria, increasingly larger fractions of RTM were observed (25%–47% vs. 23%–25%). Higher fractions of RTM corresponded with higher expected placebo responses (50% responder rate [RR50]: 2%–9% vs. 0%–8%) and lower statistical efficacy (RR50: 47%–67% vs. 47%–81%). The exclusion of baseline from eligibility criteria was shown to decrease the number of patients needed by roughly 30%.

Significance: The manipulation of eligibility criteria for RCTs has a predictable and important impact on RTM, and therefore on placebo response; the difference between drug and placebo was more easily detected. This in turn impacts trial efficacy and therefore cost. This study found dramatic improvements in efficacy and cost when baseline was not included in eligibility.

KEYWORDS
epilepsy, RCT, statistics

1 | INTRODUCTION

Given the ongoing struggle to achieve lasting seizure freedom in two of every five patients,[1] there is an urgent need for new antiseizure therapies. Meta-analyses have demonstrated rising placebo response rates in randomized controlled trials (RCTs) over time.[2,3] When a drug is 20% more effective than placebo and placebo response increases, statistical power is known to decrease[4] and cost goes up.[5] A key to bringing new treatments to market is inexpensive RCTs. It is therefore critical to assess ways to optimize RCT power, and therefore placebo response.

There are presumed to be at least three main drivers to placebo response[4]: natural variability,[6] psychological factors,[7,8] and regression to the mean (RTM).[9] The most common form of RTM[4,10] represents patients who will be

enrolled during transient periods of higher seizure rates and will soon return to their mean rate (i.e., regress) without any intervention needed.[11,12] Such RTM is presumed to reflect the interaction between natural variability and the study design. For example, when entry into a trial requires a minimum seizure rate that is higher than a patient's usual rate, such patients may transiently qualify for the study from time to time. Conversely, sometimes patients who would always qualify for a study might transiently have a higher temporary seizure rate that would motivate them to enroll in an RCT. The former type of patient would be more sensitive to the precise eligibility criteria, whereas the latter would not. Both examples would be expected to regress to their mean and therefore appear to respond to drug or placebo. It is currently unknown how much RTM contributes to placebo response in epilepsy RCTs.

A seizure diary simulator called CHOCOLATES[13] was recently developed to produce seizure diary data. It includes representation of known statistical features of seizure diaries: (1) a different average seizure frequency for each patient[14] (following a known distribution), (2) the "L-relationship" in seizure counts[15] (a linear relationship between the log of mean seizure rates and the log of SD of those rates), (3) multiple coexisting seizure risk cycles[16,17] (periods of higher or lower susceptibility to seizures following set patterns), (4) seizure clustering[18,19] (the effect seen when groups of seizures occur within a brief time period), and (5) limitations on maximum number of seizures[14,20,21] (too many seizures per day should be considered all part of one prolonged seizure). CHOCOLATES produces seizure counts for as many days as desired from as many patients as desired. The tool can recapitulate historical RCT placebo results without requiring any psychological factors to be included (i.e., using only natural variability and the consequent RTM). Each patient simulated by CHOCOLATES has a different underlying long-term seizure rate, such that a simulated population would match population studies of epilepsy. CHOCOLATES also accounts for the short-term changes in seizure rate experienced by patients seemingly at random (some of the changes can be attributed to cycles and clusters, although others are modeled as random fluctuations). The tool does not differentiate seizure subtypes; it assumes that combinations of all seizure types (on average) have similar statistical patterns. In silico RCTs allows us to have total control over all relevant variables while allowing sample sizes that would be unrealistic in real-world settings.

Recent empiric evidence[22] found that overly strict eligibility criteria are hampering RCT recruitment. Finding ways to loosen the criteria, even a little, could increase the enrollment for critical new therapies. It is possible that a deeper understanding of how to decrease RTM effects could enable this scenario.

Key Points

- Eligibility criteria influences the relative amount of RTM in a randomized controlled epilepsy trial
- Larger RTM typically results in higher placebo rates and lower trial efficacy
- Excluding the baseline from eligibility can reduce RTM, reduce placebo rate, and improve trial efficacy

The present study aimed to use CHOCOLATES to explore the impact of eligibility criteria on RTM, and therefore on RCT power and cost.

