Innovative Designs and Analyses for Pediatric Drug Development

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Biometrics and Advanced Analytics
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*presenting
Overview of Talk

• Application of Bayesian methods and Adaptive Design to Pediatric Trial Design

• Setting: pediatric plan lags behind an adult indication
  – More information in adults, but comparatively less data in pediatrics, and the
  – Primary goal of the pediatric trials is to provide definitive efficacy and safety evidence to impact product labeling
  – Pediatric indication is rare, and difficult to enroll
Opportunities for the use of Bayesian modeling and simulation in Pediatric Drug Development

The Typical Problem

- Small Population\(^1\)
- Recruitment Barriers
- Logistics/Technical\(^2\)
- Ethics/Parental Concerns\(^3,4\)

fosinopril. essential hypertension in children and adolescents.\(^5\)

- Adult study: 220 patients, 9 US sites, 5 mo. to complete
- Pediatric study: 253 patients (6 - 16y), 70 sites, 3 countries, 1 y to complete
“Need to minimize number of subjects enrolled in pediatric clinical trials and the need to maximize the usefulness of the data obtained, while ensuring that the trials are feasible, robust, and interpretable.” – Dunne et al. (2011)
We are thinking about extrapolation early in our drug development programs.

Weights of these factors determine **extent of extrapolation**

- Adult trials efficacy outcome data
- Pediatric trial efficacy outcome data
- Exposure-Response
- Disease progression
- Response to therapy

Bayesian extrapolation
Bayesian extrapolation

Design Trial

- Specify a prior: Adult Efficacy Data
- Collect data + compute likelihood: Pediatric Trial Efficacy data
- Apply Bayes Theorem: Posterior distribution

Bayesian approach formalizes what pediatricians do when they combine the results from large adult trials with the results of smaller pediatric trials to make treatment decisions.” - Schoenfeld et al. 2009
Example 1: Bayesian analysis

- **Treatment:** Infliximab 5mg/kg
- **Indication:** Ulcerative colitis
- **Adult Trial design:** 2 completed Placebo-Controlled
- **Pediatric Trial design:** Open-label

<table>
<thead>
<tr>
<th></th>
<th>ACT 1</th>
<th>ACT 2</th>
<th>T72</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Infliximab 5mg/kg</td>
<td>Infliximab 5mg/kg</td>
<td>Infliximab 5mg/kg</td>
</tr>
<tr>
<td><strong>Endpoint</strong></td>
<td>N = 121</td>
<td>N = 121</td>
<td>N = 60</td>
</tr>
<tr>
<td><strong>Clinical response</strong></td>
<td>84 (69.4%)</td>
<td>78 (64.5%)</td>
<td>44 (73.3%)</td>
</tr>
<tr>
<td><strong>Clinical remission</strong></td>
<td>47 (38.8%)</td>
<td>41 (33.9%)</td>
<td>24 (40.0%)</td>
</tr>
<tr>
<td><strong>Mucosal healing</strong></td>
<td>75 (62.0%)</td>
<td>73 (60.3%)</td>
<td>41 (68.3%)</td>
</tr>
</tbody>
</table>

Summary level data obtained from Rutgeerts et al, 2005\(^9\), and Hyams, et al., 2012\(^{10}\). Placebo response not shown. Other information found Gastrointestinal AC meeting on this link: [http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/GastrointestinalDrugsAdvisoryCommittee/UCM266697.pdf](http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/GastrointestinalDrugsAdvisoryCommittee/UCM266697.pdf)
**“Cursory” extrapolation**

**Step 1:** Assume combined placebo response in adults is the same as placebo response in pediatrics.

**Step 2:** Check pediatric clinical response within reasonable range of adult response.

**Step 2:** Compare confidence interval limits.

- 73.3 (61.0, 82.9)
- 61.0 > 39.3
- 33.2 (27.6, 39.3)
Bayesian extrapolation

Step 1: Predict placebo response rate in pediatric trial

Step 2: Incorporate adult information to estimate pediatric clinical response

Step 3: Compare credible interval limits of the estimated pediatric clinical response and predicted placebo response rate.

