Bayesian Techniques Using Historical Controls in Clinical Trials
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Introduction
• Historical data refers to data which was collected prior to the start of a trial i.e. data from a previous study or other published data. Large amounts of clinical data may be available prior to the start of a study.
• Historical data is commonly used in the design of a trial e.g. to aid in sample size calculations or to determine a threshold for success. It is only recently that it’s been considered in the analysis of a trial.
• What are some of the approaches when using historical data in the analysis of a trial, and what are the benefits? How about any areas of caution?

Historical Control: Data Considerations
To use historical control data in the analysis of a trial, we need to consider:
- Similarities between historical and current data (e.g. patient demographics such as age, gender).
- Consistency in trial design.
- Geographical location of the studies.
- Pocock (1976) suggests further criteria which should be similar such as inclusion/exclusion or type of study design.

Generally, more data is replaced when historical and current data are most similar.

Two possible approaches to bring in historical control data:

1. Replace current control data with historical data
2. Substitute a proportion of current control data with historical control data

Methodology

Bayesian methods are a way of using historical data in analyses. Two Bayesian methods which discount historical data: Power Prior and Meta-Analytic-Predictive (MAP) Prior.

Bayesian Posterior Distribution (Traditional Form):

\[ p(\theta|D) \propto L(\theta|D) \pi(\theta) \]  

where \( D \) represents the data and \( \theta \) is the model parameters.

Power Prior Approach

- Power prior distribution:

\[ \pi(\theta|D, a_0) \propto L(\theta|D) a_0^{a_0} \pi(\theta) \text{ with } 0 \leq a_0 \leq 1 \]  

where \( D_0 = (n_0, y_0, X_0) \) is the historical data.
- Posterior distribution for Power Prior: \( \pi(\theta|D, a_0) \) replaces \( \pi(\theta) \) in equation (1).
- \( a_0 \) generally chosen based on similarity of historical to current trial.
- \( a_0 \) can be fixed or can consider a prior on \( a_0 \).

Meta-Analytic-Predictive (MAP) Approach

- Create random-effects model on historical data. Following this obtain predictive distribution of \( \theta^* \).
- Use this predictive distribution to construct a prior on \( \theta^* \) and use it in the current analysis.

Method is prospective. \( \theta^* \) is stated at the design stage.

Results: Power Prior

Simulated Data
• Considered patients: 150 active, 150 current control, 100 historical control.
• 2 treatment groups. Historical and current control receiving same. Endpoint: Normal. \( a_0 \) fixed. Non-informative priors. Parameters: Sigma, slope and intercept estimated using PROC MCMC.

Note: Sigma = Standard Deviation of the response.

Results
• Figure 1: Bringing in historical data has lowered sigma.
• Figure 2: Can see effect of poorly chosen data on sigma: bringing in historical data has increased sigma.
• Width of confidence intervals for sigma slightly larger in Figure 2.

Interpretation
• Similar results. Slope: Similar results - slope estimate decreased with addition of poorly chosen historical data.

Historical Control: Pros and Cons

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<th>Pros</th>
<th>Cons</th>
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<td>• More efficient trial design due to smaller sample size required.</td>
<td>• Need to consider biases (E.g. Type I error, Power).</td>
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<td>• Decreased trial cost.</td>
<td>• Logistics – was data collected in a similar format?</td>
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<td>• Beneficial for rare diseases: It can be difficult to recruit patients.</td>
<td>• More time needed for study design (however overall trial time is reduced).</td>
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<td>• Less patients on placebo or control arm – more ethical e.g. for Oncology trials it would not be ethical to give placebo, or even in some cases control.</td>
<td>• Considered statistically more challenging.</td>
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<td>• Accelerate overall trial time and thus accelerate clinical decision timelines.</td>
<td>• Regulatory bodies may be less familiar/accepting of approach.</td>
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Conclusion
• Historical control data can accelerate clinical decision timelines, amongst other benefits.
• Care to be taken when incorporating and choosing historical control data.
• Various methods are available for the analysis.
  - Some Bayesian techniques for analysis: Power prior, MAP.

References