2 | MATERIALS AND METHODS

Our purpose is to determine the impact of different eligibility scenarios on RTM, placebo response, and trial efficiency.

Synthetic patients with epilepsy were simulated using CHOCOLATES, an open-source tool.[13] This tool first selects a unique long-term seizure frequency for the individual from a population distribution, and then generates the natural fluctuations expected for that individual. Long-term seizure frequencies vary widely, but the median is 2.9 seizures/month. The SD in the rates follows the "L relationship"; therefore, larger long-term seizure rates exhibit wider variability.

For the purposes of this study, the standard form of parallel design, placebo-controlled RCTs are employed, with 2 months of baseline followed by a titration period to steady state, and then a testing period for 3 months.[23,24] RCTs were analyzed in the typical fashion used for epilepsy studies,[5,25] employing the 50% responder method (RR50), and the median percentage change method (MPC). MPC is typically accepted by the US Food and Drug Administration (FDA) for US studies, and RR50 is often accepted by the European Medicines Agency (EMA) in European studies.

As shown in Figure 1, there is a baseline period and a testing period. The monthly seizure rate is observed during each period: baseline rate and test rate. An additional period prior to the start of the trial represents the pre-enrollment period (this period is obtained entirely by self-report from the participant, without formal observation). Eligibility can be obtained in one of two typical forms (Figure 1): either using the pre-enrollment

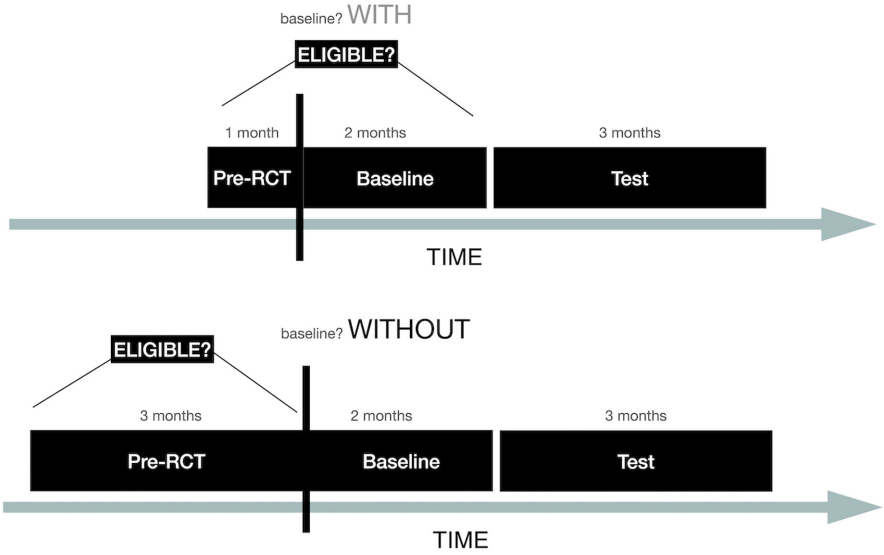

FIGURE 1 Two common forms of epilepsy randomized controlled trial (RCT). There is a period of time before the RCT starts ("pre-RCT"), a 2-month baseline period, and a 3-month test period. The vertical bar indicates the moment when a patient is technically enrolled into the study. The two common methods to ascertain eligibility are shown. In the first form ("with"), a pre-RCT rate for 1 month is obtained from the patient (this period was not observed by the investigators), followed by a formal observation period ("baseline"). The combined period of pre-RCT and baseline are used to determine eligibility for the trial. In the second form ("without"), the entire eligibility period is determined based on the patient's rate of seizure prior to the start of the trial, that is, entirely during the Pre-RCT period, and therefore not observed by the investigators. The formally observed baseline period is not used to verify eligibility in the second form. In both forms, the trial design is to compute the percentage change in seizure rate between the baseline period and the test period. Of note, the true long-term seizure frequency of a patient is not known a priori; therefore, this figure represents two ways of approximating it.

