Outside Help:
Can Bayesian Borrowing Help Supplement Limited Sample Sizes in Pediatric and Rare Disease Trials While Mitigating Risk of Bias?

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Disclosure

- Advisor at Inka Health, an HEOR analytics consulting company
- No conflicts of interest related to this presentation
- Opinions expressed are my own

Background

- Evaluating efficacy of therapies in rare disease settings presents unique challenges
  - May be extremely **difficult to recruit** enough patients to adequately power a conventional randomized controlled trial (RCT)
  - Ethical considerations **could preclude use of a concurrent control arm or placebo control**
- Similar challenges can arise in pediatric trials
- Growing receptiveness to the use of Bayesian borrowing methods and synthetic or hybrid control arms where conventional trials are impractical/infeasible[1,2,3]

[1] US FDA. Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials. Guidance for Industry and FDA Staff. 2010.
[2] US FDA. Adaptive Designs for Clinical Trials of Drugs and Biologics Guidance for Industry. 2019.
[3] US FDA. Interacting with the FDA on Complex Innovative Trial Designs for Drugs and Biological Products: Guidance for Industry. 2020.

Rationale for External Borrowing

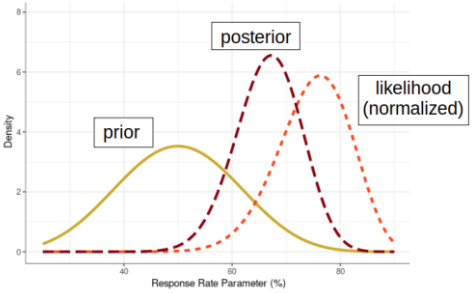
- Can we supplement limited sample sizes in pediatric or rare disease trials by incorporating external data?
- Perhaps we could
  - Augment a **concurrent control arm** in an RCT using historical controls and allocate more patients to the experimental arm
  - Augment limited **pediatric trial** sample sizes by borrowing some patients from similar trials in adult populations
  - Compare a **single arm trial vs. an external control arm** constructed from historical controls or real-world data
- Need to exercise caution in choosing external data sources!

Why Use a Bayesian Approach for Rare Diseases?

- Provides a principled framework for incorporating external information:
  - Start with our prior (which can be informed by external data)
  - Update our beliefs after observing new data

$$p(\theta \mid \text{Data}) = \frac{p(\text{Data} \mid \theta) \cdot p(\theta)}{p(\text{Data})}$$

posterior; likelihood (contribution of new data); prior; normalizing constant



- Conducive to sequential 'Bayesian updating'
- Posterior inference allows us to **quantify the amount of evidence** in favour of a conclusion and allows for more **nuanced decision rules**
- See Mackay & Springford (2023) for additional discussion[4]

[4] Mackay EK, Springford A. Evaluating treatments in rare indications warrants a Bayesian approach. Frontiers in Pharmacology. 2023.

How Should we Go About Borrowing?

- Borrowing from an **external data source** not subject to randomization **could introduce bias** in our effect estimates
- Would be desirable to
  1) Down-weight the contribution of the external data--i.e. control the amount of borrowing
  2) Reduce the amount of borrowing when outcomes are heterogeneous across our data sources ("**dynamic borrowing**")
- **Key aim is to borrow to increase precision while being mindful of potential to introduce bias**
- See Viele et al.[5] and Neuenschwander & Schmidli[6] for a more detailed introduction to borrowing historical control data

[5] Viele K, Berry S, Neuenschwander B, Amzal B, Chen F, Enas N, Hobbs B, Ibrahim JG, Kinnersley N, Lindborg S, Micallef S. Use of historical control data for assessing treatment effects in clinical trials. Pharmaceutical statistics. 2014.

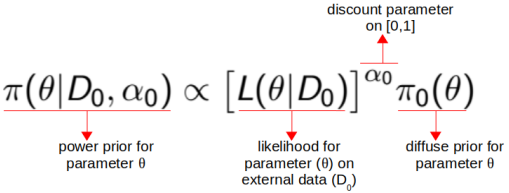
[6] Neuenschwander B, Schmidli H. Use of historical data. In Bayesian methods in pharmaceutical research. 2020. (pp. 111-137). Chapman and Hall/CRC.

Prior-Based Approaches to Borrowing

- Idea is to incorporate the external data into the formulation of a prior
- Advantages:
  - Can pre-specify a prior or a basis for constructing a prior prospectively (e.g. to augment a small concurrent control arm for an RCT, etc.)
  - Static or dynamic down-weighting of the contribution of the external data can be incorporated
- Will focus on two prior-based approaches:
  - Power priors
  - Meta-analytic predictive (MAP) priors

The Power Prior

- Power priors[7,8]:
  - Down-weight the contribution of the external data by means of a discount parameter, α_0, with values between 0 and 1



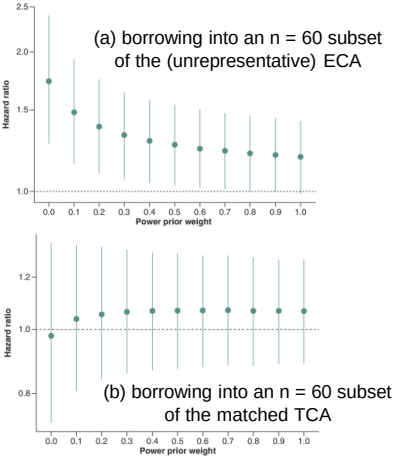
  - As $\alpha_0 \rightarrow 0$ we ignore the external data (**no pooling**)
  - As $\alpha_0 \rightarrow 1$ we give it full weight (**full pooling**)
- Several approaches to choosing α_0: 'tipping point' approach[9], target effective sample size for borrowing[10], dynamic borrowing based on consistency between data sources[8]

[7] Ibrahim JG, Chen MH. Power prior distributions for regression models. Stat. Sci. 2000.
[8] Ibrahim JG, Chen MH, Gwon Y, Chen F. The power prior: Theory and applications. Statistics Med. 2015.
[9] Best N, ..., Keene ON. Assessing efficacy in important subgroups in confirmatory trials: An example using Bayesian dynamic borrowing. Pharm. Stat. 2021.
[10] Richeldi L, ..., Maher TM. Trial of a preferential phosphodiesterase 4B inhibitor for idiopathic pulmonary fibrosis. NEJM. 2022.

