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Modeling and Validating Bayesian Accrual Models on Clinical Data and Simulations Using Adaptive Priors

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Abstract

Slow recruitment in clinical trials leads to increased costs and resource utilization, which includes both the clinic staff and patient volunteers. Careful planning and monitoring of the accrual process can prevent the unnecessary loss of these resources. We propose two hierarchical extensions to the existing Bayesian constant accrual model: the accelerated prior and the hedging prior. The new proposed priors are able to adaptively utilize the researcher's previous experience and current accrual data to produce the estimation of trial completion time. The performance of these models, including prediction precision, coverage probability, and correct decision-making ability, is evaluated using actual studies from our cancer center and simulation. The results showed that a constant accrual model with strongly informative priors is very accurate when accrual is on target or slightly off, producing smaller mean squared error, high percentage of coverage, and a high number of correct decisions as to whether or not continue the trial, but it is strongly biased when off target. Flat or weakly informative priors provide protection against an off target prior, but are less efficient when the accrual is on target. The accelerated prior performs similar to a strong prior. The hedging prior performs much like the weak priors when the accrual is extremely off target, but closer to the strong priors when the accrual is on target or only slightly off target. We suggest improvements in these models and propose new models for future research.

Keywords

clinical trials; hedging prior; objective prior; patient accrual; data monitoring committee

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1. Introduction

Evaluating and monitoring subject recruitment is important in clinical trials [1]. Delayed subject recruitment can contribute to an increase in the cost of studies and/or can lead researchers to settle for smaller sample sizes than originally proposed. If the proposed sample size is not achieved, the study may not have adequate power to demonstrate a treatment effect. Slow recruitment in clinical trials tends to increase resource utilization, which includes both the clinic staff and patient volunteers. Furthermore, slow enrollment in clinical studies may also lead to a delay in the availability of new therapies and, therefore, slow the advancement of medical progress [2]. For example, a year delay in access to Herceptin would represent a total loss of \$8 billion dollars of benefit for breast cancer patients in the United States [3]. Development of reliable and practical tools for accrual prediction is critical in clinical trials.

Modeling subject recruitment is a topic of interest to both clinicians and statisticians. The available accrual models are reviewed by Barnard [4] and Zhang [5]. According to Barnard [4], the simplest approach is an unconditional model [6]. The unconditional model assumes the accrual rate (e.g., subjects recruited per month) is fixed. The total accrual time is estimated by dividing the planned sample size by the number of subjects expected to enroll in the study each month. A conditional model allows the accrual rates to vary in any given time, depending on other factors that may accelerate or delay the accrual [7]. Compared with the unconditional model, the conditional model matches more closely to real situations. Both unconditional and conditional models fail to consider variations in actual accrual progress; therefore, their predictions are less accurate. The Poisson models assume that the number of participants recruited within a fixed time follows a Poisson distribution [7]. Anisimov and Fedorov [8] applied the Poisson model to multi-center clinical trials, assuming that the rate parameter for the Poisson was different for each center of a multi-center study, and overall the accrual process followed a Poisson-Gamma distribution. Bakhshi, Senn and Phillips [9] extended the approach with a hierarchical model using historical data from similar trials in the specific center via an empirical Bayesian approach. Other models, such as the Monte Carlo simulation Markov model by Abbas [10], time series model by Hadich and Ioannidis [11], and a model based on nonhomogeneous Poisson process by Zhang and Long [12] have also been proposed as a method to predict enrollment.

Gajewski, Simon and Carlson [13] developed a Bayesian method for constant subject accrual based on an exponential waiting model, which is equivalent to Poisson counts over a specified time [14]. A unique feature of this model is the incorporation of subjective knowledge about subject accrual rates through an informative prior distribution [13]. The strength of the prior distribution is controlled by a parameter P between 0 and 1. If $P=1$, the prior is given weight equivalent to the proposed sample size of the study. If $P=0.5$, the prior is given weight equivalent to half the proposed sample size. This means that halfway through the study, the prior and the actual subject accrual data are given equal weight. If $P=0$, the prior is effectively ignored [13]. If the researcher has strong confidence in the subject accrual rate (for example, he/she has extensive research experience with many similar studies in the same patient setting), the posterior distribution will be weighted heavily towards the prior distribution, especially early in the trial. This avoids an

unnecessary alarm when the enrollment of the first few subjects is slower than expected. However, if the researcher has a weak prior, early evidence of slow accrual will be given greater weight, encouraging a rapid response to address the slow accrual [13].

As discussed above, assessment and specification of control parameter P is critical in the simple constant accrual model [13]. The researchers should constantly monitor/change prior P subjectively during the accrual process, and the assessment of P is totally based on researchers' knowledge and previous experience. There are several limitations regarding this method. One of the concerns is the researcher's over-confidence. What if the researcher provides a strongly informative prior distribution that is substantially off target? In our experience, researchers are frequently overly optimistic about accrual rates and they are overly confident in their estimates. Overly optimistic and unrealistic accrual rates have been noted by others as well. For example, a study of 78 projects in eight departments of general practice conducted at the Netherlands Institute for Health Services Research and the Centre for Quality of Care Research, found that only 46% recruited the planned number of patients within the planned time frame [15]. Other examples of this overconfidence can be found in Williams and Seed [16], Breau, Carnat, and Gaboury [17], Jayakaran Saxena, and Yadav [18], Keen, Pile, and Hill [19]. The mis-specification of prior by researchers will lead to huge bias in the prediction of accrual, which in turn impairs the management of the trial. Another concern of the existing method is the assessment of P is not always practical. A third party who lacks sufficient knowledge about a specific clinical trial may have difficulty specifying P . For example, when a clinical trial is evaluated by an Institutional Review Board (IRB), it may be difficult for the IRB to propose an appropriate subjective prior P to evaluate the trial process. This lack of sufficient knowledge may also introduce bias in P .

To avoid a poor choice of prior, a more general and objective approach is to incorporate the historical opinion through power prior [20]. The power prior was evaluated and modified by several groups of researchers, which is now well recognized as the modified power prior [21, 22]. The amount of borrowing of strength of historical data is controlled by the power parameter. Another way to utilize historical data is through a commensurate prior, which is proposed by Hobbs et al. [23].