period exclusively (referred to as "without baseline") or using some pre-enrollment period in combination with the baseline period (referred to as "with baseline"). Both forms have been used in standard RCTs for epilepsy: the "with" form[26–28] and the "without" form.[29–31] In the examples illustrated in Figure 1, both use a 3-month window for eligibility, which either partially or entirely occurs before the onset of enrollment. The key to understanding the distinction between the two cases in Figure 1 lies in understanding the way RCT outcomes are generated, in the form of a percentage change at the individual patient level. This percentage change is computed from the baseline period. When in the "with" condition for eligibility, there is an artificial "pressure" for higher seizure rates than average rates, which is mostly absent in the "without" condition. As a result, a patient with a typical rate of X who would not ordinarily qualify for the RCT might become temporarily eligible due to random fluctuations, and therefore enrolled. This hypothetical patient is more likely to experience RTM in the "with" condition because their baseline was measured at a value higher than X. The same patient in the "without" condition would be expected to regress to the mean by the time of their baseline period starting. This means that they would be less likely to experience further regression because during the baseline period their seizure rate would be more similar to their typical rate, X.

2.1 | Definition of RTM

If the baseline rate is higher than the typical rate, and the testing rate is closer to the typical rate (above or below but still closer), this represents RTM. For example, if a patient has a typical rate of 4 seizures/month, and is measured to have a baseline rate (by statistical chance alone) of 6 seizures/month, followed by a testing rate of 3 seizures/month, even though that patient was in the placebo arm, this patient would be considered to have had RTM.

Mathematically, let m be the mean seizure rate of the patient, and let baseline rate be r_B and test rate be r_T. RTM is defined as:

$$RTM\ occurs\ if \begin{cases} r_B > m, and \\ (r_B - m) > |r_T - m| \end{cases} \quad (1)$$

2.2 | Simulation 1: How much RTM is present?

Although placebo response is known to include RTM, the exact contribution is typically unknown. Through simulation, we can determine the fraction of measured placebo response that is attributable to RTM. Then, by changing eligibility criteria (minimum seizure rate), we can re-measure this fraction and see how eligibility influences

it. Moreover, if the eligibility rate is determined before or during baseline, we can see what influence that decision has as well.

A set of patient diaries were produced using CHOCOLATES. Each diary was sampled daily, and then downsampled to monthly seizure counts, for a certain recruitment duration (several values between 6 months and 10 years were evaluated; see Appendix S1). For illustration purposes, a total study (recruitment and observation) period of 2 years was used in the Results section. Using a moving eligibility window of 3 months (taking steps of 1 month at a time), eligibility was determined sequentially 18 times (enough to run a 5-month study with 1-month pre-enrollment data during the 2-year period for the "with" case) or 16 times (enough to include 3 months of pre-enrollment data for the "without" case). Whenever eligible, an RCT was simulated with 2-month baseline and 3-month test. Based on prior evidence,[6,13,32] placebo response was assumed to be entirely related to a combination of natural variability and RTM, without any psychological influence. For those times when eligibility criteria were met, the relative fraction of times when RTM occurred was computed. For example, if a patient met criteria eight times in 3 years, and four of those times RTM occurred, then the fraction 50% would be recorded. Individual fractions were averaged across 5000 simulated patients. The average percentage change from the RCT was computed across all eligible times as well. One set each was recomputed for each of two dimensions: minimum eligibility seizure rate (between 0 and 8) and the inclusion or exclusion of the baseline for eligibility. Note that a minimum eligibility rate of 0 simply means all patients would be eligible.

