Assessment of Bayesian expected power via Bayesian bootstrap

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The Bayesian expected power (BEP) has become increasingly popular in assessing the probability of success for a future trial. While the traditional power assumes a single value for the unknown effect size $\Delta$ and is thus highly dependent on the assumed value, the BEP embraces the uncertainty around $\Delta$ given the prior information and is therefore a less subjective measure for the probability of success than the traditional power especially when the prior information is not rich. Current methods for assessing BEP are often based in a parametric framework by imposing a model on the pilot data to derive and sample from the posterior distributions of $\Delta$. The model-based approach can be analytically challenging and computationally costly especially for multivariate data sets, and it also runs the risk of generating misleading BEP if the model is misspecified. We propose an approach based on the Bayesian bootstrap (BBS) technique to simulate future trials in the presence of individual-level pilot data, based on which the empirical BEP can be calculated. The BBS approach is model-free with no assumptions about the distribution of the prior data and also circumvents the analytical and computational complexity associated with obtaining the posterior distribution of the $\Delta$. Information from multiple pilot studies is also straightforward to combine. We also propose the double bootstrap technique, a frequentist counterpart to the BBS, that shares similar properties and achieves the same goal as the BBS for BEP assessment. Simulation and case studies are presented to demonstrate the implementation of the BBS technique and the double bootstrap technique and to compare the BEP results with model-based approach.

KEYWORDS
assurance, double bootstrap, future trial simulation (FTS), probability of success, weighted average power

1 INTRODUCTION

The probability of success (POS) of a future clinical trial is affected by many factors such as patient recruitment, ethical considerations, local regulations, resources, study designs, and execution, among others. The part where statisticians get involved the most during the trial planning stage is study design, including sample size determination and power calculation. Power is defined as the probability of rejecting the null hypothesis $H_0$ if the alternative hypothesis $H_1$ is true in a future trial. The probabilistic nature of power makes itself a natural choice for measuring how the statistical design
aspect of the future trial affects its POS. On the other hand, the classical power is a conditional probability given a specific effect size \( \Delta = \mu / \sigma \); the value of which is an unknown quantity and is often the parameter of primary inferential interest in the planned trial. As such, the power is sensitive to the assumed effect size and not a robust measurement of POS.

A less sensitive and more stable measurement for POS compared with the classical power is the Bayesian expected power (BEP) or the weighted average power (WAP). The BEP is defined as the expected power over the distribution of the effect size \( \Delta \) given existing data \( y \): \( \Pr(\text{reject } H_0 | y) \), which is in contrast to the classical power calculated at the estimated effect size \( \hat{\Delta}(y) \) given \( y \): \( \Pr(\text{reject } H_0 | \hat{\Delta}(y)) \). In other words, the BEP is a measure of the POS given what is known \( y \) by integrating out the unknown \( \Delta \) over its posterior distribution given the pilot data. Given the conceptual difference between the BEP and the power, it is expected the two values are often different numerically especially when \( y \) is small in size.

The BEP has been “reinvented” several times under different names in various contexts. Brown et al. suggest using Bayesian methods to obtain a posterior distribution representing the state of knowledge of the parameters of interest and to predict the outcome of a specified comparative trial. The approach is implemented and demonstrated in several examples in Spielgelhalter et al. O’Hagan and Stevens and O’Hagan et al. use “assurance,” and Chuang-Stein uses “average success probability” to describe the BEP. In all these cases, only the uncertainty around \( \mu \) concerned by the hypothesis in the future trial is considered. Liu extends the BEP by accounting for the uncertainty around both \( \mu \) and the variance \( \sigma^2 \), an equally important parameter in power calculation, and introduces two additional versions of the BEP by removing the “type I error” component from the regular BEP metric. Some recent reviews, discussion, and applications of the BEP in early and late phased clinical trials and meta-analysis are given in Kirby et al., Carroll, Ibrahim et al., Du and Peggy, and Zierhut et al. The BEP is now routinely calculated alongside the traditional power in some pharmaceutical companies to aid decision making, and it is also implemented in several sample size and power calculation software.

The current approaches to assessing the BEP often start with constructing the joint parametric posterior distributions of \( \mu \) and \( \sigma \) given the pilot/existing data (the pilot data are assumed to be representative of the population of interest in the future trial). In many cases, the posterior distributions of \( \mu \) and \( \sigma \) may not have closed-form expressions; even when they do, iterative approaches, such as the Markov chain Monte Carlo (MCMC) algorithms and other sampling techniques, might still be necessary to sample from the posterior distributions. In the case when there are coprimary hypotheses, \( \mu \) is multidimensional and the model-based approach becomes more challenging analytically and more costly computationally. In addition, there is always the risk of misspecifying the likelihood of the parameters with the pilot data, which would affect the formulation of the posterior distribution of the model parameters and could lead to a misleading BEP value subsequently.

We propose an approach based on the Bayesian bootstrap technique, referred to as the BBS approach, to assess the BEP when individual-level pilot data \( y \) are available. The Bayesian bootstrap is a Bayesian version of the bootstrap technique. Rubin proves that the Bayesian bootstrap is operationally and inferentially similar to the frequentist bootstrap. In the BBS approach, we repeatedly simulate the future trial data given \( y \) via the Bayesian bootstrap technique without imposing any distributional assumptions on \( y \) and test \( H_0 \) according to the planned analysis in each simulated future trial, and the overall rejection rate of \( H_0 \) over the repetitions is a Monte Carlo (MC) estimate of the BEP. The uncertainty around the underlying true distribution of the pilot data is accounted for by placing a Dirichlet prior on the probability of each individual. The BBS approach is straightforward to implement with minimal analytical work except for running the planned analysis on the simulated future data. Computationally, a few lines of codes will do to implement the sampling and trial simulation steps, and the whole BBS procedure can be easily parallelized for fast computation.

We also come up with the “double bootstrap” (BS2) technique, a frequentist counterpart to the BBS, that propagates the uncertainty around the distribution of the pilot data and achieves the same goal as the BBS for BEP assessment. Procedurally, the BS2 first bootstraps the pilot data and then samples the bootstrapped pilot data to generate repetitions for the future trials based on which a MC estimate of the BEP is obtained. Similar to the BBS, only a few lines of codes are needed to implement the BS2, and it is easy to parallelize computationally. Note that directly applying the regular bootstrap to the pilot data to simulate future data does not propagate the uncertainty around the distribution of the pilot data and will not lead to a BEP-type POS measurement. As a matter of fact, the overall rejection rate based on the future data simulated this way is a MC estimate of the classical power assuming that the estimated effect size from the pilot data is the true effect size.