In this paper, we propose two adaptive Bayesian priors in monitoring accrual process. The first approach is the accelerated prior. The initial prior probability (P) is associated with the proportion of data collected. In the beginning of a clinical trial, when no data are collected, the model will weigh entirely on the investigator's historical experience, with $P=1$. As data collection progresses, P declines linearly. This places less weight on the prior and more weight on the data. While all Bayesian models place less weight on the prior as data collection progresses, the accelerated prior accelerates this process to avoid the lingering effects of an off target prior.

The second approach we proposed is the hedging prior. This model treats P as a hyper parameter that follows a uniform distribution. If the prior is off target, the hyper parameter converges to zero as more accrual data arrives. The hedging prior is equivalent to the modified power prior, but the hedging prior is easier to implement.

With adaptive priors, P is monitored and determined with the progress of the clinical trial. Detailed model descriptions are provided for the accelerated prior and the hedging prior in section 2. Section 3 shows the application and evaluation of the methods using real clinical data. In section 4, the model efficiency and robustness of the new proposed methods and the previous proposed Bayesian model are examined using simulated data under nine different scenarios. Section 5 is the discussion and conclusions.

Model

2.1 Closed form of constant exponential waiting time model

Gajewski, Simon and Carlson [13] introduced a Bayesian model for constant accrual. Suppose in the original clinical trial protocol, the investigator planned to recruit n subjects in T days. Assume that the waiting time (w) for each successive patient follows an exponential distribution, $w_i \sim \exp(\theta)$, where θ represents the average accrual time for the i th subject. The

distribution of the waiting time (w) is $f(w|\theta) = \frac{1}{\theta} e^{-w/\theta}$. The prior distribution of θ is assumed to be inverse gamma, $\theta \sim IG(nP, TP)$, where P is the investigator's confidence in the original plan, measured on a 0–1 scale. During the trial, m subjects have been collected in T_m ($T_m = \sum_{i=1}^m w_i$) time period. Then the posterior distribution for θ is updated to $\theta|W \sim IG(np + m, TP + T_m)$ with $W = (w_1, w_2, \dots, w_m)$ [13]. For fixed n , the waiting time for the rest of the sample size is $\tau = \sum_{i=m+1}^n w_i$.

The prediction interval produced by this model provides a rule for stopping a trial with slow accrual. The researcher will specify a decision point, typically 25% or 50% larger than the planned accrual time T , that is $T_{decision} = 1.25T$, or $T_{decision} = 1.5T$. The decision point represents a delay large enough to threaten the successful completion of a study. If the 95% prediction interval lies entirely above the decision point, then there is sufficient justification to discontinue the trial for poor accrual.

In this paper, we present a new method for the predicted time to recruit a fixed number of subjects, whereas Gajewski et al used simulation [13]. The conditional distribution of τ is

$\tau \sim G(m - n, \theta)$, with $f(\tau|\theta) = \frac{1}{\Gamma(n - m)\theta^{n-m}} \tau^{n-m-1} e^{-\tau/\theta}$. Then, the predictive distribution of τ can be derived by integration, and we obtain:

$$g(\tau) = \frac{1}{(TP + T_m) \left(1 + \frac{\tau}{TP + T_m}\right)^{nP+n}} \left(\frac{\tau}{TP + T_m}\right)^{n-m-1} \frac{\Gamma(nP+n)}{\Gamma(nP+m)\Gamma(n-m)} \quad (1)$$

Let $\phi = \frac{\tau}{TP + T_m}$, then $\tau = \phi(TP + T_m)$; therefore,

$$g(\phi) = \frac{1}{(1+\phi)^{nP+n}} \phi^{n-m-1} \frac{\Gamma(nP+n)}{\Gamma(nP+m)\Gamma(n-m)}. \quad (2)$$

This is an inverted beta distribution [24], with $\alpha = n - m$ and $\beta = nP + m$. When $\beta > 1$, the mean of ϕ is $E(\phi) = \frac{\alpha}{\beta - 1} = \frac{n - m}{nP + m - 1}$. Then, the predictive mean of τ can also be calculated directly as.

$$E(\tau) = \frac{n - m}{nP + m - 1} (TP + T_m). \quad (3)$$

Similarly, the variance of τ can also be calculated as

$$Var(\tau) = \frac{(n - m)(n + nP - 1)}{(nP + m - 2)(nP + m - 1)^2} (TP + T_m)^2. \quad (4)$$

The percentile of τ can be obtained by

$$p(\tau) = (TP + T_m) \frac{p(B)}{1 - p(B)}, \quad (5)$$

where $p(B)$ represents the percentile for the beta distribution $beta(n - m, nP + m)$.

To evaluate the sensitivity and stability of the model in accrual prediction, we can also calculate the mean square error. Suppose the true accrual time is T_{truth} , the total recruiting time is $T_p = \tau + T_m$. Then,

$$MSE(T_p) = \frac{(n - m)(n + nP - 1)}{(nP + m - 2)(nP + m - 1)^2} (TP + T_m)^2 + \left[\frac{n - m}{nP + m - 1} (TP + T_m) + T_m - T_{truth} \right]^2. \quad (6)$$

2.2 Hierarchical extensions of the constant accrual model

In the Bayesian accrual model [13, 25], the prior P needs to be specified by the researcher. However, in the evaluation by an ethical review committee, it is not practical to do prior specification for each study. In addition, in the monitoring of accrual, it may be too subjective for clinical researchers to choose a single value for the confidence level even if they are familiar with similar previous trials and the current trial. Therefore, we proposed two adaptive priors for the Bayesian accrual model to make the choice of P more objective, as well as to avoid a poor choice of prior mean.

2.2.1 Accelerated Prior—We define the accelerated prior (AP) as

$$P = 1 - \frac{m}{n}. \quad (7)$$

P decreases proportional to the number of subjects recruited. In the beginning of the trial, when there are no subjects recruited, m is 0 and P is 1. The posterior distribution of θ relies entirely on the prior specification. As more accrual data are collected, the value of P will shrink. While all Bayesian models place less weight on the prior distribution as more data

are collected, this particular approach accelerates the transition. When m is equal to n , P will be 0 and the posterior estimation of θ will only be based on collected data.