2.3 | Simulation 2: Statistical efficiency

The statistical efficiency of epilepsy therapy trials (i.e., power) represents the probability that a comparison of an effective therapy to placebo would reach statistical significance. Anything that makes this comparison more challenging is expected to decrease the efficiency of the trial. Thus, if changes to eligibility impact that comparison, they would also impact power. We sought to characterize the difference in statistical efficiency generated by changing the minimum seizure rate for eligibility, as well as the inclusion or exclusion of the baseline for eligibility. Several recruitment durations between 6 months and 10 years were used for each patient, thus allowing patients to become eligible over time. To do this, a drug with efficacy 20% higher than placebo was assumed (a value found to be in meta-analysis of antiseizure medications).[2] Drug was simulated by removing individual seizures with a probability of 20% from the test period in drug-treated patients. As stated above, both placebo and drug arms were assumed to be free from psychological effects, but still subject to natural variability and RTM. In Simulation 1, the trial used 2 months of baseline and 3 months of test. There was no assumed placebo effect; therefore, all placebo response was due to RTM and natural variability.[13] There were $N = 400$ patients simulated per trial, similar to a prior RCT for lacosamide.[33] There were 5000 trials done in each set. A set was computed for each value of minimum seizure requirements from 0 to 8, including or excluding the baseline for eligibility (as in Simulation 1). Each trial assigned half the patients to drug, and half to placebo. RCTs were analyzed in the standard fashion,[5,13,25] that is, using the Fisher exact test to compare the fraction of 50% responders (RR50 method) and using the rank sum test[25] to compare nonparametrically the percentage changes (MPC method). The statistical power was defined as the fraction of the set that achieved statistical significance ($p < .05$) when comparing placebo to drug.[34]

2.4 | Simulation 3: Minimum patients needed

Could changing the eligibility criteria result in a smaller trial size? To answer this question, we computed the minimum number of patients needed to achieve a set statistical power for several possible eligibility rules.

Using an approach analogous to Simulation 2, a set of simulated RCTs were conducted using number of patients, N, from $N = 350$ to 1150 in steps of 50 until the goal was reached. The statistical power goal was 90% (chosen for convenience; typically desired power is chosen between 80% and 95%, depending on the goals of the investigator).[35] This was done again with sets of 5000 RCTs each, with a drug 20% more effective than placebo. There were four sets computed, covering minimum eligibility rate of 2 or 4 seizures/month and covering with or without baseline included. The minimum N required for >90% power was recorded in each set. A minimum of 4 seizures/month represents a typical RCT requirement, whereas 2 seizures/month would be lower than usual, and might be low enough to recruit additional typical clinic patients.[22]

2.5 | Source code

The software used for this study is open source and available at https://github.com/GoldenholzLab/RTMsim.

3 | RESULTS

Simulations 1 and 2 were using 6, 12, 18, 24, 36, 48, and 120 months for the trial enrollment durations. Shown in Figure 2 is a typical trial enrollment period of 2 years.[36] Other potential enrollment durations are explored in the Appendix S1. Seen here, there is a larger fraction of RTM seen when baseline is included for eligibility, and the effect is more pronounced with higher eligibility rates. Similarly, the MPC values and RR50 values from the placebo arm are expected to have higher values in the "with" baseline case compared to the "without," for any eligibility rate. Moreover, the statistical efficiency of both MPC and RR50 trials is high when the baseline "without" case is used, as compared to "with," for any eligibility rate.

In Figure 3, Simulation 3 is summarized. It is clear from these plots that approximately 30% fewer patients would be required in an otherwise identical trial if the baseline was not included in the eligibility. Moreover, it is shown that an RCT that uses the eligibility criterion of 2 seizures/month without baseline can be accomplished with fewer patients than one with eligibility of 4 seizures/month with baseline included.

4 | DISCUSSION

In this study, we explored the contribution of RTM to RCT analysis, specifically focusing on how the eligibility criteria can impact RTM. Choosing to use eligibility criteria

