The Benefits and Risks of Borrowing Historical Placebo Data in Early Phase Randomized Control Trials

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Outline

- Context of Early Phase Trials
- Overview of Borrowing Historical Data
- Challenges and Benefits of Borrowing in General
- Methods of Borrowing Data
- Conclusions

Context of Early Phase

- First-in-Human and First-in-Patient studies
- Studies are often limited at this stage of development (long-term extensions not possible due to tox coverage; Active comparator studies too time-consuming)
- Problem: How do we design proof-of-concept (POC) studies under these limitations that will also finish in a timely manner?

High Demand for Patients

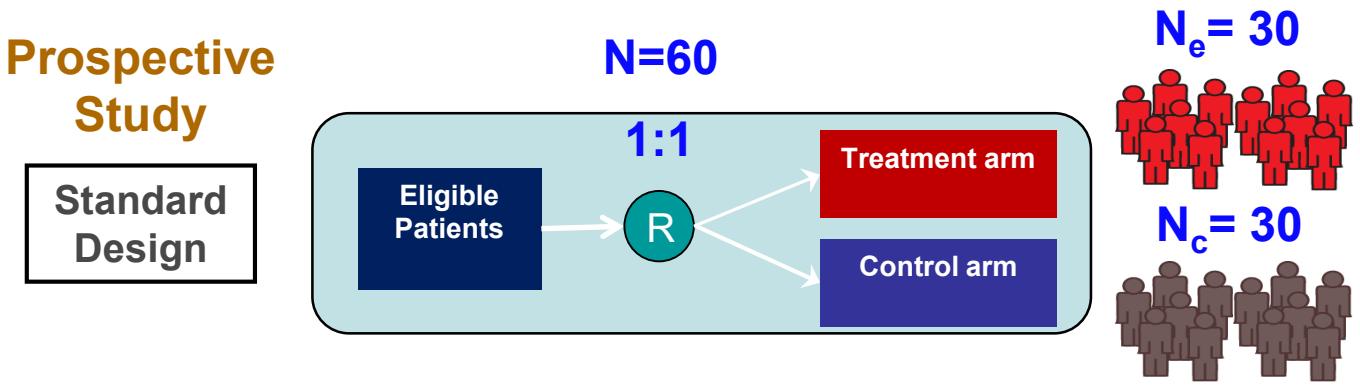
- Includes 30 Phase 3 or Phase 4 studies, all of which can offer either a proven drug and/or long-term dosing
- High-prevalence diseases draws a lot of competition
- With high competition, enrollment rates suffer universally

