Applications of robust MAP priors in quantitative trial design

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Introduction

Methodology and overview

- **Context:**
  - Planning Novartis early development clinical trials
  - Desire to incorporate historical control information

- **Methodology:**
  - MAP priors commonly used to obtain equivalent sample size (Neuenschwander et al. 2010)
  - Concerns about prior-data conflict and analytical intractability
  - Mixture priors of conjugate distributions are appealing in this setting (Schmidli et al. 2014)

- **Application:**
  - Case study from infectious disease proof of concept study design
  - Mixture prior approach fully implemented in design and analysis
Overview

- New compound intended to treat an infection and its resulting disease
  - Infection is common (>50% world-wide)
  - Latent infection – immune system fails to clear the virus

- Most infections are asymptomatic or mild but significant disease can appear in at-risk persons
  - Bacterial and fungal infections
  - Deafness/blindness
  - Mental retardation
  - Death

- Currently available therapies are efficacious, but also associated with serious toxicities
  - Neutropenia, thrombocytopenia, seizures, anemia
  - Carcinogenicity/teratogenicity in animals
Disease prevention and treatment

*Treatment strategies for patients at risk*

- Due to mortality and morbidity associated with infection/disease, most common strategy is preventative treatment

- **Prophylaxis:**
  - Therapy given during period of highest risk to prevent virus growth

- **Preemptive:**
  - Therapy initiated after virus is detected (viral load exceeds given threshold) but before disease develops

- Prophylaxis more efficacious than preemptive strategy, but also associated with increased risk of toxicity
ABC123

Background and high-level study design

- Novel compound (ABC123) has the potential to be used in a prophylaxis setting
  - Well tolerated in preclinical toxicity studies at 10 times highest (expected) human dose
  - Well tolerated in first-in-human healthy volunteer study

- First clinical study in patients – randomized, double-blind, placebo-controlled
  - Evaluate efficacy, safety and PK of ABC123 when given as a prophylaxis
  - Recruit patients that are at relatively high risk of infection
  - Goal is to prevent infection, i.e. prevent viral loads from reaching a pre-defined threshold
  - If this threshold is reached, then treat patients with standard-of-care
  - Placebo-controlled study is ethical in this setting
ABC123 patient study

Key statistical aspects of study design

- **Primary endpoint is binary (infection yes/no)**
  - Efficacy represented in terms of relative risk $p_T/p_C$

- **Use beta-binomial (conjugate) model for analysis**
  - Non-informative Beta(1/3,1/3) prior for $p_T$
  - Informative prior on $p_C$ based on historical data (details to follow)
  - Prior mean 0.41 and 90% CI (0.21,0.64) – Effective sample size 42

- **3:1 randomization ratio in favor of ABC123 with total N = 64**

- **Quantitative PoC criteria:**
  1. Posterior probability that $p_T/p_C < 1$ is at least 0.9
  2. Posterior probability that $p_T/p_C < 0.5$ is at least 0.5

- **Outcomes**
  - 1) and 2): “Positive result”
  - Neither 1) nor 2): “Negative result”
  - 1) or 2), not both: “Indeterminate”
Meta-analysis for the placebo arm

**Mathematical model**

- **Mathematical setup for H historical studies:**
  
  \[ r_h \sim \text{Binomial}(p_h, n_h), \quad \text{logit}(p_h) \sim N(\mu, \tau^2), \quad h = 1, \ldots, H \]

  **Priors:** \( \mu \sim N(0, 1\varepsilon 10) \) and \( \tau \sim \text{Half-Normal}(0, 1) \)

  **Prediction for this study:** \( \text{logit}(p^*) \sim N(\mu, \tau^2) \)

- **6 similar historical studies with 747 total placebo patients**
  - Pooled mean event rate = 40%

- **JAGS** used to simulate draws from prior predictive distribution of \( p^* \)

- **Forest plot** shows results of this analysis
Meta-analysis for the placebo arm