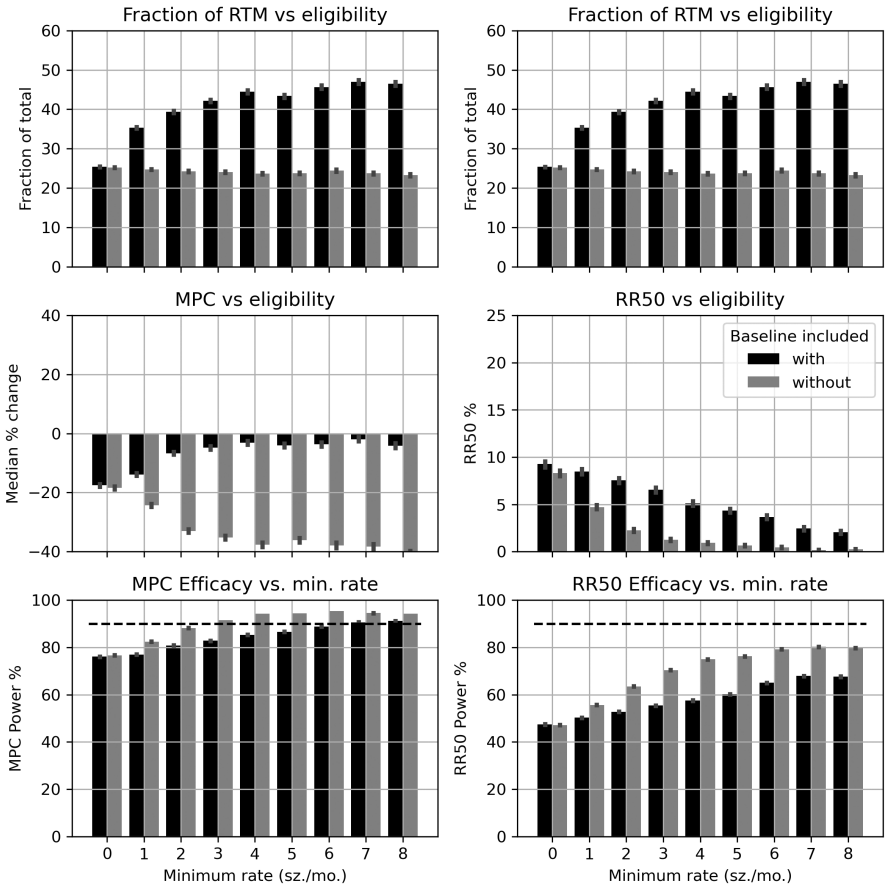

FIGURE 2 Simulations 1 and 2, simulating various randomized controlled trial (RCT) eligibility scenarios. The two main scenarios compared here are the "with" (black bars) and "without" (gray bars) baseline cases (see Figure 1). In addition, minimum eligibility seizure rates between 0 and 8 are displayed (x-axis in all six graphs). The first row shows the same graph twice, comparing the fraction of regression to the mean (RTM) in different eligibility scenarios (with and without baseline, and with differing eligibility rates). In this top row, 5000 placebo-exposed patients were observed for fraction of RTM in each eligibility scenario. The second row shows the expected placebo rate for the same set of differing eligibility scenarios. The third row shows the statistical efficacy in each scenario, given an RCT with 400 patients, a drug that is 20% more effective than placebo, and no psychological influence from placebo. Error bars for this row were produced using bootstrapping (sampling 1000 trials with replacement, 1000 times). The left column shows median percentage change (MPC) values (second row) and MPC efficacy (third row). The right column shows 50% responder rate (RR50) values (second row) and RR50 efficacy (third row). In all six plots, it is apparent that the "with" case is less desirable than the "without" case. Error bars in all plots represent the 95% confidence interval. sz., seizures.

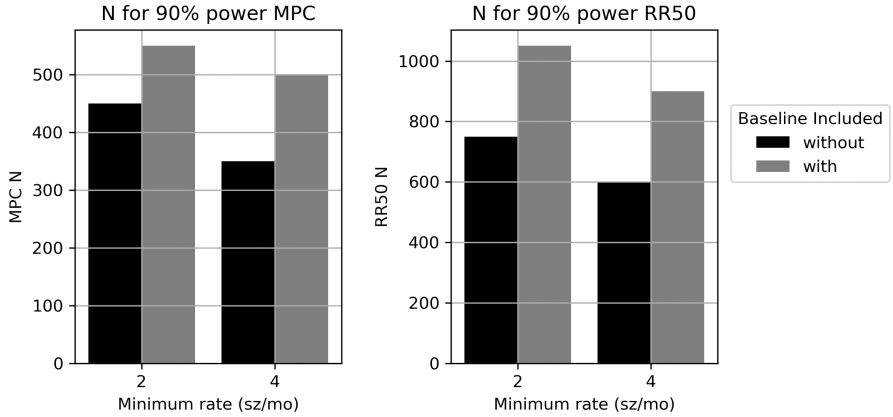

FIGURE 3 Simulation 3, comparing the minimum number of patients for differing eligibility. Shown here are the number of patients needed (*N*) for achieving 90% statistical power in randomized controlled trials that use either median percentage change (MPC; left graph), or 50% responder rate (RR50; right graph). Four different eligibility criteria are explored here: minimum eligibility seizure rate of two or four per month, and baseline included or excluded. It can be seen here that a 30% reduction in *N* is possible when not using baseline. If one compares the case of 2 seizures/month without baseline to the case of 4 seizures/month with baseline, it can be seen that the former is still dramatically more efficient. sz, seizures.