The rest of the paper is organized as follows. Section 2 introduces the BBS and BS2 approaches for assessing the BEP. Section 3 compares the BBS and BS2 approaches with the parametric approaches in the BEP assessment in a simulation study. Section 4 implements the BBS and BS2 approaches to assess BEP for an equivalence study and for a HIV survival study. Section 5 concludes the paper with some final remarks. The key R codes for running the BBS and BS2 procedures are provided in the Appendix.
2 | METHODS

2.1 | Assessment of BEP

By definition, the BEP is the probability of rejecting $H_0$ in a future trial given existing data $y$. Denote the classical power by $\beta(\theta) = \Pr(\text{rejecting } H_0 | \theta, n)$, where $\theta$ refers to the parameters involved in the power calculation and $n$ is the sample size of the future trial, then

$$\text{BEP} = \mathbb{E}[\beta(\theta) | y] = \int \beta(\theta)p(\theta | y)d\theta. \quad (1)$$

To calculate the BEP, we may first draw $\theta$ from its posterior distribution $p(\theta | y)$ and then plug in the drawn $\theta$ in the power function $\beta(\theta)$ to obtain a classical power value. Repeating the 2 steps many times, say $m$, will lead to the posterior distribution of the power $\beta$ given $y$; the average $\sum_{j=1}^{m}\beta(\theta^{(j)})$ of the posterior samples is a MC estimate for BEP for the future trial for a given $n$. If interpreted from the perspective of WAP, the BEP is a weighted average of $\beta(\theta)$, where the weight associated with $\theta$ and $\beta(\theta)$ is proportional to $p(\theta | y)$. Besides the BEP, other statistics from the posterior distribution of the power can also be reported, such as mode, standard deviation, and quantiles (median, $10\%$, $25\%, 75\%$, $90\%$, etc).

If a closed-form function $\beta(\theta)$ is not available, the MC method can be applied to numerically approximate the power by simulating the future trial data $\tilde{y}$ on which $H_0$ will be tested. Denote the event of rejecting $H_0$ in the future trial by $I(R(\tilde{y}))$, where $R$ is the rejection rule and $I(R(\tilde{y})) = 1$ if $H_0$ is rejected in $\tilde{y}$ and 0 otherwise, then

$$\text{BEP} = \mathbb{E}[I(R(\tilde{y})) | y] = \mathbb{E}[\mathbb{E}[I(R(\tilde{y})) | \theta, y] | y]$$

$$= \int \int I(R(\tilde{y}))p(\tilde{y} | \theta, y)p(\theta | y)d\tilde{y}d\theta$$

$$= \int \left( \int I(R(\tilde{y}))p(\tilde{y} | \theta)d\tilde{y} \right)p(\theta | y)d\theta. \quad (2)$$

Equation 2 suggests that we can first draw $\theta$ from the posterior distribution $p(\theta | y)$ given pilot data $y$ and simulate the future data $\tilde{y}$ of size $\pi$ given the drawn $\theta$, then perform the planned statistical analysis and hypothesis testing on the simulated data $\tilde{y}$, and record 1 if rejected and 0 if not. Repeating the process many times, say $m$, and the rejection rate over the $m$ repetitions is an MC estimate of the BEP. We refer to this MC approach for assessing the BEP as the future trial simulation (FTS) approach.

Regardless of whether Equation 1 is used when closed-form $\beta(\theta)$ is available or Equation 2 is applied when it is not, the current approaches for the BEP assessment are mainly model-based by imposing distributional or model assumptions on the pilot data $y$ to obtain the posterior distribution $p(\theta | y)$ with a posterior sampling step. If $\tilde{y}$ and $\theta$ are multidimensional, the sampling of $\theta$ and simulation of $\tilde{y}$ can be computationally costly, not to mention the risk of misspecification of the parametric model that could lead to misleading BEP subsequently. Alternative techniques that avoid making strong parametric assumptions about $y$ and at the same time are computationally less complicated are desired.

We propose a FTS technique, referred to as the BBS approach, motivated by the Bayesian bootstrap to evaluate the BEP numerically. The BBS assesses the BEP without imposing a model on the pilot data or sampling from complicated posterior distributions via MCMC approaches. Instead, the BBS approach obtains the posterior distributions of the underlying population distribution given $y$, from which the future data will be simulated. We will also present a frequentist version of the BBS approach—the “double bootstrap” (BS2) technique that achieves the same goal as the BBS and yields a BEP-type POS measure.

2.2 | Construction of posterior distribution of the population distribution via Bayesian bootstrap

Define a finite population of size $N$ with $K (K < \infty)$ distinct values over $p$ attributes. Let $\pi_k$ denote the probability that value $d_k$ occurs for $k = 1, \ldots, K$. Denote by $\pi_k = (\pi_1, \ldots, \pi_K)$ the probabilities associated with the $K$ distinct values ($\sum_k \pi_k = 1$). The Bayesian bootstrap can be used to obtain a posterior distribution of the population distribution $f$ for a given data set $y$. As $\pi$ fully characterizes $f$, obtaining the posterior distribution on $f$ is equivalent to obtaining the posterior distribution of $\pi$. A convenient choice on the prior of $\pi$ is the Dirichlet distribution $D(\pi | \alpha_1, \ldots, \alpha_K) \propto \prod_{k=1}^{K} \pi_k^{\alpha_k-1}$, with hyperparameters $\alpha = (\alpha_1, \ldots, \alpha_K) \geq 0$ ($\alpha = 0$ would lead to an improper prior). Since Dirichlet priors are conjugate priors...
for the multinomial likelihood, the posterior distribution of \( \pi \) given \( y \) (of size \( n \)) also follows a Dirichlet distribution
\[
D(\pi_1, \ldots, \pi_K|n) \propto \prod_{k=1}^{K} \pi_k^{n_k + \alpha_k - 1},
\]
where \( n = (n_1, \ldots, n_k) \), \( \sum_k n_k = n \), and \( n_k \) is the number of observations in the sample that take the value \( d_k \).