"Cursory"

73.3 (61.0, 82.9)

33.2 (27.6, 39.3)

Bayesian

71.3% (61.4, 80.4)

35.3% (31.7, 48.3)

Pr(Inf>Pred.Pbo)=1

Bayesian extrapolation turns out more conservative!
Example 2: Bayesian Design

- **Treatment:** Trt
- **Indication family:** Analgesia
- **Objective:** Design Pbo-controlled Fixed Sample design in pediatrics borrowing results from adult data

**Assumptions:**
- Partial extrapolation applicable
- Pediatric study uses the same endpoint/measurement and time of assessment

**Scenarios of Truth:**
- Effect sizes: 0, **0.15**, 0.30, 0.325, 0.35;
- SD: 3.789

\[
\text{Adult Pbo N}(-3, 0.98^2); \quad \text{Trt N}(-4.3, 0.98^2)
\]
Success is defined as $\Pr(\text{Trt} > \text{Placebo}) > 0.975$

Simulated average conditional power can also be calculated given that treatment effect has a distribution over a certain range.

Expected sample size can be further in either scenario (informative or diffuse) reduced using group sequential/adaptive designs.

*Discounted Prior $Pbo \ N(-3, 0.98^2)$; $\text{Trt} \ N(-3.65, 0.98^2)$ – this is a less optimistic informative prior
Ensuring interpretability and robustness

- Alignment of adult and pediatric clinical trial
  - **Dose** needs to be correct!
  - Emphasis on **sufficient quality of data** from adult population, e.g., Study design, Data collection, Measurement

“Unquantifiable” sources of bias if there are differences in patient populations

- Constrained/robust prior (avoid too much optimism!)
Example: ECMO Trial – Response Adaptive Randomization (RAR)

Two arm trial comparing Extracorporeal Membrane Oxygenation (ECMO) and Conventional Medical Therapy (CMT) for treatment of Persistent Pulmonary Hypertension in newborns (Bartlett, 1985)

**Part 1:** 1:1 randomization
Until 4 deaths on an arm

- ECMO
- CMT

**Part 2:** “Play the winner”
Randomize to best arm until 4 deaths OR stat. significance

- ECMO – OR – CMT
After part 1,

- ECMO – 9 survived out of 9
- CMT – 6 survived out of 10

**Part 1: Estimated Survival**

- Evidence suggests ECMO superiority
- P-value: 0.116

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**ECMO Part 2: Adaptation & Final Data – What was learned from part 2?**

- Given the data & design, the trial allocated future patients to ECMO until 4 deaths or stat. significance
- Result: **ECMO 19** survived out of **20**

**Part 2: Estimated Survival**

- ECMO Likelihood: Part 1 + Part 2
- CMT Likelihood: Same as Part 1

**Part 2: Estimated Difference in Survival**

- Part 2 data increases the likelihood that ECMO is superior
- Unadjusted P-value: 0.015
ECMO: Adaptation, Efficiency & Alternatives

- Part 1 + Part 2 ECMO was superior to CMT (statistically significant)
- Did not provide a dramatically different precision on difference (see histogram)
- Hypothesis test versus estimation
- Uncertainty driven by CMT rate
  - How many patients on CMT?
- Alternative designs?
What prior information was available?

- Clinical experience - CMT mortality ~80%
- Previous ECMO trial with 12 patients (11/11 ECMO Survived, 0/1 CMT survived) (Bartlett, 1985)
Bayesian analysis & incorporating historical data

♦ Bayesian methods offer a means to incorporate historical information in a quantitative manner.
ECMO Revisited – Bayesian analysis & incorporating historical data

Bayesian Evidence Synthesis (illustration)

- Literature & Trials
- Case Reports
- Expert Opinion
- Prior
- ECMO Prior
  - Expect: 80%
  - N Equivalent: 4
- CMT Prior
  - Expect: 40%
  - N Equivalent: 10

Key points

- Meta-analysis to quantify the prior
- Consider the amount of information to “borrow” from historical data
- Methods available to adaptively borrow from historical data
ECMO Revisited – Bayesian analysis & incorporating historical data

Bayesian Modeling and Analysis

♦ Prior + Data to generate posterior

Key points

• Leveraging prior data in analysis
• The influence of the prior can be assessed
• Bayesian probability statements about the likelihood that ECMO > CMT (rather than p-values)
  • E.g. \( \text{Prob(Survival ECMO-CMT > 20\%)} = 0.97 \)
ECMO Example – Discussion and Key Points

♦ Ultimately the ECMO trial proved controversial

♦ UK Collaborative ECMO Trial (1993-1995) – Evaluate survival and morbidity (cost effectiveness)
  • Trial stopped early by DSMB (mortality outweighed potential differences in morbidity
    – ECMO survival 63/93 = 68%
    – CMT survival 38/92 = 41%
    – Relative risk: 0.55 (95% CI 0.39—0.77; p=0.0005)

♦ What design would have made the UK trial unnecessary?
Example: Pediatric PAH Study: Issues