that does not include baseline (Figure 1) has important implications for the fraction of RTM expressed, the expected placebo response, and the statistical efficiency (Figure 2). This finding appears true for MPC (relevant to the FDA in the United States) and to RR50 (relevant to the EMA in Europe). Using the "without" method, RCTs can be run with approximately 30% fewer patients (Figure 3).

Using a more permissive eligibility criteria (i.e., 2 seizures/month) while employing the "without" method will still benefit the trial, because it is cost-effective in comparison to the "with"" method and stricter (4 seizures/month) criteria (Figure 3). These ideas had been considered in the 1970s in the context of diet therapy trials.[37] In their case, they found evidence that classifying patients before measuring a baseline in repeated measures of cholesterol resulted in lower RTM for their data. The application here is similar, although the comparison of serum cholesterol levels to seizure rates (a proxy metric composed of seemingly random seizure events) is so different that direct mapping ideas would be nonintuitive.

Our finding is clinically relevant because of the challenges faced in modern clinical trials with recruitment[22]; specifically, a large fraction of typical patients in clinic would not meet standard RCT eligibility. Thus, using this strategy could widen the net of potential participants, as well as reduce costs for RCTs.

It is notable that the precise values of placebo response from Figure 2 row 2 are readily modifiable by changing various assumptions (see Appendix S1). What is not easily changed are the two key findings: (1) increasing minimum eligibility rates impact placebo response and (2) using or not using baseline in eligibility criteria will influence placebo response magnitude. This is important because MPC placebo responses from 23 historical trials was 17% with SD = 10%, which is very different than the values seen in Figure 2 row 2. Our goal here was not to precisely replicate every detail of historical RCTs, but rather to identify controllable elements.

Anecdotally, studies that used the "with" form[26–28] had an average RR50 difference between placebo and drug of 16%, whereas the "without" form[29–31] had an average difference of 25%. Each of those studies differed on multiple dimensions that can influence this difference; nevertheless, the point that including baseline may adversely impact the ability of the trial to compare drug to placebo is loosely illustrated.

4.1 | Limitations

The limitations of this study are related to the assumptions being made. First, the choice between the use of eligibility with or without baseline may be overidealized. In practice, the case of "without" implies a high degree of trust in self-reported historical seizure rates, whereas the case of "with" implies a very low degree of trust, with considerable oversight added ("trust, but verify"). Because it is suspected that self-reported seizure rates would be less accurate if not generated during a study, one must consider that there is an increased risk of inaccurate historical eligibility in pre-RCT rates being presented in the "without" case. Because this would be highly subject dependent, it is unclear whether there is a general pattern that can be guaranteed in this regard, but it is an important psychological effect that was not accounted for in the present study. Some observers

believe that the use of wearables or implanted seizure detectors[38] may allow for more accurate measurement of long-term seizure rates, although such ideas would present considerable technical,[39] financial, and psychological[40] challenges.

Next, the present study compared the two cases, "with" and "without," using a total of 3 months of seizures to determine eligibility. This duration, 3 months, was chosen for convenience. The same basic argument would work for 2 months or 4 months, although the details would obviously be expected to change. One could design an RCT with more or less pre-RCT observation period and more or less baseline period than modeled here. Regardless of the choice, our simulations suggest that a greater reliance on a baseline period for eligibility may have adverse consequences on RCT power. Using 3 months in both canonical "with" and "without" cases allowed a direct comparison that would be "fair" (rather than differing durations).

Moreover, the number of months that a trial is conducted influences how often a patient who should not be eligible has a chance to "by chance" become temporarily eligible. In Appendix S1, we explore other durations besides 2 years, with findings similar but not identical to what is shown in Figure 2.

