Bayesian Statistics at the Division of Biostatistics CDRH, FDA

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Talk Outline

I. Introduction

II. CDRH Draft Guidance Document on the use of Bayesian Statistics for Medical Device Clinical Trials

III. Examples of the use of Bayesian Statistics for Medical Device Clinical Trials
   - Likelihood based methods for incomplete data
   - Adaptive Designs
   - Confirmatory Trials
Working Philosophical Approach

- Accept Bayesian mathematics
- Undecided on Subjectivity
- Occasionally depart from Likelihood Principle
Bayesian Mathematical Paradigm

Prior + Data $\rightarrow$ Posterior

Accept posterior probability as measure of study success.
PP $> \text{prespecified threshold}$
(usually 95%)
Subjectivity

Regulatory pressure to be as objective as possible.
In my experience, non-informative priors have been more common.
Departures from Likelihood Principle

Care about information beyond likelihood:

• False positive rate from interim analyses.
• Require simulations to assess and control Type I-like error and study power.
CDRH Draft Guidance: What is Bayesian statistics?

“Bayesian statistics is a statistical theory and approach to data analysis that provides a coherent method for learning from evidence as it accumulates… the Bayesian approach uses a consistent, mathematically formal method called Bayes’ Theorem for combining prior information with current information on a quantity of interest. This is done throughout both the design and analysis stages of a trial.”
Draft Bayesian Guidance

Link

http://www.fda.gov/cdrh/osb/guidance/1601.html

Or search Google for

“CDRH Guidance Bayesian Statistics”
Examples of Bayesian Designs for Device Trials

Likelihood based methods for incomplete data- making use of 12 month data for 24 month results

Adaptive trials using predictive probability

Incorporating prior data in a confirmatory study.
Likelihood based methods for incomplete data

In trials of orthopedic devices, the primary endpoint is commonly the 24 month success rate.

May have 12 month results without knowing the outcome at 24 months.
## Likelihood Success Parameters

<table>
<thead>
<tr>
<th></th>
<th>24 Month Failure</th>
<th>24 Month Success</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 Month Failure</td>
<td>$p_{00}$</td>
<td>$p_{01}$</td>
</tr>
<tr>
<td>12 Month Success</td>
<td>$p_{10}$</td>
<td>$p_{11}$</td>
</tr>
<tr>
<td></td>
<td>$p_{.0}$</td>
<td>$p_{.1}$</td>
</tr>
</tbody>
</table>
Likelihood Function

\[ L = p_{00}^{n_{00}} \cdot p_{01}^{n_{01}} \cdot p_{10}^{n_{10}} \cdot p_{11}^{n_{11}} \cdot (p_{00} + p_{01})^{n_0} \cdot (p_{10} + p_{11})^{n_1}. \]
Combining this likelihood with non-informative, uniform Dirichlet priors we can derive the unstandardized posterior distribution.

Using Markov Chain Monte Carlo we can obtain a sample from the posterior distributions of the parameters.
We can then find a sample from the posterior of the quantities of interest:

\[ p_{24} = p_{01} + p_{11} \]

Study success is then determined by

\[ P(p_{24T} - p_{24C} > 0) > 0.95 ? \]

Caveat: Assuming missing data and complete data are exchangeable
Need for Adaptive Designs

Non-inferiority trials of active controlled orthopedic devices where endpoint is the device success rate.
The required sample size depends critically on the control and treatment success rates.
Example of Non-Inferiority Sample Size- FDA

True control success rate = 0.65
True treatment success rate = 0.65
Non-inferiority margin = 0.10
Type I error = 0.05
Power = 0.80

Sample size = 282 per group
Example of Non-Inferiority Sample Size - Company

True control success rate = 0.70
True treatment success rate = 0.75
Non-inferiority margin = 0.10
Type I error = 0.05
Power = 0.80

Sample size = 110 per group
Adaptive Sample Size- Best way to resolve disagreement