It is possible that not every distinct \( d_k \) from the population will occur in the sample data \( y \), that is, \( n_k \)’s associated with these “nonappearing” values are 0. Denote by \( L \) the number of distinct values in the sample \((L \leq K)\), the posterior distribution of the subset of \( \pi \) that is associated with the sample is \( D(\pi_1, \ldots, \pi_L|n) \propto \prod_{k=1}^{L} \pi_k^{n_k + \alpha_k - 1} \). In practical applications, we can always set \( L = n \) because of 2 reasons: It does not affect the posterior distribution of \( \pi \) associated with the distinct values given the aggregation property of the Dirichlet distribution, and every individual in the sample can be distinct from each other when there are continuous variables among the \( p \) attributes or \( p \) is large. With \( L = n \), \( n_k = 1 \) for \( k = 1, \ldots, n \), and the posterior distribution of \( \pi \) can be simplified to
\[
p(\pi_1, \ldots, \pi_n|y) = \frac{\prod_{k=1}^{n} \pi_k^{(\alpha_k + 1) - 1}}{B(\alpha_1 + 1, \ldots, \alpha_n + 1)} = D(\alpha_1 + 1, \ldots, \alpha_n + 1).
\]

Note that the individuals mentioned above in the sample data \( y \) are the smallest experimental units that are independent from each other. If several observations belong to the same “cluster” that are correlated, say either genetically or environmentally, then “individual” in this context would be the “cluster” instead of a single observation.

In terms of the choice for the hyperparameters \( \alpha_k \), proper priors should have \( \alpha_k > 0 \forall k = 1, \ldots, n \). If there is minimal prior information about \( \pi \), setting \( \alpha_k \) at small positive values between \((0, 1) \) (e.g., \( 0.1 \), \( 0.5 \), and \( 1 \)) would lead to noninformative to weakly informative priors for \( \pi \). While it is not necessary that all \( \alpha_k \)’s are set at the same value, there is no reason not to especially if it is decided that all \( \alpha_k \)’s should be small, unless there is prior belief on which distinct value will occur more frequently in the population to be studied. An improper noninformative but convenient choice is \( \alpha_k = 0 \forall k = 1, \ldots, n \), which, combined with the multinomial likelihood, still leads to a proper posterior distribution for \( \pi \),
\[
p(\pi_1, \ldots, \pi_n|y) = (\Gamma(n))^{-1} = D(1, \ldots, 1).
\]

We expect that the BEP is relatively insensitive to the choice of \( \alpha_k \) in general especially when \( \alpha_k \)’s are small. We run some sensitivity analysis in Section 3; the results of which were consistent with our expectation.

### 2.3 BEP assessment with Bayesian bootstrap

The Bayesian bootstrap is used to simulate data \( \tilde{y} \) for the future trial, the posterior predictive distribution of which, given pilot data \( y \), is
\[
p(\tilde{y}|y) = \int p(\tilde{y}|y, \pi)p(\pi|y)d\pi = \int p(\tilde{y}|\pi)p(\pi|y)d\pi = \int M(\tilde{\pi}, \pi)p(\pi|y)d\pi,
\]
where \( p(\pi|y) \) is given in Equation 3 (Equation 4 if \( \pi = 0 \)). Plugging Equation 5 in Equation 2, we have
\[
\text{BEP} = \int \int I(R(\tilde{y}))M(\tilde{\pi}, \pi)p(\pi|y)d\pi d\tilde{y}.
\]

Equation 6 suggests that BEP can be calculated via the steps given in Table 1, which produces the BEP directly and does not yield the posterior distribution of power. If the posterior distribution of power is desired, an inner loop will be needed, as given in Table 2. When the number of iterations of the inner loop \( t \) is 1, Table 2 reduces to Table 1.

**Table 1** BEP assessment via the BBS

| DO \( j = 1, \ldots, m \) |
|--------------------------|
| (1) draw \( \pi^{(j)} \) from the Dirichlet distribution in Equation 3; |
| (2) draw \( \tilde{y}^{(j)} \) from \( M(\tilde{\pi}, \pi^{(j)}) \); |
| (3) test \( H_0 \) in simulated trial \( \tilde{y}^{(j)} \) and record \( I(R(\tilde{y}^{(j)})) \) (1 if \( H_0 \) is rejected; 0 otherwise); |

**END**

**OUTPUT**: calculate \( \text{BEP} = \frac{1}{m} \sum_{j=1}^{m} I(R(\tilde{y}^{(j)})) \).
2.4 | Double bootstrap

The BBS procedures in Tables 1 and 2 for assessing the BEP are based in the framework of the Bayesian bootstrap. The frequentist counterpart to the BBS approach is the BS2 given in Table 3. The outer-loop bootstrap corresponds to the sampling of \( \pi \) from its posterior distribution in the BBS procedure and captures the uncertainty around the population distribution. The inner-loop bootstrap propagates the sampling variability and error for the future trial, serving the same purposes of drawing a sample data set given \( \pi \) in the BBS procedure. Since the BS2 is not a Bayesian concept, the distribution of the power generated from the procedure is not a posterior distribution. On the other hand, the BS2 technique is a proper procedure and is asymptotically equivalent to the BBS approach as \( m \to \infty \) when the hyperparameters \( \alpha = 0 \), and outputs a distribution of power given pilot data \( y \), the average of which gives the WAP (equivalent to the BEP). Setting \( t = 1 \) in the inner loop in Table 3 yields a single WAP estimate (similar to Table 2 being reduced to Table 1 in the BBS procedure).

If we directly simulate the future data \( \tilde{y} \) via the regular bootstrap, we end up having a procedure (Table 4) that leads to a MC estimate of the classical power assuming what’s observed in the pilot data is the truth. This is because this procedure does not take into account the uncertainty around the unknown population distribution underlying \( y \) and implicitly assumes that the observed pilot data are the population and the estimated effect size from \( y \) is the true effect size.

3 | SIMULATION STUDY

We run a simulation study to implement the bootstrap-based BBS and BS2 procedures and compare the results with the model-based BEP. Since the true distribution of data was known in the simulation study, we could correctly specify the

**TABLE 2** Generation of posterior distribution of power via the BBS

| DO \( j = 1, \ldots, m \) |
|--------------------------|
| 1) draw \( \pi^{(j)} \) from the Dirichlet distribution in Equation (3); |
| 2) given the drawn \( \pi^{(j)} \) |
| \( \text{DO } l = 1, \ldots, t \) |
| 2.1) draw \( \tilde{y}^{(l, j)} \) from \( M(\bar{n}, \pi^{(j)}) \); |
| 2.2) test \( H_0 \) in simulated trial \( \tilde{y}^{(l, j)} \) and record \( I(R(\tilde{y}^{(l, j)})) \) (1 if \( H_0 \) is rejected; 0 o.w.); |
| END DO |
| 3) calculate power \( \beta(\pi^{(j)}) = t^{-1} \sum_{l=1}^{t} I(R(\tilde{y}^{(l, j)})) \). |

**OUTPUT:** \( m \) samples from the posterior distribution of power: \((\beta(\pi^{(1)}), \ldots, \beta(\pi^{(m)}))\) and BEP \( = m^{-1} \sum_{j=1}^{m} \beta(\pi^{(j)}) \).