We did not include titration periods in our analysis, although epilepsy RCTs typically include a titration period between baseline and test. The seizure rate is not presumed to have reached steady state during the titration period, and therefore there are additional modeling complexities beyond the scope of the present study. That being said, the same basic concepts about ways to decrease RTM would be relevant to studies that do use the titration period due to the structure of the trial.

Patient dropout from RCTs was not included in the present analysis. Many epilepsy RCTs report dropout on the order of 20% or so, and the last-observation-carried-forward method may have subtle impacts on trial outcomes.[2] Prior simulation found that dropout did not have a strong impact on trial efficacy or cost, although explicit evaluation of RTM was not done.[34]

Also, synthetic seizure diaries were generated using CHOCOLATES,[13] a simulator with potential differences from real patient diaries. It is currently unknown in what ways CHOCOLATES-simulated diaries would differ from real patient diaries (because known statistical features are currently included); however, as we continue to learn more about the statistical properties of seizure diaries, the simulator will likely require further refinements. To mitigate this problem, the source code for CHOCOLATES and the present simulations are presented as open source for future investigators to expand upon.

Another concern reflects the many unknowns in modeling a standard epilepsy RCT. For our purposes, we selected a drug effect that was 20% stronger than placebo, as this was shown in meta-analysis to be typical for nearly any antiseizure medication.[2] We also assumed that the placebo has no psychological effect at all in epilepsy RCTs, a suggestion that has support from multiple indirect lines of evidence.[6,13,32] For other medical conditions, researchers have argued that placebo response in RCTs may include little or even no psychological factors (i.e., perhaps the "placebo effect" does not exist in many contexts).[11,41,42] Nevertheless, even if psychological effects do exist in epilepsy RCTs, they would be expected to be present in equal portions between placebo and drug groups; therefore, the overall conclusions found here would still be relevant. A related issue concerns the probabilistic model for drug efficacy. One alternative model could modify the underlying seizure rate that generates the random diary in CHOCOLATES. Here, we employed a data-driven approach that was sufficient to recapitulate 23 historical RCTs.[13] It is currently unknown what model is most accurate in this context. Furthermore, it should be noted that the present study does not account for other eligibility criteria, such as the presence of clusters, or status epilepticus. There are additional nuances associated with these factors that are beyond the scope of the present study. Our study did not make any additional requirements beyond the minimum seizure rate within the eligibility window. Some epilepsy RCTs may include additional requirements related to seizure subtypes, such as generalized tonic–clonic. Although the numerical count of any one subtype of seizure is expected to be lower than the total count, the overall findings would still be expected to apply in such RCTs.

Finally, the entire analysis assumes the classical organization of a long-term trial based on discrete events organized in a fashion typically used in epilepsy drug trials.[23,24] If a trial is organized differently, uses dramatically different outcome metrics, or has other special features, this analysis may not apply.

It is likely that the findings presented here are not unique to epilepsy at all, because the fundamental concept is that RTM (and therefore excessive placebo response) will be mitigated if eligibility determination is dissociated from the baseline measurement. We think this is a generalizable principle that could have implications in many other areas of RCTs beyond epilepsy trials.

5 | CONCLUSIONS

The placebo response continues to perplex generations of clinical trialists, who primarily aim to study the impact of a treatment and hope that placebo response is small. The

present study finds a way to isolate the impact of a common form of RTM and how to reduce that impact on RCT efficiency. These results may have implications beyond epilepsy RCTs. Validation studies are needed to confirm these simulated findings.

AUTHOR CONTRIBUTIONS

Daniel M. Goldenholz conceived and oversaw the project, conducted coding experiments, and wrote the manuscript. Eliana B. Goldenholz conducted coding experiments, helped interpret the results, and edited the manuscript. Ted J. Kaptchuk helped interpret the results and edited the manuscript.

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CONFLICT OF INTEREST STATEMENT

D.M.G. has received grants from the NIH and BIDMC. He serves as an advisor for Magic Leap, Eysz, and Epilepsy AI. He has received compensation for speaking before the AAN, and AI in Epilepsy and Neurology. He also has performed consulting for Neuro Event Labs and IDR. None of the above disclosures is relevant to the present publication, but they are reported in the spirit of open disclosure. Neither of the other authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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