Uncertainty

• Little information available to design study
  – Different primary endpoints and powering for FDA & EMA
  – Duration differences for endpoints

• Need a clear positive or negative result for labeling
  – Requires estimate of variability to right size the study
  – Rare disease in pediatric population <1000 cases globally

Urgency

• No approved therapy in pediatrics
  – Expected to be difficult to enroll
  – Need study to complete prior to patent expiration
Estimating Variance

- **Historical information**
  - 1 pediatric study (differences in population)
  - 3 adult studies
    - 2 studies same treatment mechanism as pediatric study
    - 1 study same treatment as pediatric study under design

- **Endpoint for FDA (invasive biomarker)**

- **Bayesian Approach**
  - Estimate the variance from the “posterior” of the historic pediatric study
  - Utilize the adult studies as the prior
**Power Prior on SD Mean Change**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>$s_0$</td>
<td>SD from the 3 adult studies (prior for pediatric study)</td>
</tr>
<tr>
<td>$s$</td>
<td>SD from the pediatric study</td>
</tr>
<tr>
<td>$\sigma^2_1, \sigma^2_2$</td>
<td>Variance for individual response for placebo and treatment respectively</td>
</tr>
</tbody>
</table>

\[ \alpha_0 = 0.25 \text{ down-weight adult studies; } \alpha_0 = 1 \text{ equally-weight adult studies} \]

**Parameter Definition**

Since variances are proportional to chi-square, assume:

\[ (n_{ik} - 1)s_{ik}^2/\sigma_k^2 \sim \chi^2(n_{ik} - 1) \]

<table>
<thead>
<tr>
<th>$s_{ik}$</th>
<th>SD from study $i$ and arm $k$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$n_{ik}$</td>
<td>Number of patients from study study $i$ and arm $k$</td>
</tr>
</tbody>
</table>
Power Prior on SD Mean Change

Pediatric study greater variability
Down-weighting resulted in a more conservative estimate
# Power Prior on Treatment Mean Differences

## Posterior of Effect Size

\[ \pi(\mu, \tau, \delta_1^2, \delta_2^2 | y_0, y, \alpha_0) \]

\[ \propto \pi(\mu, \tau, \delta_1^2, \delta_2^2) \cdot L(y_0 | \mu, \tau, \delta_1^2, \delta_2^2)^{\alpha_0} \cdot L(y | \mu, \tau, \delta_1^2, \delta_2^2) \]

## Parameter Definition

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<thead>
<tr>
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<tbody>
<tr>
<td>(y_0)</td>
<td>LSMeans from the 3 adult studies (prior for pediatric study)</td>
</tr>
<tr>
<td>(y)</td>
<td>LSMeans from the pediatric study</td>
</tr>
<tr>
<td>(\mu)</td>
<td>Placebo effect</td>
</tr>
<tr>
<td>(\tau)</td>
<td>Placebo-adjusted treatment effect (parameter of interest)</td>
</tr>
<tr>
<td>(\delta_1^2, \delta_2^2)</td>
<td>Variability of LSMeans across studies for placebo and treatment respectively</td>
</tr>
</tbody>
</table>

Non-informative priors used on \(\mu, \tau\) (normal) and \(\delta_1^2, \delta_2^2\) (inverse-gamma)

## Modeling

Modeling utilized to estimate expected effect size

Expected to be safer but with similar efficacy to previous pediatric trial
IA for Early Stopping at ~60% Information
Pocock Spending Function
If success is met with invasive biomarker, discontinue measurement, may continue for EMA endpoint

<table>
<thead>
<tr>
<th>Design Element</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Planned Total N</td>
<td>121 completers, 134 enrolled</td>
</tr>
<tr>
<td>Proposed Type 1 Error</td>
<td>1-sided 0.05</td>
</tr>
<tr>
<td>Alpha Spending Function</td>
<td>Pocock</td>
</tr>
<tr>
<td>Interim Information</td>
<td>Information Fraction</td>
</tr>
<tr>
<td></td>
<td>60%</td>
</tr>
<tr>
<td></td>
<td>100%</td>
</tr>
</tbody>
</table>

M&S Effort
- Used East
- Scenarios across range of alpha, efficacy and variability

Proposed Design
~85% power, ~65% early success for expected scenarios
Proposed Design

• Type I error 1-sided 0.05
  – Rare disease with few patients
  – Poor prognosis

• Powered on expected effect size
  – If enrolled ALL existing patients, may not be sufficient to power on a minimal effect size

• GSD: Pocock spending function
  – Early stopping for efficacy only
    • Unlikely to meet high hurdle needed to declare futility
Feedback

