Considerations on Mixture Priors for Historical Borrowing in Confirmatory Studies

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Outline

- Motivation/Background
- Operating Characteristics
- Proposed Strategy
- Takeaways

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Motivation

- Clear Savings in Re-using Historical Information
  - Fewer Patients on Placebo, Time, Money
- However:
  - Need to guard against bad decision making.
  - Methods need to be statistically sound.
  - We also have to communicate the results to non-statisticians.

How?

- Explosion of Methods the last few years:
  - Power Priors
  - Commensurate priors
  - Hierarchical Models
  - Finite Mixtures
  - Matching/Weighting/Hybrid
- How To Choose Which Approach?
  - Simplicity
  - Interpretation
  - Operating Characteristics

Operating Characteristics

- These strategies are not going to increase power while controlling type 1 errors conditioning on external data.
  - Hard to beat a UMP test (Kopp-Schneider et al. 2019).
  - *Do we always need to condition on the external data?*
  - Why do I need to control type 1 error to 5% when I have outside evidence to the contrary?
- But, type 1 error/power are not the only operating characteristics
  - P(Correct Decision), conditional or not
  - Decision Theory
  - Reduced Time/Resources/Patients Exposed to Placebo

Motivating Example

Historical Phase 2 Data:

$$r_p^h \sim Binomial(n_p^h, p_p)$$
$$r_d^h \sim Binomial(n_d^h, p_d)$$

Proposed Phase 3 Trial Data:

$$r_p \sim Binomial(n_p, p_p)$$
$$r_d \sim Binomial(n_d, p_d)$$

Parameters:

p_p =probably of an event under placebo

p_d =probably of an event under drug

$$\theta = OR = \frac{p_d/(1-p_d)}{p_p/(1-p_p)}$$

Proposed Strategy

- Set a Bayesian decision rule that has the required type 1 error rate under “No Borrowing”.

$$P(\theta < 1|Ph\ 3\ Data) > 0.975$$

- Use a mixture prior for the parameter(s) with historical data (Ye and Travis, 2017).

$$\pi(\theta) = \psi \times N(0, l) + (1 - \psi) \times \pi(\theta|Ph\ 2\ Data)$$

- Use the tuning parameter(s) to “Optimize” any operating characteristics of interest.

$$l \text{ and } \phi$$

Why a Mixture Prior?

- The Posterior can have a closed form or nearly closed form!

$$\pi(\theta|r_p, r_d) = \frac{f(r_p, r_d|\theta)\pi(\theta)}{m(r_p, r_d)}$$

$$\begin{aligned} f(r_p, r_d|\theta)\pi(\theta) &= \psi \times N(0, l) \times f(r_p, r_d|\theta) + (1-\psi) \times \pi(\theta|Ph\,2\,Data) \times f(r_p, r_d|\theta) \\ &= \psi \times m_{Flat}(r_p, r_d) \times \pi_{flat}(\theta|r_p, r_d) + (1-\psi) \times m_{ph2}(r_p, r_d) \times \pi_{ph2}(\theta|r_p, r_d) \end{aligned}$$

Thus,

$$\pi(\theta|r_p, r_d) = \frac{\psi \times m_{Flat}(r_p, r_d)}{m(r_p, r_d)} \times \pi_{flat}(\theta|r_p, r_d) + \frac{(1-\psi) \times m_{ph2}(r_p, r_d)}{m(r_p, r_d)} \times \pi_{ph2}(\theta|r_p, r_d)$$

- Can often use simpler models (no covariates and single time point) to power a study.

Why A Mixture Prior

- It Follows Bayes Theorem
  - You are updating the model probabilities

$$\psi \text{ to } \frac{\psi \times m_{Flat}(r_p, r_d)}{m(r_p, r_d)} \text{ for the flat prior.}$$

You could convince me to just use a Bayes Factor, however few can interpret them properly.

- We have “optimality” in decision theoretic settings.

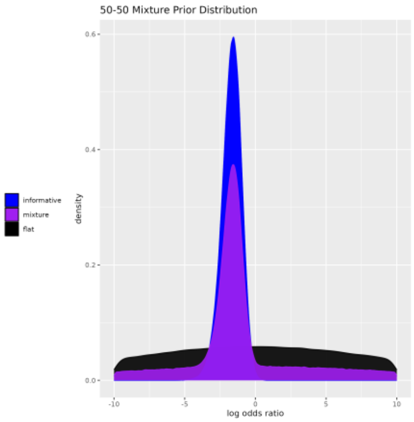
Interpretation

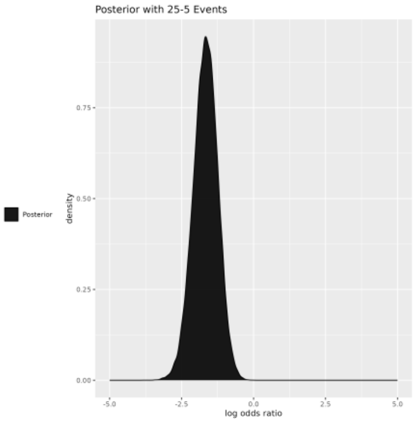
- Data Decides if We Borrow (Dynamic)
  - Posterior mixture weights clearly show how much borrowing is used
- Can be easily contrasted with the extremes of no borrowing and fully borrowing of phase 2 data
- Prior effective sample size can be computed (Morita et al, 2012)

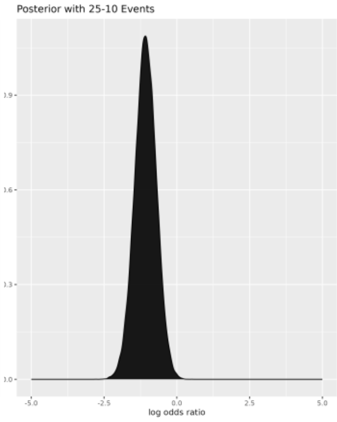
Example

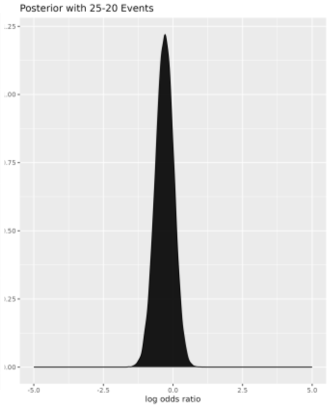
Phase 2 Data:
13/100 and 3/100

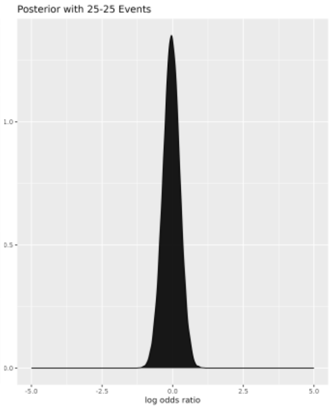
Phase 3 Data:
250 patients per arms











Closing Thoughts

- Many methods are out there for “Historical Borrowing”.
  - *Focusing on simpler approaches may help us communicate the approach.*
- Important to choose operating characteristics that are relevant to the situation.

References

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