The Value of Bayesian Approaches in the Regulatory Setting

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Outline

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   3. Simulations
   4. Predictive Probabilities

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III. Opportunities

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I. The Use of Bayesian Approaches in the Regulatory Setting

[1] [2] [8]

1. Prior information

- Increase power and precision of clinical trials
- Reduce the size and duration
- Synthesize and express the totality of prior evidence [3]

Sources

- Phase 2 trials
- Adult prior extrapolated to pediatric [7]
- Safety data for different indications of same drug [4]
- Information on same control group used in other trials
- Natural history studies used to augment control group
- Prior from other clinical trials [5]
- Information on subgroups from different trials
- Priors derived from pharmacological or engineering models [6]

Important Considerations

- Agreement to be reached in advance between sponsor and FDA (suitability of the prior; exchangeability)
- Avoid selection bias: unfavorable prior may have been omitted (treatment group) or selected (control group)
- Avoid subjective priors (expert opinion)
- Clinicians: often unsure about suitability of prior
- Caution: future advisory panel experts could disagree

Important Considerations

Priors might be too informative: discount

Static Discount

- Direct discount (%)
- Power priors
- Maximum effective sample size
- Increase the stringency of the success criterion
- Increase the sample size of the pivotal trial

Dynamic Discount

Discount is based on similarity between prior and current data

Ex: Bayesian Hierarchical Models

Borrowing ⇑ as Variability among studies ⇓

New study sample size ⇑ as Borrowing ⇓

Multi-site trials: borrowing strength across different sites (large variability across sites: e.g. medical devices)

2. Bayesian Adaptive Designs

- Can reduce the size (length) of a trial ➔ faster decision
- Can increase the size (length) of a trial when needed
- Interim analyses to decide to stop or continue **recruiting** based on predictive distributions ➔ sample size decided and optimized during the trial
- ***Modeling****: results at early follow-up times ("surrogates") predict final follow-up result. Model refined at interim looks based on all follow-up results from patients recruited early*
- Adaptive randomization

✓ Probability of assignment to treatment depends on data obtained thus far

✓ May be ethically appealing if allocates more patients to best treatments

Ex: Bayesian Adaptive Design + Modeling [9]

- Treatment vs. Control at 24 months
- Follow-up times: 6, 12, 18 and 24 months
- Interim looks
  - For sample size adaptation
  - For effectiveness
  - For futility
- Constant or varying accrual rate
- ***Model: earlier visits are used to predict 24-month results of patients that have not yet reached the 24-month follow-up***

Important Considerations

- Increase the probability of trial success (insurance)
- Achieve almost optimal sample size
- Advantageous when there is no prior information
- **Crucial when using prior information** (e.g. hierarch. model): amount of strength to be borrowed is uncertain ➔ avoid failure for lack of power
- Very advantageous when Bayesian modeling is used to predict an endpoint from earlier follow up visits – increases in power and savings in sample size

Important Considerations

- **Stopping early** occurs when **surprises** arise:
  - ✓ Treatment is better (success) or worse (futility) than predicted
  - ✓ Sample variability is smaller than predicted
  - ✓ Bayesian model makes good predictions

- **Simulations:**
  - ✓ needed to assess operating characteristics of the trial design
  - ✓ mathematical formulas for Bayesian adaptive designs are not available

3. Simulations

Simulate the trial thousands of times making assumptions about the true value of the endpoints and look at the average performance:

How often does it get the right answer?
How often does it lead to an erroneous conclusion?

- Estimate error probabilities
- Increase trial predictability
- Estimate expected sample size, trial duration, cost
- Optimize clinical trial design features
- Prepare and budget for different scenarios and surprises
- Readily understood by clinicians: what will happen under various scenarios

Important Considerations

- Simulations are conducted at the design stage
- Devise a comprehensive number of scenarios to generate data (need clinicians input)
- Make assumptions to generate data
- Assess and control error probabilities (type I and II) under "all plausible scenarios and assumptions"
- May be more difficult for the FDA to review
- May take more effort to reach agreement with the FDA at the design stage
- Sponsor's documentation including the simulation code is useful to facilitate the review

Design features to be optimized

- Stopping rules for success and futility
- Number and timing of interim analyses
- Prior probabilities; hierarchical model parameters; discount factors
- Predictive model
- Minimum sample size **(*should also consider safety*)**
- Maximum sample size
- Randomization ratio
- Accrual rate (not too fast and not too slow)
- Dose/treatment selection
- Number of sites
- Use of covariates or subgroup analysis

4. Predictive Probabilities

- Probability of future events given observed data
- Probability of results for missing patients
- Help decide when to stop a trial or recruiting
- Help decide whether to stop or to continue recruiting
- Labeling [9]
- Predict a clinical outcome from a valid surrogate (modeling)

II. Lessons Learned

- Use of prior distribution and strict control of type I error probability at traditional α are incompatible
  - ✓ If α fixed at traditional level (e.g. 0.05), all prior distribution is discounted
  - ✓ Discount factors are arbitrary and difficult for clinicians to provide input on
- Factors to consider for selecting α:
  - ✓ Rare disease
  - ✓ Unmet medical need
  - ✓ Decision analysis
  - ✓ Patient input: See [10] *Patient Centered Clinical Trials (Drug Discovery Today)*

II. Lessons Learned (continued)

- Possible Strategy for success criterion:
  - ✓ Full Bayesian approach using **posterior probability** *(Ebola trial - Clinical Trials* [11])
  - ✓ Threshold could be determined via full decision analysis

- Hierarchical models:
  - ✓ Hyperparameters: difficult to assess due to scarcity of clinical input (hard to understand)
  - ✓ Problematic when used with only 2 studies (variability between 2 studies cannot be estimated)

II. Lessons Learned (continued)

- Adaptive Bayesian Design:
  - ✓ **A must** when prior distributions are used: avoid near misses
- Simulations:
  - ✓ Helpful at the design stage to strategize and optimize trial designs

III Opportunities

- Borrowing information when is difficult to recruit
  - rare conditions
  - pediatric studies [7]
- Borrowing information, when relevant data are available and hard to ignore
  - pediatric trials [7]
  - safety for other indications of the same drug [4]
- Synthesizing information across multiple
  - trials
  - programs
  - sites
  - subgroups
  - countries

III Opportunities (continued)

- Update knowledge or make decisions as information accumulates:
  - safety monitoring
  - CV safety trials [3]
  - Ebola-type trial with limited drug supply and critical unmet need [11]
- Need for efficient trials:
  - unmet needs for life threatening and severely debilitating diseases
- Use modeling where early follow up results can predict later follow up results
  - Bayesian adaptive designs are much more efficient
  - long follow up trials (survival)

IV. The Value of Bayes in the Regulatory Setting

1. Account for the totality of external evidence via prior info
2. Interpretability of posterior distribution
3. Likelihood principle: flexible clinical trial designs
4. Use modeling to build likelihood functions
5. Decision analysis to develop rational / transparent decision rules:
   - Rational thresholds for approval
   - Use patients' and physicians' input
6. Required strength of evidence can be rationally determined by:
   - Medical need
   - Patient tolerance for risk and perspective on benefit
   - Severity and chronicity of the disease

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