**TABLE 3** Generation of conditional distribution of power given pilot data via the BS2

| DO \( j = 1, \ldots, m \) |
|--------------------------|
| 1) bootstrap a sample \( S^{(j)} \) of size \( n \) from \( y \) with replacement; |
| \( \text{DO } l = 1, \ldots, t \) |
| 2.1) bootstrap \( \tilde{y}^{(l, j)} \) of size \( \bar{n} \) from \( S^{(j)} \) with replacement; |
| 2.2) test \( H_0 \) in simulated trial \( \tilde{y}^{(l, j)} \) and record \( I(R(\tilde{y}^{(l, j)})) \) (1 if \( H_0 \) is rejected; 0 o.w.); |
| END DO |
| 3) calculate power \( \beta^{(j)} = t^{-1} \sum_{l=1}^{t} I(R(\tilde{y}^{(l, j)})) \). |

**OUTPUT:** \( m \) samples from the conditional distribution of power given \( y \): \((\beta^{(1)}, \ldots, \beta^{(m)})\), and EP \( = m^{-1} \sum_{j=1}^{m} \beta(\pi^{(j)}) \).
was randomly set at a value between 0 and 1. \( \sigma \) was the sample standard deviation for \( y_j \). In the sensitivity analysis in Figure 1, the true power \( \Pr(\text{reject } H_0| \Delta(y)) \) was known in the simulation study, we could obtain the estimated power \( \Pr(\text{reject } H_0| \Delta(y)) \). Since the true effect size \( \Delta \) was known in the simulation study, we could obtain the estimated power \( \Pr(\text{reject } H_0| \Delta(y)) \). If \( \Delta(y) \) was not close to \( \Delta \) even with the correct model specification (eg, due to sampling variability especially when \( n \) is small), then a big difference between the estimated power and the true power would be expected. The true power can be regarded as the asymptote of the BEP when \( p(\Delta|y) \), the posterior distribution of \( \Delta \) given plot data \( y \), degenerates into the true value \( \Delta \) when the sample size of \( y \) goes to \( \infty \).

We run 1000 repetitions in the simulation study. In each repetition, a pilot study was simulated from a tri-variate normal distribution \( y = (y_1, y_2, y_3)^T \sim N(\mu = (0.2, 0.2, -0.15)^T, \Sigma) \) where \( \sigma_j^2 = 1 \) for \( j = 1, 2, 3 \), \( \sigma_{12} = 0.5 \), \( \sigma_{13} = -0.6 \), and \( \sigma_{23} = -0.8 \) in \( \Sigma \). We examined 3 pilot study size cases: \( n = 25, 50 \), and 75. The future study had \( \bar{n} = 250 \), and the hypotheses were \( H_0: (\mu_1 \leq 0) \cup (\mu_2 \leq 0) \cup (\mu_3 \geq 0) \) vs. \( H_1: (\mu_1 > 0) \cap (\mu_2 > 0) \cap (\mu_3 < 0) \). The true power was 74% at a type I error rate of 5%. The model-based estimated power was based on the multivariate noncentral \( t \) distribution with degrees of freedom of \( n-1 \), the sample mean and \( \sigma_j \) was the sample standard deviation for \( y_j \) for \( j = 1, 2, 3 \). The bootstrap estimated power was based on the procedure in Table 4. The BBS and BS2 BEP values were calculated via the procedures in Tables 1 and 3 \( (t = 1) \). The model-based BEP was calculated by first deriving the joint posterior distribution of \( (\mu, \Sigma) \), which was \( f(\Sigma|y) f(\mu|\sigma^2, y) = \text{Inv} -W_{n-1}(S^{-1}) \times N(y, \Sigma/n) \), given prior \( f(\mu, \sigma^2) \propto \Sigma^{-2} \) and the Gaussian likelihood. We then drew \( (\mu, \Sigma) \) from the posterior distribution, at which the classical power was calculated. The process was repeated for 2500 times to obtain 2500 posterior power values, the average of which gave the model-based BEP. In addition, we examined the sensitivity of the BBS procedure to the hyperparameter \( \alpha \) in Equation 3 by comparing the BEP results for 4 \( \alpha \) specifications: All entries in \( \alpha \) were 0, all entries in \( \alpha \) were 0.1, all entries in \( \alpha \) were 0.5, and each component in \( \alpha \) was randomly set at a value between 0 and 1.

First, the sensitivity analysis in Figure 1 suggests that the BEP values were similar regardless of the specification of \( \alpha \), which was expected for small-valued \( \alpha \) and noninformative or weakly informative priors for \( \pi \). Given this, only the results from \( \alpha = 0 \) were plotted in Figures 2 and 3. Figure 2 presents the comparison between the bootstrap and the
model-based procedures for computing BEP and power. The BEP calculated via the model-based, BBS, and BS2 techniques were similar and so were the estimated power between the model-based and the bootstrap procedures, providing empirical evidence for the validity of the bootstrap procedures (since the model-based BEP and power were based on the model used to simulate the data and were correct). There were slight differences in BEP between the model-based and the bootstrap procedures when \( n \) was small (25 and 50) due to the small size of pilot study (we also examined \( n = 200 \) in which case the differences disappeared; since \( n = 200 \) was an unlikely large pilot study size given that the future trial was planned for \( n = 250 \), the results are not presented). Figure 3 depicts the distributions of the BEP and the estimated power over the 1000 repetitions. There are several interesting observations and take-home messages. First, the estimated power had wide dispersion and bimodality (with the 2 modes located around 0% and 99%) in its distribution across the 1000 repetitions regardless of \( n \), suggesting the estimated power highly depends on the pilot data, and can be a poor estimation for the true power (74%) especially when \( n \) was small. Second, the distributions of the BEP across the 1000 repetitions were less disperse and more stable, had much narrower interquartile ranges, and were less likely to take extreme values (eg, \( \sim 0 \% \) and \( \sim 100 \% \)) compared with the estimated power, which is not unexpected as the BEP embraces the sampling variability of the pilot data and is more stable as a weighted average across all possible effect sizes. As the information in the pilot study became richer as \( n \) increased, effect sizes around the true values would take on more weight and the BEP would get close to the true power (74%). In summary, this simulation study suggests that the BEP is a less sensitive and a more stable estimate for the POS of the future study than the estimated power.
We implemented the BBS and the BS2 procedures in 2 examples, where the pilot data were obtained from real-life studies. In the first example, the pilot study is a 3-period crossover study and the future trial is a 2-period crossover study with an equivalence hypothesis. In the second example, the future trial is a study comparing the survival time of AIDS patients on 2 different treatments via the joint modeling of survival data and longitudinal CD4 count data while the pilot study is of the same design but is smaller in size. The type I error rates in the future trials in both examples are 5%, and the hyperparameter $\alpha$ was set at 0 in the BBS procedure.

