Additional Practical and Computational Issues

Potential Information Requested by FDA

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Outline

- Section 6.4, 9.2 (Model Checking and Selection)
- Section 9.1, 9.3 (Additional Information Requested by FDA)
- Computational Issues

6.4 Using the Posterior Predictive Distribution for Model Checking

- Whether Bayesian or frequentist, FDA recommends verifying important assumptions in your analysis. One Bayesian tool for model checking is the posterior predictive distribution.
- Posterior predictive distribution is the distribution of a new, hypothetical observation from the trial, under the assumptions of the current model .
- Model checking idea: Generate new, hypothetical data from posterior predictive distribution and see how well it "matches" observed data from trial.

6.4 Using the Posterior Predictive Distribution for Model Checking

- Example 1:
  - A model might assume a constant event rate across time. However, a rate could be nonconstant due to: mid-course modifications to trial, physician learning curve, availability of new therapies, etc.
  - Constant event rate might be checked by predicting the observed event rate in the second half of the trial, using the posterior predictive distribution computed the data from the first half of the trial.

6.4 Using the Posterior Predictive Distribution for Model Checking

- Example 2:
  - Missing data are often assumed to follow the same distribution as observed data.
  - Posterior predictive distribution can be used to check this assumption and to perform a sensitivity analysis to that assumption.
  - See SSE for PMA P980048 BAK/Cervical Interbody Fusion System, Sulzer Spine-Tech.

6.4 Using the Posterior Predictive Distribution for Model Checking

- Assessment of "matching" can be made using the "Bayesian p-value", the (posterior predictive) probability of observing a result at least as extreme as what you observed. (see Gelman, et al., 2004; Carlin & Louis, 2000)
- Bayesian deviance measures also use the predictive distribution and can be used for model checking.

9.2 Model Selection

- FDA recommends that the general form of any statistical model be chosen a priori, perhaps in collaboration with FDA.
- Posterior odds can be used to compare two or more possible models. Posterior odds refer to the ratio of the posterior probability of the model to its complement.

9.1 Additional Information Potentially Requested by FDA

1. Prior Information you are proposing to incorporate

2. Criterion for success for your study

9.1 Additional Information Potentially Requested by FDA

3. Your method for choosing sample size

- This might involve simulation assuming a range of different treatment effects and sample sizes.
  - Calculate the posterior probability of study claim for each sample size and expected treatment effect in the range chosen.
  - Choose sample size consistent with a reasonable assumption about the treatment effect.
- One possible approach is to ignore prior information and calculate sample size using a frequentist method.

9.1 Additional Information Potentially Requested by FDA

4. Frequentist Power Tables
   - Tabulates the probability of satisfying the study claim, given various treatment effect sizes and sample sizes.
   - This table also provides type I error rate (probability of satisfying the claim, given the null treatment effect).
   - Often, power must be approximated via simulation.

9.1 Additional Information Potentially Requested by FDA

4. Frequentist Power Table example

	True Rate	Sample Size	Probability meet endpoint	
H1: p > 0.50	0.60	30		Power
		60		
		90		
H0: p ≤ 0.50	0.50	30		Type I error rates
		60		
		90		

9.1 Additional Information Potentially Requested by FDA

5. Simulate interim looks when computing operating characteristics

	True Rate	Cumulative Sample Size at each look	Probability meet endpoint	
H1: p > 0.50	0.60	30,60,90		Power
		60,90		
		40,70,90		
H0: p ≤ 0.50	0.50	30,60,90		Type I error rates
		60,90		
		40,70,90		

9.1 Additional Information Potentially Requested by FDA

6. Prior predictive probability of study claim

- Probability of study claim prior to seeing any new data. It can be used as a measure of the informativeness of the prior information.
- Evaluated at the design stage (IDE), using simulation
- Prior predictive probability should be reasonably lower than the posterior probability needed to meet the study claim. This is so that prior information does not overwhelm the current data.

9.1 Additional Information Potentially Requested by FDA

6. Prior predictive probability of study claim
   - If the prior predictive probability of the study claim is too high, remedies are available for reducing the probability (e.g., inflating the between-study variance in a hierarchical model).
   - To evaluate the magnitude of the prior probability of the claim, FDA considers the quality of the prior information as well as the gain in study efficiency from using the prior information as opposed to when ignoring it.

9.3 Computations

- Many quantities of interest in a Bayesian analysis involve calculating a mathematical integral (e.g., posterior mean, posterior probability of a hypothesis).
- Markov Chain Monte Carlo (MCMC) techniques provide Monte Carlo approximations to these integrals, allowing the use of more realistic, complex statistical models and resulting posterior distributions.

9.3 Computations

- Typical MCMC techniques simulate draws from a *proposal distribution*, which is a simple approximation to the posterior distribution.
- Each draw is either accepted or rejected as a valid draw from the posterior distribution based on a comparison of the posterior distribution to the proposal distribution at the drawn value.
- If the drawn value is rejected, the simulated draw is taken to be the previously accepted drawn value.
- The draws form a Markov chain which eventually *converges* so that subsequently sampled draws actually come from the posterior distribution, and can be used for posterior inference (e.g., computing posterior probabilities)

9.3 Computations

- The point at which convergence of the chain is achieved is not known a priori, and must be assessed using the sampled values from the chain.
- FDA recommends that you check convergence of the chain. (Diagnostic methods can be found in Gilks, et al., 1996)
- Remedies for slow convergence include:
  - Employing an alternative model parameterization
  - Using a proposal distribution that more closely resembles the posterior distribution
  - Introducing auxiliary variables to simplify MCMC sampling (data augmentation)
  - Avoiding improper priors (a type of noninformative prior)

9.3 Computations

- Typical Software: WinBUGS, custom code, SAS, R
- FDA requests electronic submission of calculations and program code.
- FDA may review calculations using alternative software.