2.2.2 Hedging Prior—As P represents the investigator's confidence in the trial, it actually indicates the similarity of the current trial with historical information. Instead of fixing P as a single value, we can set a hierarchical model, specifying the prior distribution for P as uniform (0, 1). Therefore, we define the hedging prior (HP) as:

$$\pi(\theta, P|n, T) = \frac{(TP)^{nP}}{\Gamma(nP)} \left(\frac{1}{\theta}\right)^{nP+1} e^{-\frac{TP}{\theta}}. \quad (9)$$

If the prior is off target, the accumulated accrual data will force the distribution of P downward, representing a down weighting of the strength of the prior distribution. As more data are accumulated that are inconsistent with the off target prior the down weighting should become greater.

The proposed hedging prior is actually a special case of modified power prior. In Bayesian analysis, the modified power prior provides an efficient way to incorporate and down weight historical data [20, 21, 22]. In our exponential waiting time model, the modified power prior can be written as

$$\pi(\theta, P|n, T) = C(P) L(\theta|n, T)^P \pi_0(\theta) \pi(P), \quad (10)$$

Denote the initial prior $\pi_0(\theta) = \frac{1}{\theta}$, which is a special inverse gamma with both shape and scale parameter equaling 0. Assuming the initial prior for P is $\pi(P) \sim \text{beta}(a, b)$. When both a and b equal to 1 $\pi(P) = 1$, The researcher's experience and opinion on the accrual are expressed as $L(\theta|n, T) = \theta^{-n} e^{-T/\theta}$. The normalizing coefficient $C(P)$ can be obtained by

$$C(P) = \frac{1}{\int L(\theta|n, T)^P \pi_0(\theta) d\theta} = \frac{1}{\int_0^\infty (\theta^{-n} e^{-T/\theta})^P \frac{1}{\theta} d\theta} = \frac{1}{\int_0^\infty \left(\frac{1}{\theta}\right)^{nP+1} e^{-\frac{TP}{\theta}} d\theta} = \frac{1}{\frac{\Gamma(nP)}{(TP)^{nP}}} = \frac{(TP)^{nP}}{\Gamma(nP)}. \quad (11)$$

Finally, the full expression of the prior is

$$\pi(\theta, P|n, T) = C(P) L(\theta|n, T)^P \pi_0(\theta) \pi(P) = \frac{(TP)^{nP}}{\Gamma(nP)} \left(\frac{1}{\theta}\right)^{nP+1} e^{-\frac{TP}{\theta}}, \quad (12)$$

which is exactly the same as we defined for hedging prior. Thus, the hedging prior is a special case of modified power prior. The hedging prior has a simple and intuitive motivation and can be fit using off the shelf software, such as BUGS.

Using the hedging prior, the posterior distribution of θ and P is

$$\pi(\theta, P|n, T, m, T_m) \propto \frac{(TP)^{nP}}{\Gamma(nP)} \left(\frac{1}{\theta}\right)^{nP+m+1} e^{-\frac{TP+T_m}{\theta}}, \text{ and} \quad (13)$$

$$\pi(P|n, T, m, T_m) = \int_0^\infty \frac{(TP)^{nP}}{\Gamma(nP)} \left(\frac{1}{\theta}\right)^{nP+m+1} e^{-\frac{TP+T_m}{\theta}} d\theta = \frac{(TP)^{nP} \Gamma(nP+m)}{\Gamma(nP) (TP+T_m)^{nP+m}}, \quad (14)$$

where m is the number of subjects that have been recruited and T_m is the time since trial started, which remains the same as previously defined.

3. Application in clinical trial data

In order to evaluate the performance of the constant accrual model and the two hierarchical extensions, we applied the various models in three clinical studies that were conducted at the University of Kansas Medical Center. Each of these studies was completed prior to the use of our accrual model.

For each of the three studies, the 95% credible intervals of the predicted total accrual time were estimated using three weak priors: a flat prior ($P=0$), a very weak informative prior ($P=0.01$), and a weak informative prior ($P=0.1$). We also considered two strong priors: $P=0.5$ and $P=1$. Finally we used the accelerated prior and hedging prior. We evaluated the actual accrual data when 1/8, 1/4, or 1/2 subjects were recruited. The mean square error was calculated according to equation (5).

In addition, we also evaluated whether the methods have the ability to make a correct decision on whether the method can alert slow trials. If the accrual is delayed, then $T_{truth} > T$. As it would be too strict to use T directly, we defined a tolerance coefficient δ , which will produce a decision point $T_{decision} = \delta T$ that can be used for decision making. We also estimated the probability that the predicted total accrual time is less or equal to the cut-off time, which is $P(T_p \leq \delta T)$. In the current study, the decision point for each trial was set to 1.25T.

3.1 Application Study A: Colorectal Cancer Prevention

Study A investigates “Tailored Touch screen Computers for Colorectal Cancer Prevention in Urban Core Clinics.” In this study, the total proposed sample size is $n=460$, and total time for accrual is 16 months (487 days). In the real data, the total number of recruited subjects is 471. Assuming the accrual rate is constant, the corresponding T is 561 days. The decision point (701) is set 25% larger than the planned accrual, that is, $T_{decision}=561 \times 1.25$. The total days to recruit 471 subjects is $T_{truth}=610$ days, which indicates that the trial is slower than planned.

An important feature of this accrual is the lack of constancy over time (Figure 1A). The accrual is slightly below target for the first quarter of the time, and even slower as the trial progresses. There is a sudden surge, however, near the end of the trial, not enough to get the trial back on time, but sufficient to cause difficulty for all of the accrual models.

Figure 2A shows the performance of each method, assuming 1/8, 1/4, and 1/2 of the subjects are recruited. The solid line represents T_{truth} , and the dotted line represents the decision point, 1.25T.