*As of 02Oct2019

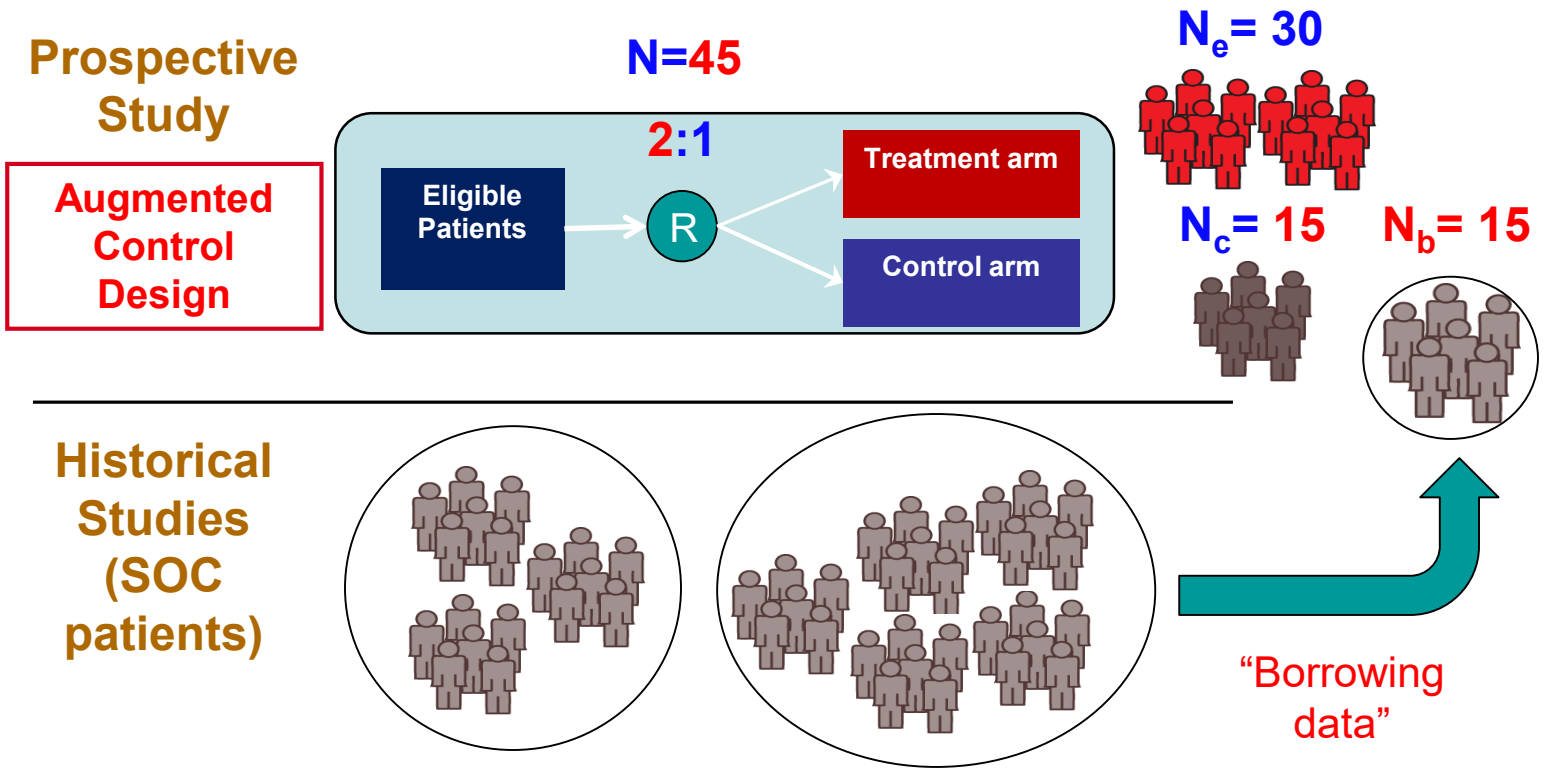
Making the Most out of Our Patients

- Powering a POC study is getting increasingly tricky due to either
  - Not enough patients to go around, or
  - Not enough patients period
- But, POCs must produce robust, timely results in order to deliver novel medicines to patients
- Can we use what we (and others) have learned to streamline future POC studies?

Standard Phase IIa Design

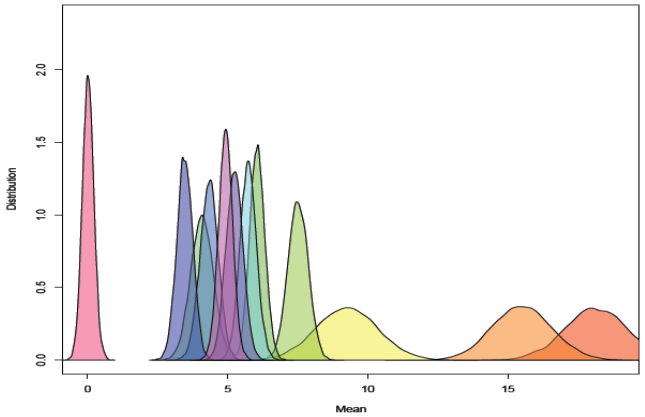


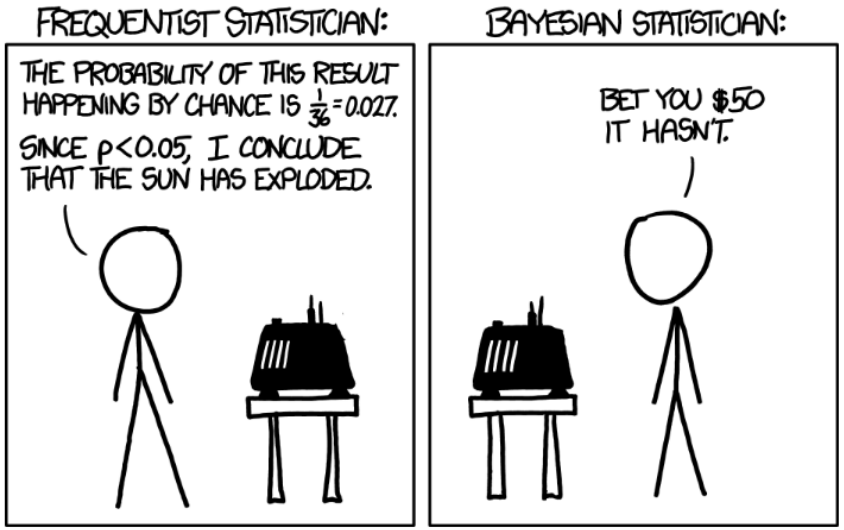
Alternative Phase IIa Design



Bayesian Augmented Controls

- The Bayesian paradigm is ideally structured to incorporate the use of historical information
- Historical data already captured commonly through Bayesian Network Meta Analyses





https://xkcd.com/1132/

General Considerations of Borrowing

- Key Assumption: Exchangeability of the historical data with the data in the prospective study
- How much information to borrow needs to be determined
  - How much data is available?
  - How sensitive will the posterior be to the information in the prior?
- It is vital that the method for incorporating historical data in inference be prespecified and independent of study outcome