Static Borrowing using a Power Prior: An Example

- Example from Struebing et al. (2024)[11]
- Goal was to replicate the results of an RCT by
  - Constructing an external control arm (ECA) from real-world data
  - And augmenting limited sample sizes in the ECA by borrowing from a historical control arm
- ECA analysis failed to replicate RCT results for chemotherapy with or without cetuximab in first-line (1L) non-small cell lung cancer (NSCLC)
- Bayesian borrowing was conducted using a static power prior with a sliding scale of fixed borrowing weights (tipping point approach)

Posterior medians and 95% credible intervals for the hazard ratio for different Bayesian borrowing weights

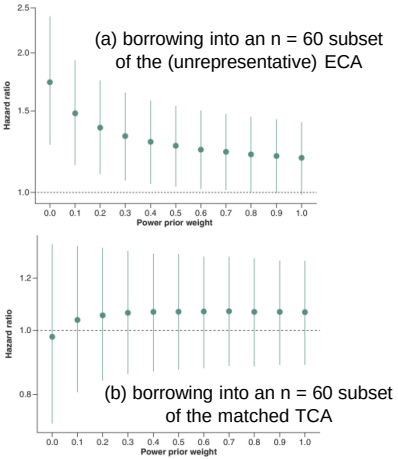


[11] Struebing A, McKibbon C, Ruan H, Mackay E, Dennis N, Velummailum R, He P, Tanaka Y, Xiong Y, Springford A, Rosenlund M. Augmenting external control arms using Bayesian borrowing: a case study in first-line non-small cell lung cancer. JCER. 2024.

Static Borrowing using a Power Prior: An Example

- Borrowing from the historical control was able to
  - Mitigate bias from the real-world ECA
  - Improve precision (especially when supplementing a small ECA of n = 60 patients)
- Also demonstrated approach for an ‘ideal scenario’ where the trial control arm (TCA) in the RCT was used as a ‘hypothetical ECA’
- Takeaway: worth considering whether Bayesian borrowing approaches can be used to provide a structured means for incorporating additional external data sources (including aggregate data) beyond our ECA alone

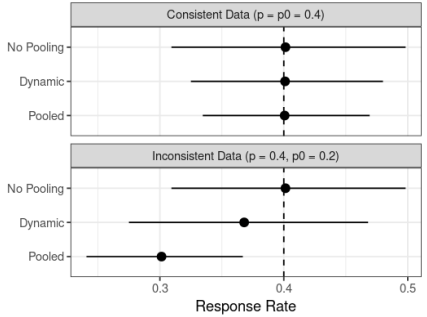
Posterior medians and 95% credible intervals for the hazard ratio for different Bayesian borrowing weights



Dynamic Borrowing using a Power Prior: An Example

- Example derived from Mackay & Springford (2023)[12]
- Goal is to partially borrow information from an external data source to improve precision of response rate estimates for SoC treatment
- Sample sizes $n = n_0 = 100$, response $p = 0.4$, vary p_0
- Want to 'learn' amount of borrowing—we treat α_0 as a parameter with Beta(1, 1) prior
- Consider two scenarios:
  1) Response rates consistent between data sources
  2) Response rates inconsistent

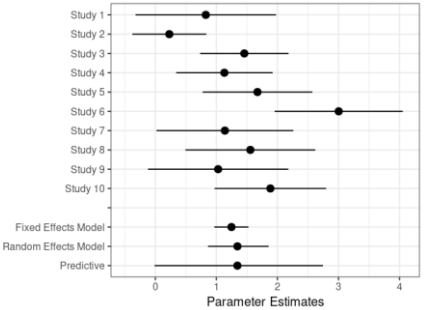
- Improved precision when data sources are compatible and reduced borrowing (reduction in bias) when data sources are incompatible



[12] Mackay EK, Springford A. Impact of Hyperprior Choice for Bayesian Dynamic Borrowing via a Normalized Power Prior. JSM Proceedings. Alexandria, VA: American Statistical Association. 2023 Oct. https://doi.org/10.5281/zenodo.10001953

Meta-analytic Predictive (MAP) Priors

- Meta-analysis approach to construct an informative prior (e.g. for the average response under a SoC treatment)[13]
- Since response may vary across trial populations, we want our prior to incorporate both **within-trial** and **between-trial uncertainty**
- Idea is to conduct a random-effects meta-analysis and use the posterior predictive distribution (predicted SoC response in a new trial) as our prior



- Robust MAP approach instead uses a weighted mixture between the MAP prior and a vague prior[14] and has seen recent uptake

[13] Neuenschwander B, Capkun-Niggli G, Branson M, Spiegelhalter DJ. Summarizing historical information on controls in clinical trials. Clinical Trials. 2010.
[14] Schmidli H, Gsteiger S, Roychoudhury S, O'Hagan A, Spiegelhalter D, Neuenschwander B. Robust meta-analytic-predictive priors in clinical trials with historical control information. Biometrics. 2014.

Thank You!

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