**FIGURE 3** Distributions of model-based BEP, BBS BEP, BS2 BEP, model-based estimated power, bootstrap estimated power (upper and lower whiskers represent the max and min)

4 | **CASE STUDIES**

We implemented the BBS and the BS2 procedures in 2 examples, where the pilot data were obtained from real-life studies. In the first example, the pilot study is a 3-period crossover study and the future trial is a 2-period crossover study with an equivalence hypothesis. In the second example, the future trial is a study comparing the survival time of AIDS patients on 2 different treatments via the joint modeling of survival data and longitudinal CD4 count data while the pilot study is of the same design but is smaller in size. The type I error rates in the future trials in both examples are 5%, and the hyperparameter $\alpha$ was set at 0 in the BBS procedure.
4.1 | A crossover study with equivalence hypotheses

Suppose that a 2-period crossover study of size $n = 200$ is under planning with the goal of developing a new formulation for a drug for dyslipidemia with similar pharmacokinetic (PK) profile as a reference formulation $R$. $H_1$ states that the geometric mean ratios (GMRs) between the new formulation and $R$ are within the interval of $(0.80, 1.25)$ on 4 PK endpoints: the area under the PK curve (AUC) and the maximum concentration (Cmax) on 2 chemical entities. There are 2 candidates for the new formulation, $T_1$ and $T_2$, and the objective is to identify the candidate formulation with the lower GMRs of the endpoints: the area under the PK curve (AUC) and the maximum concentration (Cmax) on 2 chemical entities. There are 2 candidates for the new formulation, $T_1$ and $T_2$, and the reference $R$.

When modeling a single normally distributed endpoint $y_i = (y_{i1}, ..., y_{ip})^T$ from a crossover study with $p$ repeated measures, the linear mixed-effects (lme) model

$$y_i = x_i \beta + z_i \gamma_i + \varepsilon_i$$

(7)

is often used, where the fixed-effects term $\beta$ often includes an intercept, the treatment effects, and the period effects, and the random effects term $\gamma_i \sim N(0, \Sigma)$ and the error term $\varepsilon_i \sim N(0, R)$ together define the variance/covariance $V(y_i) = \Sigma = z_i G z_i' + R$, where $\Sigma$ can be as simple as taking the “compound symmetry” (CS) structure (constant marginal variance on the diagonal and constant covariance on all the off-diagonals) or as complex as “unstructured” (UN) (fully parameterized with $p(p + 1)/2$ parameters). For the pilot study, $y_i$ would refer to the log-transformed the four AUC and Cmax endpoints collected from the 3-period crossover study and $p = 12$.

In the model-based assessment of BEP, we first obtained the posterior distribution of the treatment differences (on the log scale) between $T_1$ and $R$, and between $T_2$ and $R$ given the pilot data. The hypothesis to be established in the future trial is a union of 4 equivalence hypotheses, one per primary endpoint. To model the dependency structure among the 4 endpoints, we analyzed all 4 endpoints in one lme model with a fully parameterized (UN) covariance matrix $\Sigma_{p \times p}$. The likelihood function of $(\beta, \Sigma)$ was

$$L(\beta, \Sigma; y, x) = \prod_{i=1}^{n} (2\pi)^{-p/2} \exp\{ -\frac{1}{2} (y_i - x_i \beta)' \Sigma^{-1} (y_i - x_i \beta) \}.$$  

(8)

We imposed the prior $p(\beta, \Sigma) \propto |\Sigma|^{-(\nu_0+p+1)/2}$ on $\Sigma$, which is an inverse Wishart distribution with the a priori degrees of freedom $\nu_0$, scale matrix $|\Sigma_0|^{-1} - 0$, and $p = 12$. We tried 2 different $\nu_0$ at 0 and $p + 1$, respectively, to examine the impact of different parametric assumptions on the model-based BEP: $\nu_0 = 0$ corresponds to the (improper) Jeffreys prior; when $\nu_0 = p + 1$, the conditional posterior mean $E(\Sigma | \beta, y)$ is the same as the MLE for $\Sigma$ if $\beta$ is known. The joint posterior distribution of $(\beta, \Sigma)$ was

$$p(\beta, \Sigma | y, x) \propto |\Sigma|^{-(\nu_0+p+1+n)/2} \exp\{ -\frac{1}{2} (y_i - x_i \beta)' \Sigma^{-1} (y_i - x_i \beta) \}.$$  

(9)

In the pilot study, 5 individuals out of 36 had missing values (missing at random) from at least one period. To draw $(\beta, \Sigma)$ from the posterior distribution, we used the imputation-posterior (IP) algorithm and the Gibbs sampler, listed in Equations 10 to 12 below, by imputing $y_{mis}$ given $\Sigma$ and $\beta$ (Equation (10)) and drawing $\Sigma$ and $\beta$ respectively from their full conditional posterior distributions given $y_{obs}$ and the imputed $y_{mis}$ (Equations (11) and (12)). The technical details on the derivation of the equations are provided in Appendix A.

$$p(y_{mis} | \beta, \Sigma, y_{obs}) = N(x_{mis} \beta, M \Omega M^T)$$

(10)

$$p(\Sigma | y_{mis}, y_{obs}) = \text{Inv} \cdot \text{Wishart}(\Sigma_{obs}, \nu_0 + n)$$

$$= |\Sigma|^{-(\nu_0+n+p+1)/2} |\sum_{i=1}^{n} e_i e_i'|^{-n/2} \exp\{-\text{tr}(\sum_{i=1}^{n} e_i e_i' \Sigma^{-1}) / 2\}$$

(11)

$$p(\beta | \Sigma, y_{mis}, y_{obs}) = N((x \Omega^{-1} x')^{-1} x' \Omega^{-1} y_{mis} (x' \Omega^{-1} x')^{-1}).$$

(12)

$M_{np \times np}$ in Equation 10 was a diagonal indicator matrix of missingness on each observation with $m_{ij} = 1$ if the $j$th response was missing and 0 otherwise for $j = 1, ..., np$; $\sum_{i=1}^{n} e_i e_i' = \sum_{i=1}^{n} (y_i - x_i \beta)' (y_i - x_i \beta)$ in Equation (11) was the scale matrix and $2\nu_0 + n - p - 1$ was the degrees of freedom in the inverse Wishart distribution; $y = (y_{obs}, y_{mis})$ and $\Omega$ was the...
block diagonal matrix with \( n \) blocks of \( \Sigma \) in Equation 12. Upon the convergence of the IP algorithm, after the burn-in and thinning periods, 1000 sets of posterior samples of \((\Sigma, \beta)\) were kept, based on which, 1000 power values were calculated analytically for the future trial via a multivariate \( t \) distribution that incorporated the dependency structure among the 4 endpoints. The average of the 1000 power values yielded the model-based BEP.