When 1/8 of the data are collected (59 patients), the total accrual time is 88 days. A simple linear extrapolation of this value would indicate that the entire trial would take 704 (88×8) days. All methods provide the point estimates much larger than the planned trial duration of 561 days, with the weaker priors showing more pessimistic estimates than the stronger priors. Both the accelerated prior and the hedging prior behave similar to the stronger priors at this point. The distribution of P for the hedging prior is similar to a uniform distribution, with a mean of 0.446 (versus 0.5 for a uniform) and a 95% interval from 0.027 to 0.971 (versus 0.025 to 0.975 for a uniform). None of the intervals lies entirely above the decision point. The predicted 95% credible interval for the total accrual time covers T_{truth} (610) for each of the models.

As the trial progresses, the accrual starts to slow down. When 1/4 of the data are collected (136 patients), the total accrual time is 201 days. A simple linear extrapolation would indicate a trial duration of 804 days. All of the methods provide very large point estimates, with the weaker priors again producing the most pessimistic estimates. The accelerated prior continues to behave like a strong prior, but the hedging prior has a point estimate and a prediction interval that more closely approximates a weaker prior. The distribution of P for the hedging prior has shifted markedly, with a mean of 0.08, representing a substantial down weighting of the prior distribution.

Because of a late surge in accrual, all of the methods predict the total accrual time poorly, though the prediction interval for the two strongest priors and the accelerated prior still include T_{truth} . None of the intervals lies entirely above the decision point, indicating (correctly) that the trial should continue.

When 1/2 of the data are collected (236 patients), the total accrual time is 368 days. A simple extrapolation produces an estimated trial duration of 736 days, which is slightly better than the earlier prediction. All methods are similar, though the point estimates are slightly more pessimistic for the weaker priors and the hedging prior. All of the intervals include the decision point, but they all are completely above T_{truth} . The accelerated prior still behaves much like one of the stronger priors ($P=0.5$), while the hedging prior behaves much like a weaker prior ($P=0.1$). The mean for the distribution of P is 0.12, not quite as extreme as earlier, but still a substantial down weighting of the prior distribution. The mean squared error of prediction, which represents overall measure of the performance of each model, is shown on the left of Figure 3A. The performance of the strong priors and the accelerated prior seem to be superior to the weak priors and the hedging prior.

Figure 3A right shows for each model the estimated probability that the study will finish earlier than the decision point. Notice that the weak priors and the hedging prior are again much more pessimistic than the strong priors and the accelerated prior.

3.2 Application Study B KanQuit 2

KanQuit 2 is a project targeted to treat hospitalized smokers in rural parts of the state via telephone counseling. The proposed total sample size is 576, and $T=521$. Total time to finish recruiting is $T_{truth}=1171$ days, about twice as long as planned. We set the decision point to

652 (521*1.25). Figure 1B shows that the accrual is very slow in the beginning. The accrual rate speeds up slightly when the first 1/3 of the subjects are recruited.

Figure 2B shows the coverage of predicted total accrual time using each method. Although there is substantial variation in the location and width of the individual prediction intervals, it is worth noting that every single model would have recommended early termination of the study even only 1/8 of the data was collected.

With 1/8 of the data are collected (72 patients in 244 days), the simple linear extrapolation would estimate the total completion time to be 1,952 days, more than triple of the planned accrual rate. The weak priors are close to this estimate. The strong priors are less pessimistic, but even these priors, which weight the data much less strongly than the off target prior, still are pessimistic enough to recommend early termination for slow accrual. The accelerated prior behaves much like the strong prior. The hedging prior behaves much like a weak prior. The mean of the distribution of P in the hedging prior is 0.004, representing an almost total rejection of the off target prior. The results for all models at 1/4 and 1/2 of the subjects are similar.

Notice that the stronger priors are actually better at including T_{truth} . The downward pull of the off target prior prevents these models from overreacting to the temporary slow accrual at the start of the study.

Figure 3B left shows the mean squared error of prediction. The pattern is similar to Figure 3A. Figure 3B right shows that for this extreme study, all the models estimate the probability that the study will finish earlier than the decision point to be zero, even with only 1/8 of the accrual data available.

3.3 Application Study C KIS III study

This study evaluates the efficacy of sustained release bupropion in combination with health education (HE) counseling for smoking cessation among urban African American light smokers. The study is a two-arm, double-blinded, placebo-controlled design.

The total proposed sample size is $n=540$. The proposed total time for accrual is 24 months, with $T=730$ days. The decision point is 912 (1.25*730). The real time for accrual is $T_{truth}=670$. There is also some minor variation in accrual rates. The study was slightly slow in the very beginning. Then it sped up and finished earlier than expected. Overall, this study represents a rather small change (less than 10%), and it would be fair to characterize the prior distribution as just very slightly off target.

All the methods produced similar point estimates, which is expected for a prior distribution that is only slightly off target. None of the methods would suggest early termination of the trial for poor accrual (Figure 2C). Note that the prediction intervals are narrower for the strong priors. The accelerated prior behaves much like the strong prior, but the hedging prior also behaves like a strong prior. The distribution of P is similar to a uniform distribution—the mean is 0.446, 0.507, and 0.496 respectively. All of the prediction intervals cover T_{truth} .

Figure 3C right shows the estimated probability that the study will finish earlier than the decision point by each model. Since this study was actually accruing patients slightly faster than planned, each of the models estimates this probability effectively at 100%.

4. Simulation Studies

Motivated by the application of the various methods in real clinical studies, a simulation study was designed to evaluate the robustness and performance of proposed accelerated prior and hedging prior, and compare them to the constant accrual model.

We assume that a researcher proposed to recruit 300 subjects in 3 years. Thus n equals 300, and T is 1095 days. If the accrual is on target, the theoretical waiting time θ_0 is 3.65 days/patient recruited. We also assume that the waiting time for slow accrual θ_1 is 7.31 days/patient (off target), and for fast accrual θ_2 is 1.83 days/patient (off target). The waiting times for all 300 subjects are simulated based on the assumption that the waiting time for each subject is independently distributed as exponential (θ), or piecewise exponential (θ) to reflect a non-homogenous process.