• **Power on minimal effect size**
  – Agreement on Bayesian methodology to assess variance
  – Proceeding with powering on expected effect size at risk

• **Type 1 error rate 2-sided 0.05**
  – Biomarker endpoint
  – Single study

• **GSD sponsor risk**
  – Interim results must be definitive
  – Minimum interim timing discussed
Pediatric Type 2 Diabetes Efficacy Study

• Indication: Pediatric Type 2 Diabetes
  – Relatively rare but increasing incidence in children and adolescents
  – “More common in certain racial and ethnic groups such as African Americans, American Indians, Hispanic/Latino Americans, and some Asian and Pacific Islander Americans”*
  – Requires recruiting patients with health disparities and reduced access to care

• Key Uncertainties
  – Unknown effect size of the drug on HbA1c
  – Uncertainty variability in HbA1c
  – Uncertain recruitment and retention rate

Overview of Designs

• **Efficacy study** – 1 dose arm versus placebo on background of standard of care (Diet/exercise, w/ or w/o metformin or insulin)
  – 26 weeks duration
  – Primary Objective: Reduction in HbA1c
  – Design Goal: 90% power for -0.6% reduction in HbA1c
Design Options

• Designs Considered
  – Fixed Design – 150 patients
    • Given key uncertainties – Consider adaptive approaches to ensure appropriate power for labeling
  – Adaptive Designs utilizing sample size re-estimation (SSR)
    • Option 1: Blinded sample-size re-estimation (SSR)
    • Option 2: Information based SSR
    • Option 3: Unblinded Sample-size Re-estimation using Promising Zone Technique
Sample size re-estimation

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</thead>
<tbody>
<tr>
<td>( f )</td>
<td>Retention Rate</td>
</tr>
<tr>
<td>( \mu )</td>
<td>Mean Difference (Treat – Placebo)</td>
</tr>
<tr>
<td>( \sigma )</td>
<td>Standard Deviation</td>
</tr>
</tbody>
</table>

Sample size per group

\[ N = 4 \left( \frac{z_{1-\alpha} - z_{1-\beta}}{\mu/\sigma} \right)^2 \left( \frac{1}{1 - f} \right) \]

IA for SSR

Model the interim data to re-estimate the sample size needed to maintain power
The data we observe at a blinded interim.

Adaptive Option 1: Blinded SSR – uses only these data to re-estimate sample size.

\( \sigma_{\text{blinded}} \)
Understanding Each SSR Option

The data we **don’t** observe during blinded SSR. Unknown treatment effect explains some of the variability

![Diagram showing change from baseline, unblinded mean and standard deviation, blinded mean and standard deviation, and the relationship between them.]

Adaptive Option 2: Information based SSR
- Uses $\sigma_{\text{unblinded}}$ to re-estimate sample size

Adaptive Option 3: Unblinded SSR
- Uses $\mu_{\text{unblinded}}$ and $\sigma_{\text{unblinded}}$ to re-estimate sample size

$$N = 4 \frac{(z_{1-\alpha} - z_{1-\beta})^2}{(\mu/\sigma)^2} \left( \frac{1}{1 - f} \right)$$
Assessing design performance

- Each design option was simulated across a range of scenarios of truth
  - Evaluated on ability to maintain 90% power for effect of -0.6% HbA1c Effect
  - Simulated using combination of software: R and East

- Information based SSR performed the best across scenarios:

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Mean Effect</th>
<th>Sigma</th>
<th>Fixed Design</th>
<th>Blinded SSR</th>
<th>Information Based SSR</th>
<th>Unblinded SSR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expected</td>
<td>↔</td>
<td>↔</td>
<td>Green</td>
<td>Green</td>
<td>Green</td>
<td>Green</td>
</tr>
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<th>Scenario</th>
<th>Design Performance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name</td>
<td>Mean Effect</td>
</tr>
<tr>
<td>Expected</td>
<td>↔</td>
</tr>
<tr>
<td>Higher Variability</td>
<td>↔</td>
</tr>
<tr>
<td>Lower Effect</td>
<td>↓</td>
</tr>
<tr>
<td>All Higher</td>
<td>↑</td>
</tr>
</tbody>
</table>
Discussion

- Bayesian methods and Adaptive Design have many applications to improve Pediatric Trial Design
  - Topics covered:
    - Extrapolation to leverage adult data
    - Informative Priors
    - Adaptive Design - Adaptive randomization, group sequential design, sample size re-estimation
References

2. CTTI. Pediatric trials in antibacterial development. https://www.ctti-clinicaltrials.org/file/16/download?token=Garh7Fl4