The BEP assessment via the BBS and BS2 techniques was much more straightforward than the model-based approach. Not only they involved minimal analytical work, coding of the procedures was also easy. After the steps in Tables 1 and 3 \((m = 1000 \text{ and } t = 1)\), we tested the 4 equivalence hypotheses via the lme model in Equation 7 by endpoint in each of the simulated trials via the BBS and BS2 procedures. If the 90% CIs of the log treatment differences for all 4 endpoints fell within \((\log(0.8), \log(1.25))\), the future trial was claimed a success. The success rate out of the 1000 simulated trials was the BEP.

We also computed the classical power analytically and via the bootstrap approach (Table 4). In the model-based approach, the treatment differences on the log scale in the 4 endpoints and the variance/covariance structure \( \Sigma_{12 \times 12} \) were estimated from the pilot study by fitting the lme model in Equation 7. We modelled \( \Sigma \) with 2 different structures to examine the sensitivity of the model-based power to the assumed model: a UN \( \Sigma \) and a Kronecker product \( \Sigma = \Sigma_1 \otimes \Sigma_2 \) between a UN \( \Sigma_1 \) across the 4 endpoints and a CS \( \Sigma_2 \) across the 3 periods on the same endpoint. The estimated treatment differences and \( \Sigma \) were then plugged in the multivariate \( t \) distribution to obtain the power. In the bootstrap approach, 1000 future trials were generated and the hypothesis testing in each simulated trial was the bootstrapped power.

Although the pilot study was a 3-period crossover study while the future study is 2-period, the model-based power and BEP values calculated above were legitimate since the treatment differences were adjusted for the period effects through the lme models fitted to the pilot data (model-based) or to the future data (bootstrap-based), and it was not necessary to produce the “exact” 2-period crossover data in the FTS approach. In other words, the design inconsistency between the pilot and future trials was not a concern from the perspective of the treatment comparison as long as the period effects were properly taken care of.

The results are presented in Table 5. The BEP values via the BBS and BS2 procedures were similar (except for some MC errors), as expected. The model-based BEP values were notably sensitive to the underlying parametric assumptions, reflected by the large differences \((\sim 25\%)\) in the BEP values, depending on which prior on \( \Sigma \) was applied in analyzing the pilot data (although both were considered as “weakly informative”). Similar observation occurred with the model-based estimated power, where different assumptions on the \( \Sigma \) structure led to 25\%–35\% differences. Given the high sensitivity to the model-assumption in the model-based POS assessment, we relied on the bootstrap-based procedures. The bootstrap-based estimated power reached \( \sim 100\% \) for both T1 and T2, which seemed overconfident and was also potentially dangerous as it did not consider the sampling variability of the pilot data. With the integration of the uncertainty around the unknown parameters, the bootstrap-based BEP was \( \sim 13\% \) lower in estimating the POS for T1 in contrast to the estimated power and \( \sim 20\% \) lower for T2; in addition, the BEP-based POS assessment also helped to better differentiate between T1 and T2 (the POS of T1 was 6% higher). All taken together, we would recommend T1 with a POS of \( \sim 87\% \) for the future trial.

4.2 | Joint modeling of survival time and longitudinal data

Suppose the pilot study is a randomized trial in 40 AIDS patients who had failed or were intolerant of zidovudine (AZT) therapy (randomly sampled from a published data set in Goldman et al\textsuperscript{15} to mimic real-life data). The patients were

| TABLE 5 | POS assessment of each test formulation in the future BE study |
| --- | --- | --- | --- | --- |
| Treatment | BEP (%) | Power (%) |
| | Model-based\textsuperscript{1a} | Model-based\textsuperscript{2a} | BBS | BS2 | Model-based\textsuperscript{1b} | Model-based\textsuperscript{2b} | BS |
| T1 | 51.0 | 74.3 | 86.3 | 87.6 | 99.98 | 65.8 | 100.0 |
| T2 | 42.6 | 68.0 | 79.4 | 81.6 | 99.39 | 78.6 | 99.3 |

\textsuperscript{a}Prior \( f(\Sigma | \alpha, \Sigma^2) \sim \chi^2 \) in parametric\textsubscript{1}; \( \alpha | \Sigma^2 \sim \gamma^2 \) in parametric\textsubscript{2} \((p = 12)\)

\textsuperscript{b}A fully parameterized \( \Sigma_{p \times p} \) \((p = 12)\) was assumed on the pilot data in parametric\textsubscript{1}, and \( \Sigma = \Sigma_{\text{UN}} \otimes \Sigma_{\text{CS}} \) was assumed in parametric\textsubscript{2} \((\Sigma_{\text{UN}} \text{ was fully parameterized across 4 endpoints, and } \Sigma_{\text{CS}} \text{ followed a CS structure across the 3 repeated measures per endpoint).}
allocated to 2 antiretroviral drug treatment groups (A and B) in a 1:1 ratio. The time to death due to AIDS and the CD4 count at 4 times points (0, 2, 6, and 12 months) were collected in the pilot study. Each patient was followed up for a minimum of 12 months and with an average of 15.6 months. Suppose that a larger study of size \( \hat{n} \) is under planning to compare the 2 treatments in a more confirmatory manner and to test the hazard ratio of death between the 2 against 1. The objective is to find \( \hat{n} \) that leads to an acceptable level of POS (\( \geq 80\% \)). Note that the future trial is hypothetical, and the example is mainly used to demonstrate the application of the BBS and BS2 techniques when the planned statistical analysis is somewhat complicated and power analysis is not straightforward (in real life, a replication of the HIV pilot study would be unethical, as pointed out by one reviewer, and the science and clinical practice of HIV treatment has advanced very far in the last 2 decades).