Based on the different combinations of θ_0 (on target accrual), θ_1 (off target, slow accrual), θ_2 (off target, fast accrual). We designed nine studies to mimic the situations commonly encountered in real clinical trial studies. Study 1 represents an unbiased situation, where the whole accrual process is on target. The waiting time for each subject is exponential with $\theta_i = \theta_0$ (i is from 1 to 300). Study 2 represents a slow accrual, in which the waiting time is two times as long as planned, during the whole study. Study 3 is a fast accrual and the accrual time is only half of the proposed time. The other six studies resemble a step wise accrual process. Study 4 shows a situation where the accrual is slow for the first tenth of the subjects, $\theta_i = \theta_1$ (i is from 1 to 30). The recruitment then goes back to normal for the rest of the subjects $\theta_i = \theta_0$ (i is from 31 to 300). Study 5 mimics a trial that is slow at both the first and last tenth of the subjects. Study 6 is similar to study 2, with the exception that the slow accrual period is longer, such that the first quarter of the subjects is recruited slowly. Study 7 is parallel with study 3, with slow accrual for both first and last quarter of subjects. Study 8 represents a trial that starts with slow accrual at the first quarter, goes back to normal on the second quarter, and then catches up quickly to the schedule during the last half of accrual, with $\theta_i = \theta_2$ (i is from 151 to 300). Study 9 is an example of a trial that is on time for the first half subjects, but lags for the last half. The theoretical settings of the accrual process for each study are shown in Table 1 and displayed in Figure 4. Each simulation study is repeated for 1000 times. For each simulation, T_{truth} is the sum of the waiting times,

calculated as $T_{truth} = \sum_{i=1}^{300} w_i$. The 2.5%, 50%, and 97.5% quantiles of T_{truth} are calculated from the 1000 simulated samples. In figure 4, for comparison purpose, the dotted line represents the theoretical accrual rate if the recruitment is unbiased or on target. The vertical dash line shows the theoretical time (T) for which the trial should be finished.

For each set of simulated data, we assume the first 1/8, 1/4, 1/2, 3/4 of the data are known, with $m=37, 75, 150, 225$, respectively. The total predicted accrual time is estimated using conjugate inverse gamma priors and are specified as $P=0, P=0.01, P=0.1, P=0.5$ and $P=1$, as well as the proposed accelerated prior and hedging prior. For each method in a particular

study, the mean squared error of total predicted time is calculated as $= \frac{1}{1000} \sum_{j=1}^{1000} MSE_j$, and the average of the relative bias for each study is calculated as

$RBIAS = \frac{1}{1000} \sum_{j=1}^{1000} \frac{\hat{T} - T_{truth_j}}{T_{truth_j}} \times 100\%$. The summary of *MSE* and *RBIAS* are shown in Figure 5 and Figure S1, respectively. We compared and summarized the results for all seven methods. As we found that the results between $P=0$ and $P=0.01$ are very similar, we exclude $P=0.01$ from Figure 5 and 6 for the purpose of better display.

For the first simulation study, when the whole accrual process is on target, it is not surprising that the informative prior with $P=1$ has the smallest *MSE*. The accelerated prior behaves very similarly to $P=0.5$, which is almost as good as $P=1$, when 1/8, 1/4, 1/2, 3/4 of the data are known. The hedging prior has a slightly larger *MSE*, although much better than when P is very small, $P=0.1$ or $P=0.01$, or with non-informative prior ($P=0$). However, for a biased accrual (study 2 and 3), either slow or fast, informative prior $P=1$ has the largest *MSE*. $P=0$, $P=0.01$, $P=0.1$ and hedging prior have smaller *MSE*. The accelerated prior has an *MSE* comparable to the strong priors in the beginning of the trial, but have smaller *MSE*

when $m = \frac{3}{4}n$.

When the first 10% of subjects are slow in accrual (simulation study 4), the results of *MSE* are similar to study 1. The strong priors produce the smallest *MSE*. The weak priors have much larger *MSE* values. The *MSEs* of accelerated prior are comparable to the strong priors. The hedging prior suffers from the same problems as the weak priors, giving too much weight to the early slow accrual data. The results from study 5 (slow first and last 1/10) are very similar to study 4. The remaining studies 6, 7, 8 show similar results. If the initial early accrual is slow, the weak priors and the hedging prior give too much weight to these data. The studies can recover at times when there are sufficient accrual data beyond the initial slow accrual period (that is, at $m=150$). The advantage of the strong priors is that they are not unduly swayed by the early slow accrual. The methods all behave similarly for study 9.

In each of the simulation studies, we not only estimated the total accrual time using all different methods, but also calculated the 95% credible interval $T_{0.025}$ and $T_{0.975}$. The correct coverage is defined as $CC_j = I(T_{truth_j} - T_{0.025}) + I(T_{truth_j} - T_{0.975})$. The total

percentage of correct coverage is $CC = \frac{1}{1000} \sum_{j=1}^{1000} CC_j \times 100\%$. The summary of the correct coverage is shown in Table 2. For unbiased accrual, the coverage probabilities of all methods are approximately 95% or greater. When the accrual is either slow or fast, $P0$, $P0.01$ and hedging prior provide greater coverage all the time, where informative priors ($P1$, $P0.5$, AP) fail to cover T_{truth} .

In contrast, the weak priors perform poorly if there are short slow accrual periods, as in studies 4 and 5. The hedging prior has poor coverage probability early, but seems to recover with a larger amount of accrual data beyond the slow initial period. Study 6, with a longer period of slow accrual, appears to cause problems for all of the models. Study 7, with slow

accrual during the first quarter and last quarter of the study, had no models perform consistently. All of the methods have low coverage for study 8 and 9.

More important, perhaps, than the percentage of coverage is the ability of the models to make a correct decision on the continuation of the trial. Similar as application studies in the previous section, we defined a cut-off time δT that can be used for decision making. If $T_{0.025} > \delta T$, we should stop the trial and the decision is NOGO. If $T_{0.025} \leq \delta T$, the decision is GO. For one simulation iteration, the correct decision can be calculated as $CD_j = I(T_{0.025} > \delta T) I(T_{truth_j} > T) + I(T_{0.025} \leq \delta T) I(T_{truth_j} \leq T)$. The percentage of the correct decisions is

$$CD = \frac{1}{1000} \sum_{j=1}^{1000} CD_j \times 100\%. \text{ In this simulation study, } \delta \text{ is also set up as } 1.25.$$

For the unbiased trial, all models correctly recommend continuation of the study. For the slow accrual trial, all models also correctly recommend stopping the trial, but the recommendations to stop are more likely to come early for the weak priors and the hedging prior. For the fast trial, all models correctly recommend continuation.

