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:

Replace current control data with historical data **Or** 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):

$$p(\boldsymbol{\theta}|\mathbf{D}) \quad \alpha \quad \underbrace{L(\boldsymbol{\theta};\mathbf{D})}_{\text{Likelihood given the data}} \; \underbrace{\pi(\boldsymbol{\theta})}_{\text{Prior distribution}} \qquad (1)$$

where **D** represents the data and **θ** is the model parameters.

Power Prior Approach

- Power prior distribution:

$$\pi(\boldsymbol{\theta}|\mathbf{D}_0, a_0) \quad \alpha \quad \underbrace{L(\boldsymbol{\theta}|\mathbf{D}_0)^{a_0}}_{\text{Likelihood given historical data}} \; \underbrace{\pi_0(\boldsymbol{\theta})}_{\text{Prior of theta before } \mathbf{D}_0 \text{ is observed}} \qquad \text{with } 0 \le a_0 \le 1 \qquad (2)$$

(Scaling parameter: a_0)

where $D_0 = (n_0, \mathbf{y}_0, \mathbf{X}_0)$ is the historical data.

- Posterior distribution for Power Prior: $\pi(\boldsymbol{\theta}|D_0, a_0)$ replaces $\pi(\boldsymbol{\theta})$ 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 $\boldsymbol{\theta}^*$.

(Predictive parameters for future trials)

- Use this predictive distribution to construct a prior on $\boldsymbol{\theta}^*$ and use it in the current analysis.

Method is prospective. $\boldsymbol{\theta}^*$ is stated at the design stage.

Results: Power Prior

Figure 1: Caterpillar Plot: Well Chosen Historical Data, Sigma

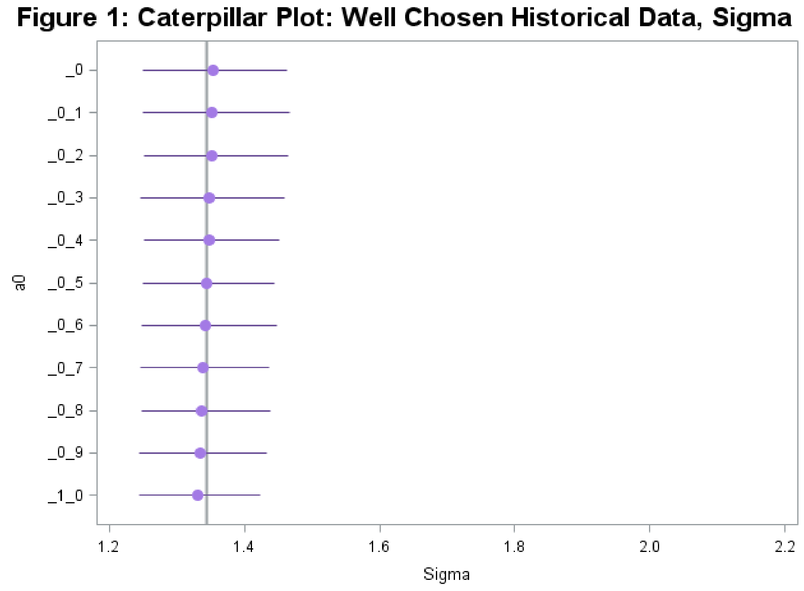
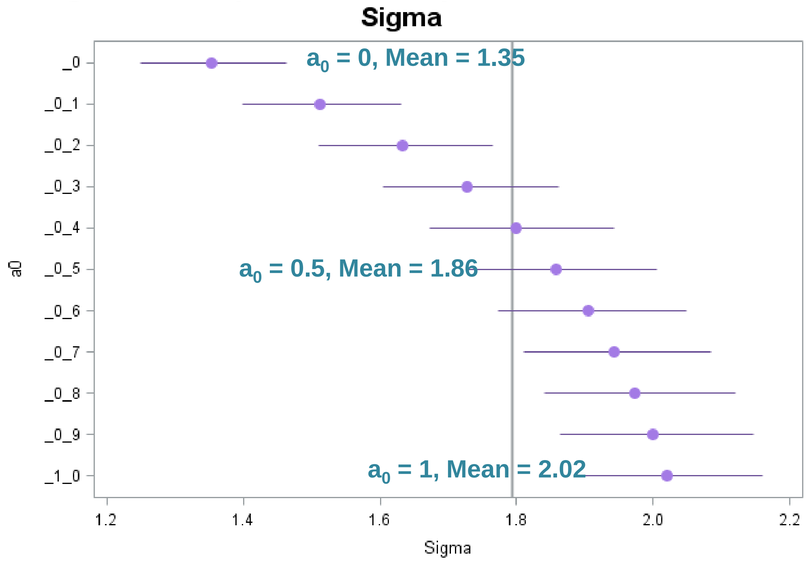


Figure 2: Caterpillar Plot: Poorly Chosen Historical Data, Sigma



Mixing: Good mixing for all parameters for well chosen and poorly chosen historical data.

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.

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

Historical Control: Pros and Cons

Pros	Cons
• More efficient trial design due to smaller sample size required. • Decreased trial cost. • Beneficial for rare diseases: It can be difficult to recruit patients. • 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. • Accelerate overall trial time and thus accelerate clinical decision timelines.	• Need to consider biases (E.g. Type I error, Power). • Logistics – was data collected in a similar format? • More time needed for study design (however overall trial time is reduced). • Considered statistically more challenging. • Regulatory bodies may be less familiar/accepting of approach.

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

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