Bayesian applications in rare disease clinical trial research

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What Makes a Disease Rare?

One thing in common: low prevalence
Challenges Necessitate Innovation

- Small Sample Size
- Limited Historical Data
- Rare Disease
- Expertise hard to come by
- Pathology not well understood
- Low expected ROI
- Few (if any) treatments

Rare Diseases and Paediatrics

Bayesian Approaches

Example: Augmented Control

Bayesian Methods

Borrowing

Precision
Borrowing in a Rare Disease Setting

- Pocock (1976) often cited when assessing appropriateness of borrowing
- Criteria set a gold standard for acceptability
- Attempts to mimic a RCT
- Some recommendations may be impractical or impossible in a rare disease setting
- Must be flexible
Two-Step Approach

1. Use Bayes rule to generate a posterior on parameter of interest using the historical data

2. Apply Bayes rule again to data from new trial

- Pooled analysis
- Discounting by increasing prior variance
- Power Priors
- Commensurate Priors
- Robust Mixture Priors
Robust Mixture

\[ \pi_{RMP}(\theta, w \mid D_0) \propto (1 - w) \pi(\theta \mid D_0) + w \pi_r(\theta) \]

- **Historical data posterior**
- **Mixture weight**
- **Robust (vague) prior**

For different values of \( w \):
- \( w = 0 \)
- \( w = 0.25 \)
- \( w = 0.5 \)
- \( w = 0.75 \)
- \( w = 1 \)
Progressive Supranuclear Palsy

- PSP is a rare neurodegenerative disorder characterized by aggregates of tau protein in the brain
- Prevalence 1 in 16,600
- Several disease-modifying agents have been studied in PSP, but nothing has shown to be beneficial

We wish to leverage the information from the previous studies, even though they were not able to meet their clinically meaningful endpoint.
PSP: Historical Data

- 52-week endpoint
- PSPRS change from baseline assessed
- Two trials
  - Tideglusib vs. placebo
  - Davunetide vs. placebo
  - 144 placebo patients who completed treatment

PSP-Rating Scale

- Daily Activities
- Behavior
- Limb Motor
- Bulbar
- Ocular Motor
- Gait/Midline

Example: Augmented Control

Rare Diseases and Paediatrics
Creating a RMP

Approximate historical control with normal distribution,

$$\theta \mid D_0 \sim N(\mu = 11.24, \sigma = 9.95/\sqrt{144})$$

And select a robust prior which is centered at the observed historical effect, but with inflated variance,

$$\theta_{\text{robust}} \sim N(\mu = 11.24, \sigma = 40).$$

Using a mixing weight of 0.5, we get the RMP

$$0.5 \times N(11.24, 9.95/\sqrt{144}) + 0.5 \times N(11.24, 40).$$
Creating a RMP (cont’d)

• The mixture becomes a heavy-tailed version of the historical prior
• The mixture matches the robust distribution in the tails

Note: the components are not plotted as densities, rather they integrate to their assigned weight (0.5 for each, in this case)
A New Trial

We plan to run a new trial in PSP, which randomly assigns 40 PSP patients to placebo.

Consider 2 extreme cases for the new trial:

- Pbo response matches historical response
- Pbo response very different from historical meal (prior-data conflict)
Impact on the Posterior

**Scenario: No Conflict**
Example with Prior-Data Agreement

**Scenario: Conflict**
Example with Prior-Data Conflict
Multiple Historical Data Sources (if we’re lucky!)

• When more than 1 historical data source is available, a meta-analytic predictive (MAP) prior may be constructed, then used as the historical component in the robust mixture.

• Alternatively, a posterior could be derived on each historical trial and used in the mixture, allowing trials to be unequally informative in the analysis (borrow more only from trials which have less drift).
Rare Diseases in Children

• Rare diseases affect approximately 30 million Americans
  – 20 million of those are children
  – <1% of diseases have FDA approved treatment
  – Numbers are higher in Europe, with similar number of treatments available

• 50%-75% of all rare diseases begin in childhood
Extrapolation. Extending information and conclusions from studies in a source population to make inferences for a target population, minimizing the need to generate additional information to reach conclusions for the target population.

While historical pediatric data may not exist, extrapolation allows us to use adult data as a source of information.

Bayesian methods particularly well-equipped to handle extrapolation, as it supposes existing information exists and may be applied as evidence to support effect in a new population.

1 or more adequate-well controlled studies powered on a clinically meaningful endpoint
- Bipolar disorder, systemic juvenile idiopathic arthritis, major depression, migraine, polyarticular JIA (pJIA), bronchopulmonary dysplasia, ADHD, nausea/vomiting, partial seizures (<4 y/o), respiratory syncytial virus, prophylaxis of venous thromboembolism, atopic dermatitis, etc.

1 or more adequate-well controlled studies powered on a surrogate endpoint
- Diabetes, anemia, Idiopathic thrombocytopenia, treatment of venous thromboembolism, hypertension, hypercholesterolemia, asthma, etc.

Controlled study without formal statistical power
- Community acquired pneumonia, nosocomial infections, skin and skin structure infections, etc.

Descriptive efficacy study without concurrent control
- Psoriasis, Neurogenic delirium over activity, pJIA (NSAIDs), etc.

Small dose-ranging studies (randomization to multiple dose levels)
- Scleroderma, ulcerative colitis, Crohn’s, etc.

Small PK/PD studies (single dose level matching adult exposures)
- HIV, erosive esophagitis (infants), anesthetics, pulmonary arterial hypertension, PK/safety only (single dose level matching adult exposures)
- gastroesophageal reflux disease, bacterial sinusitis, herpes simplex, analgesics/anesthetics (well known MOAs; over 2 y/o), imaging products, melanoma (adolescents)

~60% Pediatric Programs require at least 1 adequate, well-controlled efficacy trial (clinical or surrogate endpoint)
Changing landscape of pediatric orphan indications

- Orphan product designation usually comes with incentives
- In the US, orphan indications were exempt from paediatric requirements
- Orphan designation no longer granted for sub-populations (FDA)
- Some indications which were granted orphan designation no longer qualify
Hidradenitis Suppurativa

• Hidradenitis suppurativa (HS) is a chronic skin disease which causes painful, boil-like lumps that form under the skin and often secrete pus and blood.
• Earliest age of onset around 10 years.
• No pediatric HS trials for efficacy.
• 1 approved therapy in adolescents (based on PK data).
• HS would have been granted orphan designation 2 years ago, but now does not qualify in the US.