In the model-based assessment of the BEP, the Bayesian joint modeling of the survival time (with right censoring) and the CD4 counts was applied (Equation 13). Specifically, the square root of the CD4 count \( y_{ij} \), \( i = 1, \ldots, m \), \( j = 1, \ldots, n_i \), \( x_{ij} \), \( i = 1, \ldots, m \), \( j = 1, \ldots, n_i \), and the hazard for death at \( t \) and the CD4 count up to time \( t \) quantifies the association between the CD4 count up to time \( t \) and the hazard for death at \( t \), and \( \gamma \) is the log hazard ratio for death between the 2 treatments. The baseline hazard \( h_0(t) \) was modeled with the penalized-splines approach, where \( B(t, k) \) is the \( i \)-th basis function of the splines at knots \( k = (k_1, \ldots, k_L) \) (we set \( L = 8 \)) and \( \gamma \)'s are the spline coefficients. The R package \texttt{JMbayes} was used to fit the joint model in Equation 13. After the convergence of the MCMC algorithm, 2000 posterior samples of the model parameters, including \( b_i \), were obtained (after 1000 burn-in and 40 thinning), from which the posterior probability of survival \( p_i = \Pr(t_i \leq T) \) by some time \( T \) in subject \( i \) was obtained for \( i = 1, \ldots, 40 \). We examined 2 types of \( T \): the last recorded time in the pilot study, which was 20.87 and 20.27 months in Treatments A and B, respectively, and 24 months, which was an extrapolation of the pilot data in study duration. The model-based power for testing \( H_0^* \): HR \( = 1 \) is \( \Phi(\sqrt{\hat{n}(1-p)\gamma^2/2-\Phi^{-1}(1-\alpha/2)}) \), where \( \hat{n}(1-p) \) is the expected number of events in the future trial, where \( p = n^{-1}\sum_{i=1}^{n}p_i \) and \( \alpha \) is the type I error rate. Power was calculated at each of the 2000 posterior samples of \((p, \gamma)\), the average of which gave the model-based BEP. The model-based power given the posterior means of \( \gamma \) and \( p \) at the 2 types of \( T \) was also calculated.

In the bootstrap-based approaches, \( m = 500 \) sets of future data were generated according to the steps in Table 1 and Table 3 \((t = 1)\). In each simulated trial, the joint model in Equation 13 was applied, and the 95% posterior interval on the HR was obtained. If the lower bound of the interval was >1 or the upper bound was <1, then the future trial was claimed a success; the success rate out of 500 was the BEP. The bootstrap-based power via the steps in Table 4 was also calculated. Different from the model-based approach, extrapolation to a longer study duration \((T = 24)\) was not possible for either the BEP or power without further parametric assumptions. In other words, the BEP and power evaluated via the bootstrap-based approaches implicitly assumed the study duration in the future trial was the same as that in the pilot study.

The results of POS at different \( \hat{n} \) are provided in Table 6. Similar to the observations in Table 5, almost all the estimated power values were close to 100% for both study duration scenarios, which might be too optimistic and overconfident a measure for the POS without considering the uncertainty around the pilot data. In contrast, the BEP was a more stable and less sensitive POS assessment and showed nicely how the POS changed with increased \( \hat{n} \). When the future trial duration was set to the same as the pilot study, the model-based and bootstrap-based BEP values were similar. The BEP for the future trial reached 80~85% at \( \hat{n} = 400 \), which is an acceptable level for POS; \( \hat{n} \) increased to 600 only helps to increase the BEP by \( \sim 3\% \), probably not worth it. As expected, a longer study duration (24 months) than the pilot study led to an increase in BEP (by 5\%~10\%). In conclusion, we would recommend \( \hat{n} = 400 \) for the future trial based on its acceptable level of POS assessed by the BBS and BS2 procedures.

The take-home messages from the 2 examples in this section are as follows. First, power and BEP are conceptually different ways for assessing POS and often lead to numerically different POS values (Tables 5 and 6). Second, BEP and
power, if calculated using model-based approaches, can be very sensitive to model assumptions (Table 5). Third, the bootstrap-based BEP procedures (BS2 and BBS) are better alternatives than power and model-based BEP for assessing the POS of a future trial. They are better for 2 reasons. Unlike classical power, they acknowledge that the information in the pilot data is limited. Unlike the model-based BEP approach, they incorporate this uncertainty using a flexible nonparametric approach.

5 | DISCUSSION

We developed the BBS procedure based on the Bayesian bootstrap to calculate BEP given individual-level pilot data. We also presented a non-Bayesian counterpart to the BBS procedure, named the double bootstrap (BS2), that achieves the same goal as the BBS for BEP assessment. Neither procedures make assumptions about the distribution of the pilot data, and both can handle multidimensional data sets without imposing a dependence structure among the variables. The implementations of both procedures are straightforward: only a few lines of codes are needed and the whole procedures can be easily parallelized for fast computation. By contrast, the model-based BEP approach specifies a likelihood function on the pilot data set and priors for the model parameters, followed by posterior sampling of the parameters involved in the analytical power calculation. The derivation of the posterior distributions and the posterior sampling can be complicated and computational costly, not to mention the possibility of model misspecification on the pilot data.

In addition, if there exist multiple sets of pilot data, they can be easily combined to simulate the future trial in the bootstrap-based BBS and BS2 procedures. The weight associated with each pilot study, in terms of their contribution to the future data, by default is proportional to the size of the pilot study: the larger the sample size of a pilot study, the more likely the subjects from that study will be bootstrapped into the future trial. However, if there are legitimate reasons to believe some pilot sets deserve a higher weight than the default, such as the design agreement between them and the future trial or high data quality, this can be conveniently achieved by adopting a 2-stage sampling procedure: First sampling the studies with probabilities proportional to the user-specified weights, after which the regular BBS and BS2 procedure can be applied within each pilot study.

The bootstrap-based approaches require the pilot information to be available in the form of individual-level data. When there exist only historical summary/aggregate statistics, the bootstrap-based approaches are not directly applicable. Although future data can be simulated from the aggregate statistics, it would require additional distributional assumptions, defeating the purposes of developing the nonparametric bootstrap methods in the first place. In practice, the pilot study might not be perfect for simulating the future trial such as due to design discrepancy between the two. Some design differences may not have direct impacts or can be adjusted for in the BEP calculation and thus is not a concern (eg, the first example). If a discrepancy that relates to the effect size in the power calculation is not easy to adjust for without making further parametric assumptions (eg, the second example where the study duration could be different), the model-based approaches might be the only choice. However, if unreasonable extrapolation has to made, the parametric approaches would not be appropriate either.