- Sponsor will only have to enroll larger sample size if they really need it.
- The investigational treatment has sometimes performed better than the control.
- A smaller sample size can be sufficient and a smaller sample size can be enrolled.
Mechanism for Adaptive Design: Predictive Probability

- Interim analysis
- Impute results for patients with incomplete data, using data from current completers.
- \( P(24\text{-}m \text{ success} | 6\text{-}m \text{ success}) \sim \text{Beta} (a_1 + SS, b_1 + SF) \)
- \( a_1, b_1 \) can be informative for purposes of sample size determination
• Examine the results of “completed” trial with imputed data.
• Repeat many times and calculate the proportion of simulated trials where study success is obtained.
• If this predictive probability of trial success is high enough (i.e. greater than 90%), stop enrolling for sample size.
Operating Characteristics

- Because of the interim analyses, sponsor must demonstrate that the Type-I-like error is not inflated.
- Sponsor should also demonstrate that the study is adequately powered.
- This is usually done through simulations.
## Example Simulation Table

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Control</th>
<th>P( NI )</th>
<th>Time (months)</th>
<th>Expected Sample Size</th>
<th>P( ES )</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.80</td>
<td>0.75</td>
<td>0.990</td>
<td>39.7</td>
<td>439.7 (65)</td>
<td>0.98</td>
</tr>
<tr>
<td>0.75</td>
<td>0.75</td>
<td>0.826</td>
<td>45.7</td>
<td>513.4 (68)</td>
<td>0.73</td>
</tr>
<tr>
<td>0.70</td>
<td>0.75</td>
<td>0.337</td>
<td>54.6</td>
<td>569.4 (68)</td>
<td>0.24</td>
</tr>
<tr>
<td>0.65</td>
<td>0.75</td>
<td>0.048</td>
<td>57.7</td>
<td>587.2 (51)</td>
<td>0.02</td>
</tr>
<tr>
<td>0.60</td>
<td>0.75</td>
<td>0.0010</td>
<td>50.9</td>
<td>541.5 (45)</td>
<td>0.34</td>
</tr>
</tbody>
</table>
Simulation Considerations

- Have to simulate transition probabilities. Namely, how do patients transition from 3-month to 6-month to 12-month to 24-month results.
- Model extremes: perfect interim information and independent interim time points.
- Also, have to model different scenarios for patient accrual, and
- Model different control success rates.
Confirmatory Trials

- Failure of overall trial, but success in a subgroup.
- Want to do a confirmatory trial in that subpopulation.
- Want to borrow from original subgroup results.
Choosing a Prior

• Problem: prior from subgroup of original trial may be biased due to “fishing” for significant subgroup.
• One solution: include results from other subgroups in a hierarchical model.
• Included subgroups should have been a priori “exchangeable”.

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False Positive Rate in New Trial

• Want to calculate the false positive rate in the new trial.
• Consider binary success rates.
• Type I error occurs when declare study success, i.e.
  
  \[ \text{Posterior } P(p_1 - p_2 > 0) > 0.95 \]
  
  when null is true, i.e.
  
  \[ p_1 \leq p_2 \]
Proposed False Positive Rate Calculation

\[ \iint P(\text{Type I error}\mid p_1, p_2) \cdot \pi(p_1, p_2) dp_1 dp_2 \]
Calculating the False Positive Rate (cont.)

- For given values of $p_1$ and $p_2$ find probability of Type I error.
- Integrate over the probability distribution of $p_1$ and $p_2$
- Note that for $p_1 > p_2$ the probability of Type I error $= 0$ (by definition)
- Critical importance of $\pi(p_1, p_2)$
Summary of Applications

- Methods for incomplete data
- Adaptive sample size
- Confirmatory trials
- Evaluating a modified version of an approved product
- Synthesizing data in post-market surveillance.
Difficulties

- Same requirements of good trial design
- Extensive pre-planning including simulations
- Selecting and justifying prior information
- Need to explain trial in labeling