The time varying models provide a much more difficult challenge. Study 4 has slow accrual during the first tenth of the trial, but the trial still finishes earlier than the decision point. All

of the models correctly recommend continuation of the trial when $m = \frac{1}{2}n$, but the weak priors and the hedging prior will too frequently recommend termination of the study when

$m = \frac{1}{8}n$ and $m = \frac{1}{4}n$. For study 5, 25% of the decisions are incorrect with every model, but

the two weakest priors ($P=0$ and $P=0.01$) perform even worse at $m = \frac{1}{8}n$. In study 6, the

weak priors perform slightly better at $m = \frac{1}{8}n$ and the strong priors perform slightly better at

$m = \frac{1}{4}n$ and $m = \frac{1}{2}n$, but the performance of all the models is mediocre. Performance is equally mediocre for study 7, with slow early accrual during the first quarter and last quarter of the trial. The strong priors perform especially poorly here. In contrast, the weak priors

perform especially poorly for Study 8 especially when $m < \frac{1}{2}n$. The probability of correction decision in study 9 is zero for all methods during the first half of the trial, slightly better

$$m = \frac{3}{4}n.$$

5. Discussion

Monitoring the accrual process in clinical trials is critical, as slow recruitment results in increasing costs, utilizing more resources, and wasting the goodwill contribution of patient volunteers.

From clinical studies, we find that that all of the models perform well when the prior is far off target. Even when the models do not predict the trial completion time accurately, the models recognize early that the trial is off schedule. The performance of the strong priors is a bit surprising, but perhaps some of this is an accidental result of the surge in accrual later

in the studies. The accelerated prior does not appear to behave much differently than a strong prior in any of the studies. In contrast, the hedging prior did seem to adapt its behavior somewhat, behaving more like a weak prior when the accrual was substantially off target, but like a strong prior when the accrual was only slightly off target. One important lesson, though, is that variations in accrual rates can complicate the evaluation of these models.

When there is variation in accrual rates, strong priors appear to perform better. This result is somewhat surprising. Placing a high weight on an off target informative prior would seem to be a bad idea. Perhaps, though, the weak priors are placing too much weight on the slow early accrual, which is not going to last throughout the trial. Overall, strong priors are likely to overreact to a bit of slow accrual data early in the study. Every prior, weak or strong, has difficulty with at least some of the time varying scenarios.

The simulation studies show that the informative prior, especially strong informative prior, works better when the accrual is on target, or slightly off from the target, producing smaller *MSE*, higher percentage of coverage, and more correct decisions. However, they grossly under perform when the accrual is entirely off from the target. Flat prior and weak informative prior are less efficient when the accrual is on target, but work well for very slow accrual.

Performance of the accelerated prior is typically similar to the strong priors in the early period of trial. However, it is superior to strong priors when more data are available for off target accruals. The accelerated prior was designed to transition rapidly from a strong to a weak prior when more accrual data are available. The accelerated prior is equivalent to $P=0.5$ when half the data are collected, and this is still a strong prior distribution. It might be worth examining an even stronger degree of acceleration, such as a cubed acceleration,

$P = \left(1 - \frac{m}{n}\right)^3$, which would be equivalent to $P=0.125$ when half of the data are collected.

Another alternate form of P would be set $P = 1 - \frac{2m}{n}$ for $m \leq n/2$, and $P=0$ for $m > n/2$. The degree of acceleration will be stronger than the accelerated prior we proposed. It has intuitive appeal, as in most trials, the halfway point may be considered a reasonable time to rely on the data that have been observed.

The performance of the hedging prior is difficult to characterize well: it appears to perform better than strong priors when the prior is extremely off target, but also superior to flat priors when the prior is on target or only slightly off target. We have shown that the hedging prior is equivalent to the modified power prior, but it is easier to fit. Instead of monitoring the accrual process and assessment of the prior P subjectively, the hedging prior evaluates the similarity of real accrual process and historical data simultaneously, and adjusts the weights of the prior thereafter. It could be a useful compromise between the completely data driven flat prior and the reliance on investigator's opinion that a strong prior offers. Hedging prior is a special case of modified power prior. However, it avoids an extra "missing integral step." More importantly, hedging prior preserves the prior interpretation found in original constant accrual model.

The non-constant accrual rate changes over time. If we know for sure that the accrual can be divided into a certain number of stages and an appropriate prior can be selected for each specific stage, then the strong prior will perform well in accrual prediction. However, there are many factors that affect the accrual process. The change time point of the accrual and its direction (slow or fast) is unpredictable, such as simulation studies 8 and 9. It is difficult to know what the accrual will be at a certain stage and it is impossible to choose the appropriate informative prior for each stage. There are examples of Bayesian regression models that could be adapted to this problem. We plan to consider some of these models in a future publication.

Overall, there is no obvious choice among the various models proposed here. There are trade-offs between the greater precision provided by the strong priors and the ability of the weak priors to recognize more rapidly problems with slow accrual.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix: Mathematical formulas for deriving closed form of constant exponential waiting time model

Assuming that the waiting time (w) for each successive patient follows an exponential distribution, $w_i \sim \exp(\theta)$, where θ represents the average accrual time for the i th subject. The

distribution of the waiting time (w) is $f(w|\theta) = \frac{1}{\theta} e^{-w/\theta}$. The prior distribution θ of is assumed to be inverse gamma, $\theta \sim IG(nP, TP)$, where P is the investigator's confidence on the original plan, measured on a 0–1 scale. Supposedly during a trial, m subjects have been collected in $T_m (T_m = \sum_{i=1}^m w_i)$ time period. Then the posterior distribution for θ is updated to $\theta|w \sim IG(nP + m, TP + T_m)$, which can also be written as:

$$f(\theta|m, T_m) = \frac{(TP+T_m)^{nP+m}}{\Gamma(nP+m)} \theta^{-(nP+m+1)} e^{-\frac{TP+T_m}{\theta}}. \quad (1)$$

For fixed n , the waiting time for the rest of the sample size is $\tau = \sum_{i=m+1}^n w_i$.