In summary, the BBS and BS2 approaches provide an analytically undemanding and computationally more convenient alternative to the model-based approach for assessing the BEP without making model assumptions on pilot data. With their embrace of the uncertainty around unknown parameters and the analytical and computational simplicity and easiness in implementation, the BS2 and BBS BEP procedures should be used more often for robust
decision making in practice. We provide some sample R codes on the BBS and BS2 procedures in Appendices B and C to facilitate their practical implementation.

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APPENDIX A. CONDITIONAL POSTERIOR DISTRIBUTIONS OF $\Sigma$ AND $\beta$ IN EXAMPLE 1

This appendix presents the derivation of the posterior distribution of $\Sigma$ and $\beta$ in linear mixed models. Denote the number of subjects by $n$ and the number of measurements per subject by $p$. The likelihood of $\Sigma$ and $\beta$ is

$$L(\Sigma, \beta | y) \propto \prod_{i=1}^{n} \left\{ |\Sigma|^{-1/2} \exp \left( -\frac{1}{2} (y_i - x_i \beta)^T \Sigma^{-1} (y_i - x_i \beta) \right) \right\}.$$ 

Let the prior on $\beta$ and $\Sigma$ be $p(\beta, \Sigma) = |\Sigma|^{-(\nu_0 + p + 1)/2}$. The full conditional posterior distribution of $\Sigma$ given $(\beta, y)$ is
Thus $p(\Sigma|\beta, y) \propto |\Sigma|^{-(n_0+p+n+1)/2} \exp \left( -\frac{1}{2} \sum_{i=1}^{n} (y_i-x_i\beta)^T \Sigma^{-1} (y_i-x_i\beta) \right)$

$$
\alpha |\Sigma|^{-(n_0+p+n+1)/2} \exp \left( -\frac{1}{2} \sum_{i=1}^{n} (y_i-x_i\beta)^T \Sigma^{-1} (y_i-x_i\beta) \right)
$$

$$
\alpha |\Sigma|^{-(n_0+p+n+1)/2} \exp \left( -\frac{1}{2} \sum_{i=1}^{n} (\Sigma^{-1/2}(y_i-x_i\beta))^T (\Sigma^{-1/2}(y_i-x_i\beta)) \right)
$$

Thus $p(\Sigma|\beta, y) = \frac{\Gamma_n(m/2)}{2^{|m/2|} \Gamma_n(m/2)} |\Sigma|^{-(n_0+p+n+1)/2} |\Sigma|^{n/2} \exp \left( -\frac{1}{2} tr(\sum_{i=1}^{n} e_i e_i^T \Sigma^{-1}) \right) / 2$.

which is an inverse Wishart distribution $W^{-1}(\sum_{i=1}^{n} e_i e_i^T, n)$ with scale matrix $\sum_{i=1}^{n} e_i e_i^T$ and the degrees of freedom $n$. The full conditional distribution of $\beta$ given $(\Sigma, y)$ is

$$
p(\beta|\Sigma, y) \propto |\Sigma|^{-(n_0+p+n+1)/2} \exp \left( -\frac{1}{2} \sum_{i=1}^{n} (y_i-x_i\beta)^T \Sigma^{-1} (y_i-x_i\beta) \right)
$$

$$
\alpha |\Sigma|^{-(n_0+p+n+1)/2} \exp \left( -\frac{1}{2} \sum_{i=1}^{n} (\Sigma^{-1/2}(y_i-x_i\beta))^T (\Sigma^{-1/2}(y_i-x_i\beta)) \right)
$$

$$
\alpha |\Sigma|^{-(n_0+p+n+1)/2} \exp \left( -\frac{1}{2} (\beta^T (\sum_{i=1}^{n} x_i^T \Sigma^{-1} x_i) \beta
$$

$$
- \sum_{i=1}^{n} y_i^T \Sigma^{-1} x_i \beta - \beta^T (\sum_{i=1}^{n} x_i^T \Sigma^{-1} y_i + \sum_{i=1}^{n} y_i^T \Sigma^{-1} y_i)) \right)
$$

$$
\alpha |\Sigma|^{-(n_0+p+n+1)/2} \exp \left( -\frac{1}{2} (\beta^T (x^T \Omega^{-1} x) \beta - y^T \Omega^{-1} x \beta - \beta^T x^T \Omega^{-1} y + y^T \Omega^{-1} y) \right)
$$

$$
\alpha |\Sigma|^{-(n_0+p+n+1)/2} \exp \left( -\frac{1}{2} (\beta^T (x^T \Omega^{-1} x) \beta - y^T \Omega^{-1} x \beta - \beta^T x^T \Omega^{-1} y + y^T \Omega^{-1} y) \right)
$$

Thus $p(\beta|\Sigma, y) = N((x^T \Omega^{-1} x)^{-1}(x^T \Omega^{-1} y), (x^T \Omega^{-1} x)^{-1})$, where $\Omega$ is a block diagonal matrix with $n$ blocks of $\Sigma$ on the diagonal, $x=[x_i]_{i=1,...,n}$, and $y=[y_i]_{i=1,...,n}$

**APPENDIX B. SAMPLE R CODES FOR THE BAYESIAN BOOTSTRAP PROCEDURE (BBS)**

```r
for(i in 1:m) {
  post.pi<- rdirichlet(1, rep(1+alpha,n))
  for(k in 1:t) {
    future<- NULL
    count<- c(rmultinom(1,N,post.pi))
    cum.count<- 0;
    for(j in 1:n) {
      if(count[j] != 0) {
        for(l in 1:count[j]) {
          cum.count<- cum.count+1;
          drawY<- pilot[i];
          }
        }
      }
    }
  }
}
```
APPENDIX C. SAMPLE R CODES FOR THE DOUBLE BOOTSTRAP PROCEDURE (BS2)

```r
# pilot: pilot data in data.frame format with subject ID = ID
# future: future study data
# n: sample size of pilot data
# N: sample size of planned future trial
# m: sets of bootstrapped pilot data of size n
# t: sets of bootstrapped future data of size N per bootstrapped sample data

t <- function(pilot, future, n, N, m, t) {
  for (i in 1:m) {
    draw.ID <- sample(1:n, n, replace=T)
    tmp <- NULL
    for(j in 1:n) {
      drawY <- pilot[pilot$ID==draw.ID[j],]
      drawY$ID <- j
      tmp <- rbind(tmp, drawY)
    }
    for(k in 1:t) {
      draw.ID <- sample(1:n, N, replace=T)
      future <- NULL
      for(j in 1:N) {
        drawY <- tmp[tmp$ID==draw.ID[j],]
        drawY$ID <- j
        future <- rbind(future, drawY)
      }
      # code the planned analysis on data “future”
    }
  }
}
```