Robust mixture priors

- Distribution for $p^*$ approximated with a mixture of beta priors

- Reasonably good approx. with $\geq 2$ components

\[
\begin{align*}
  w_i^* &= \frac{w_i C_i}{\sum_j w_j C_j} \\
  C_j &= \frac{B(a_j + y_C, b_j + n_C - y_C)}{B(a_j, b_j)}
\end{align*}
\]

\[
p_C \sim \sum_{i=1}^{3} w_i \text{Beta}(a_i, b_i)
\]

\[
\Rightarrow p_C | Y_C = y_c \sim \sum_{i=1}^{3} w_i^* \text{Beta}(a_i + y_C, b_i + n_C - y_C)
\]
Meta-analysis for the placebo arm

**Robust mixture priors**

- Distribution for $p^*$ approximated with a mixture of beta priors
- Reasonably good approx. with $\geq 2$ components
- Final prior is 3-component beta mixture:
  - $0.64 \times \text{Beta}(19.49, 28.80)$
  - $+ 0.31 \times \text{Beta}(3.88, 5.11)$
  - $+ 0.05 \times \text{Beta}(1, 1)$
  - ‘Simpler’ prior chosen at the time for pragmatic reasons
  - Extra weakly-informative component added for ‘robustification’

\[ w_i^* = \frac{w_i C_i}{\sum_j w_j C_j} \]
\[ C_j = \frac{B(a_j + y_C, b_j + n_C - y_C)}{B(a_j, b_j)} \]
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\[ \Rightarrow p_C | Y_C = y_C \sim \sum_{i=1}^{3} w_i^* \text{Beta}(a_i + y_C, b_i + n_C - y_C) \]
Meta-analysis for the placebo arm

Robusness

- ‘Robustified’ MAP prior responds with greater flexibility to prior data conflicts
- Number of components not too influential in this context (as long as \( \geq 2 \))
Meta-analysis for the placebo arm

*Placebo sample size*

- Effective sample size of prior computed as in (Morita et al. 2008)
  - ESS = Sample size such that expected information of the posterior under a non-informative prior is the same as the information of the robust MAP prior
  - In our case = 42

- Considerable information for placebo

- Decision: 16 placebo patients
  - Allow meaningful comparison on secondary endpoints and safety
  - Maximize prior predictive probability of observing a placebo event rate in the 90% predicted interval for $p^*$
Primary analysis

Statistical model and PoC criteria

- Primary endpoint is binary (infection yes/no)
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  - Non-informative Beta\((1/3,1/3)\) prior for \( p_T \)
  - Informative prior on \( p_C \) based on historical data (details to follow)
  - Prior mean 0.41 and 90% CI \((0.24, 0.64)\) – Effective sample size 42

- 3:1 randomization ratio in favor of ABC123 with total \( N = 64 \)

- Quantitative PoC criteria:
  1. Posterior probability that \( p_T / p_C < 1 \) is at least 0.9
  2. Posterior probability that \( p_T / p_C < 0.5 \) is at least 0.5

- Outcomes
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Trial outcomes

Visualizing outcome vs. success/failure

- With a binary endpoint we can tabulate (or plot) trial outcomes ahead of time
- Quantitative success criteria can be fine-tuned via visualization
- This illustration quite useful for clinical colleagues as a ‘gut-check’ of success criteria
Operating characteristics

3:1 randomization – 64 total evaluable subjects

- Probability of negative result is usually <0.2 (at ABC123 ≤0.2)
- Probability of positive result usually >0.8 (at ABC123 ≤0.15)
- Robust OC for range of true placebo event rates (0.35-0.5)
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Interim analysis

Quantitative futility criterion

- Team desired IA with option to terminate study based on futility
  - Analysis conducted with 50% planned sample size
- Futility defined as <0.1 predictive probability of achieving positive or indeterminate trial result

\[
Pr(\text{Pos or Ind} \mid \text{data}) = \int Pr(\text{Pos or Ind} \mid \theta)p(\theta \mid \text{data})d\theta
\]

\[
\theta = (p_C, p_T)
\]
Conclusion & discussion

- Clinical trial team was enthusiastic about the methodology
  - “Bayesian” seems popular
  - Saving placebo patients was an attractive option

- MCMC distribution can be approximated with few (≥2) mixture components

- Additional possibilities not included in final design
  - IA readout for efficacy
  - Re-estimation of placebo sample size at IA

- Choosing the placebo sample size was not straightforward
  - Some confusion about “confirming” the meta analysis

- Usefulness of graphs for illustration
  - Trial outcomes, predictive power, etc.
References