We present a new denotation in this paper for the predicted time to finish for fixed sample size, as the previous paper used simulation. The distribution of τ is $\tau \sim G(m-n, \theta)$, with

$f(\tau|\theta) = \frac{1}{\Gamma(n-m)\theta^{n-m}} \tau^{n-m-1} e^{-\tau/\theta}$. Then the predictive distribution of τ can be derived as following,

$$g(\tau) = \int_0^\infty \frac{(TP+T_m)^{nP+m}}{\Gamma(nP+m)} \theta^{-(nP+m+1)} e^{-(TP+T_m)/\theta} \frac{1}{\Gamma(n-m)\theta^{n-m}} \tau^{n-m-1} e^{-\tau/\theta} d\theta \quad (2)$$

$$= \frac{(TP+T_m)^{nP+m} \tau^{n-m-1}}{\Gamma(nP+m)\Gamma(n-m)} \frac{\Gamma(nP+n)}{(TP+T_m+\tau)^{nP+n}} = \frac{1}{(TP+T_m) \left(1 + \frac{\tau}{TP+T_m}\right)^{nP+n}} \left(\frac{\tau}{TP+T_m}\right)^{n-m-1} \frac{\Gamma(nP+n)}{\Gamma(nP+m)\Gamma(n-m)}. \quad (3)$$

Let $\phi = \frac{\tau}{TP+T_m}$, then $\tau = \phi(TP+T_m)$,

Therefore,

$$g(\phi) = \frac{1}{(TP+T_m) \left(1 + \frac{\tau}{TP+T_m}\right)^{nP+n}} \left(\frac{\tau}{TP+T_m}\right)^{n-m-1} \frac{\Gamma(nP+n)}{\Gamma(nP+m)\Gamma(n-m)} |TP+T_m|,$$

which can be simplified as $g(\phi) = \frac{1}{(1+\phi)^{nP+n}} \phi^{n-m-1} \frac{\Gamma(nP+n)}{\Gamma(nP+m)\Gamma(n-m)}. \quad (4)$

It is an inverted beta distribution, with $\alpha = n-m$, $\beta = nP+m$. When $\beta > 1$, the mean of ϕ is

$E(\phi) = \frac{\alpha}{\beta-1} = \frac{n-m}{nP+m-1}$. Then, the predictive mean of τ can also be calculated directly as

$$E(\tau) = E(\phi)(TP+T_m) = \frac{n-m}{nP+m-1} (TP+T_m). \quad (5)$$

Similarly, the variance of τ can also be calculated as

$$Var(\tau) = Var(\phi(TP+T_m)) = \frac{(n-m)(n+nP-1)}{(nP+m-2)(nP+m-1)^2} (TP+T_m)^2 \quad (6)$$

The percentile of τ can be obtained by

$$p(\tau) = (TP + T_m)p(\phi) = (TP + T_m) \frac{p(B)}{1 - p(B)}, \quad (7)$$

where $p(B)$ represents the percentile for the beta distribution $beta(n - m, nP + m)$.

To evaluate the sensitivity and stability of the model in accrual prediction, we can also calculate the mean square error. Suppose the true accrual time is T_{truth} , the predicted total recruiting time is $T_p = \tau + T_m$. Then,

$$\begin{aligned} MSE(T_p) &= Var(T_p) \\ &+ [E(T_p - T_{truth})]^2 \\ &= \frac{(n - m)(n + nP - 1)}{(nP + m - 2)(nP + m - 1)^2} (TP + T_m)^2 + \left[\frac{n - m}{nP + m - 1} (TP + T_m) + T_m - T_{truth} \right]^2. \end{aligned} \quad (8)$$

The probability that the total recruiting time is larger than critical cut-off can be calculated as the following:

$$P(T_p \leq \delta T) = P(\tau + T_m \leq \delta T) = P(\tau \leq \delta T - T_m) = P\left(\frac{\tau}{TP + T_m} \leq \frac{\delta T - T_m}{TP + T_m}\right) = P\left(\phi \leq \frac{\delta T - T_m}{TP + T_m}\right). \quad (9)$$

Figure 1.

The accumulated accrual for application studies, A (TSCCP), B (KanQuit2), C (KISIII). The solid line is the real accrual. The dotted line is proposed reference, and the vertical dash line shows the proposed T.

Figure 2.

The prediction of total accrual time for each of the studies A (cancer), B (KanQuit2), C (KISIII) using various methods assuming only 1/8, 1/4, and 1/2 of the subjects recruited. The solid line shows the true accrual time, and the dotted line shows the true decision line that should stop the trial.

Figure 3.

The mean squared error (left) and the probability that the predicted accrual time is less or equal to the cut-off time (right) for each of the application studies: A (TSCCP), B (KanQuit2), C (KISIII), study using various methods assuming only 1/8, 1/4, and 1/2 of subjects recruited. (The labels in the figure of Probability of Stop Trial for the KanQuit 2 and KIS III study are overlapped is because the results are exactly the same).

Figure 4.

The graphical display of the theoretical accrual process of the eight studies. The solid line is the designed simulation studies, dotted line is the reference if the trial is on target, and the vertical dash line shows the proposed T.

Figure 5.

The MSE on log scale of each simulation study using the various methods (P0, P0.1, P0.5, AP, HP) when recruited the first 1/8, 1/4, 1/2 or 3/4 of the subjects. As the results for study 9 *On time early 1/2 then slow* are too close, their labels are overlapped.

Table 1

Design of the eight simulation studies, including short description of the study, parameter setup, and 2.5%, 50, and 97.5% quantile of Ttruth with 1000 iterations.

Simulation Study	Parameter setup	Ttruth 2.5%	Ttruth 50%	Ttruth 97.5%
1 “Unbiased”	$\theta_i = \theta_0$ for $i=1$ to 300	973.2	1094.9	1213.2
2 “Slow”	$\theta_i = \theta_1$ for $i=1$ to 300	1946.5	2189.8	2426.5
3 “Fast”	$\theta_i = \theta_2$ for $i=1$ to 300	486.6	547.5	606.6
4 “Slow early 1/10”	$\theta_i = \theta_1$ for $i=1$ to 30 $\theta_i = \theta_0$ for $i=31$ to 300	1072.6	1202.6	1336.9
5 “Slow early and last 1/10”	$\theta_i = \theta_1$ for $i=1$ to 30 $\theta_i = \theta_0$ for $i=31$ to 270 $\theta_i = \theta_1$ for $i=271$ to 300	1171.3	1312.7	1469.9
6 “Slow early ¼”	$\theta_i = \theta_1$ for $i=1$ to 35 $\theta_i = \theta_0$ for $i=76$ to 300	1211.4	1367.8	1523.5
7 “Slow early and last ¼”	$\theta_i = \theta_1$ for $i=1$ to 75 $\theta_i = \theta_0$ for $i=76$ to 225 $\theta_i = \theta_1$ for $i=226$ to 300	1455.0	1642.0	1831.7
8 “Slow early ¼ and fast last ½”	$\theta_i = \theta_1$ for $i=1$ to 75 $\theta_i = \theta_0$ for $i=76$ to 150 $\theta_i = \theta_2$ for $i=151$ to 300	962.0	1091.3	1237.6
9 “On time first ½ and slow last ½”	$\theta_i = \theta_0$ for $i=1$ to 150 $\theta_i = \theta_1$ for $i=151$ to 300	1451.8	1641.3	1827.9

Table 2

Summary of the percentage of coverage of Ttruth using the various methods when recruited the first 1/8, 1/4, 1/2 and 3/4 of the subjects in the eight simulation studies for 1000 iterations.

Method	Unbiased	Slow	Fast	Slow early 1/10	Slow early and last 1/10	Slow early 1/4	Slow early and last 1/4	Slow early 1/2 and last 1/2	On time first 1/2 and last 1/2
	1	2	3	4	5	6	7	8	9
P0	96	95	95	8	18	10	50	0	31
P0.01	97	94	95	9	21	13	56	0	27
P0.1	99	60	12	19	48	40	92	1	6
1/8 P0.5	100	0	0	65	94	95	54	5	0
P1	99	0	0	85	97	97	10	12	0
AP	99	0	0	82	98	98	15	10	0
HP	100	85	78	35	59	45	74	3	1
P0	95	96	95	26	60	0	14	0	3
P0.01	95	95	95	27	63	0	16	0	2
P0.1	97	77	40	40	80	1	45	0	1
1/4 P0.5	98	1	0	75	97	13	96	0	0
P1	98	0	0	88	94	44	76	0	0
AP	98	0	0	83	96	30	90	0	0
HP	98	92	91	59	87	2	32	0	1
P0	95	95	95	61	95	6	95	0	0
P0.01	95	94	95	62	96	8	94	0	0
P0.1	96	88	74	70	96	12	91	0	0
1/2 P0.5	97	19	1	85	87	40	55	0	0
P1	97	1	0	90	78	65	22	0	0
AP	97	19	1	85	87	40	55	0	0
HP	96	94	94	81	91	18	89	0	0
P0	96	95	95	85	65	46	13	0	13
3/4 P0.01	96	95	95	85	64	47	12	0	12

Method	Unbiased	Slow	Fast	Slow early 1/10	Slow early and last 1/10	Slow early 1/4	Slow early and last 1/4	Slow early 1/4 and fast last 1/2	On time first 1/2 and last 1/2
	1	2	3	4	5	6	7	8	9
P0.1	96	93	89	87	59	55	8	0	8
P0.5	96	58	24	91	45	73	1	0	2
P1	96	20	4	92	36	84	1	0	0
AP	96	82	64	89	53	64	4	0	5
HP	96	95	95	91	50	62	7	0	8

Table 3

Summary of the percentage of correct decisions to either continue or stop the trial using the various methods when recruited the first 1/8, 1/4 or 1/2 of the subjects in the eight simulation studies for 1000 iterations.

Method	Unbiased	Slow	Fast	Slow early 1/10	Slow early and last 1/10	Slow early 1/4	Slow early and last 1/4	Slow early 1/2 and last 1/2	On time first 1/2 and last 1/2
	1	2	3	4	5	6	7	8	9
P0	100	88	100	31	50	58	85	15	0
P0.01	100	86	100	35	53	60	82	18	0
P0.1	100	61	100	61	69	67	58	40	0
1/8 P0.5	100	8	100	97	76	58	8	94	0
P1	100	1	100	99	75	54	2	100	0
AP	100	2	100	99	75	54	2	99	0
HP	100	57	100	67	70	67	55	44	0
P0	100	99	100	73	74	49	99	2	0
P0.01	100	99	100	76	75	49	98	2	0
P0.1	100	98	100	88	78	51	96	4	0
1/4 P0.5	100	79	100	98	76	67	78	24	0
P1	100	56	100	99	75	76	53	48	0
AP	100	65	100	99	75	73	64	38	0
HP	100	95	100	91	78	52	95	5	0
P0	100	100	100	97	78	67	80	20	0
P0.01	100	100	100	97	77	67	79	21	0
P0.1	100	100	100	98	76	72	74	27	0
1/2 P0.5	100	100	100	99	75	81	55	47	0
P1	100	100	100	99	75	82	41	61	0
AP	100	100	100	99	75	81	55	47	0
HP	100	100	100	98	76	76	69	33	0
P0	100	100	100	99	76	88	50	97	50
3/4 P0.01	100	100	100	99	76	88	50	97	49

Method	Unbiased	Slow	Fast	Slow early 1/10	Slow early and last 1/10	Slow early 1/4	Slow early and last 1/4	Slow early 1/4 and fast last 1/2	On time first 1/2 and last 1/2
	1	2	3	4	5	6	7	8	9
P0.1	100	100	100	99	76	88	47	98	47
P0.5	100	100	100	99	75	87	39	98	41
P1	100	100	100	99	75	85	34	99	37
AP	100	100	100	99	75	88	43	98	44
HP	100	100	100	99	75	88	44	98	45