General Considerations of Borrowing

- In general, the sources/amount of data to borrow should not be chosen based on manual optimization of the prospective treatment's effect
  - i.e. Don't choose to borrow only the placebo patients that failed treatment

- Consequentially, borrowing might dampen the treatment effect of the current trial
  - So borrowing will not always favor the sponsor of the current trial

General Considerations of Borrowing

- Potential Benefits:
  - Improved estimation of effects
  - Improve the operating characteristics of an existing study design
  - Reduce the sample size of a study while maintaining the operating characteristics
  - Adjust the randomization ratio of a study while maintaining the operating characteristics
  - All are especially important for small, early phase studies
- Potential Risks
  - Negative impact on operating characteristics if substantial difference between enrolled and historical populations

Potential Data Sources

- Expert opinion
- Summary level data (RCTs, observational)
  - Publications
  - CTR results
- Individual-level patient data
  - Internal to Sponsor or at FDA (or other regulators)
  - Patient registries
  - Observational studies
  - TransCelerate's Placebo and Standard of Care (PSoC) initiative

How Do We Borrow? 3 Examples

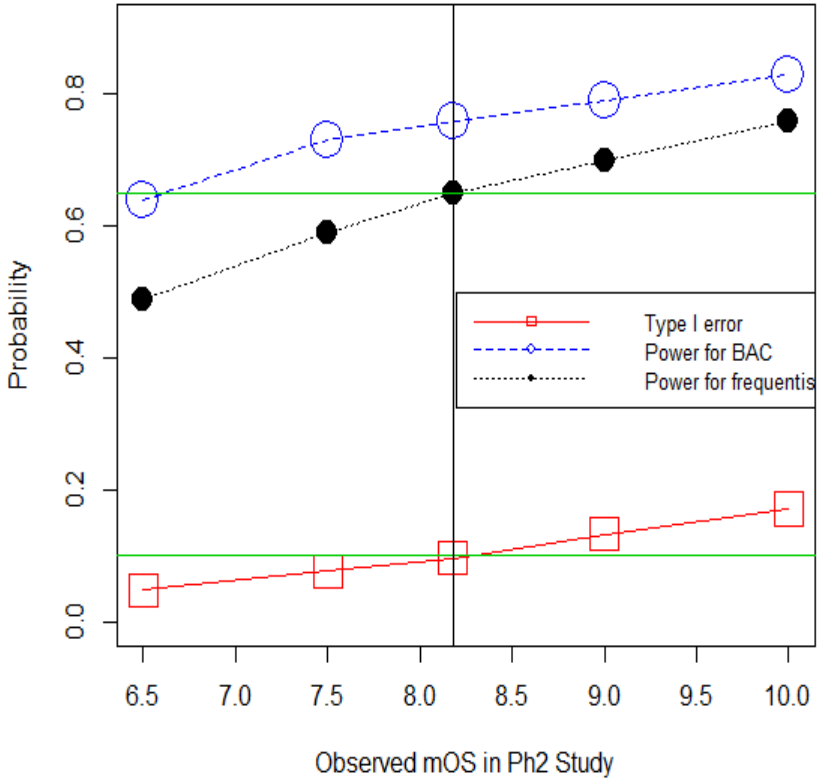
1. Static Borrowing using Informative Priors
   - Patient-level or summary-level data
2. Dynamic Borrowing
   - Mixture Priors, Hierarchical modeling, etc.
   - Patient-level or summary-level data
3. Matched Borrowing using propensity score
   - Patient-level data only

Static Borrowing

- A pre-specified amount of historical data is included in the analysis, often through the use of an informative prior distribution
- Types of Static Borrowing:
  - Pooling: Group all the patients together
  - Single-arm trials
  - Power priors

Static Borrowing (Example)

- Consider an example where a strong informative prior is used in a safety study
- Power naturally increases as the observed median overall survival (mOS) increases
- However, Type I error can also increase if the current placebo effect differs from the historical placebo effect



Dynamic Borrowing

- Blindly borrowing from a source dissimilar to the current study can compromise inference on the results.
- Dynamic borrowing controls the amount of data borrowed based on the similarity of the sources
- Types of dynamic borrowing:
  - Test then pool (Pocock, 1978)
  - Commensurate Priors (Hobbs et al, 2012)
  - Hierarchical Modeling
  - Mixture Priors

Mixture Priors: Oversimplified

Suppose you want to paint your bedroom blue. You have one can of blue paint.

Your neighbor says: “Hey, I have a can of paint! You can have it!” The neighbor’s can of paint is closed and unlabeled.

How helpful was your neighbor?

Mixture Priors: Oversimplified

Your Paint	Neighbor's Paint	Your Reaction
		Sweet! Two coats of paint!
		I could use some of this and get a thicker coat
		Ewww. No thanks.

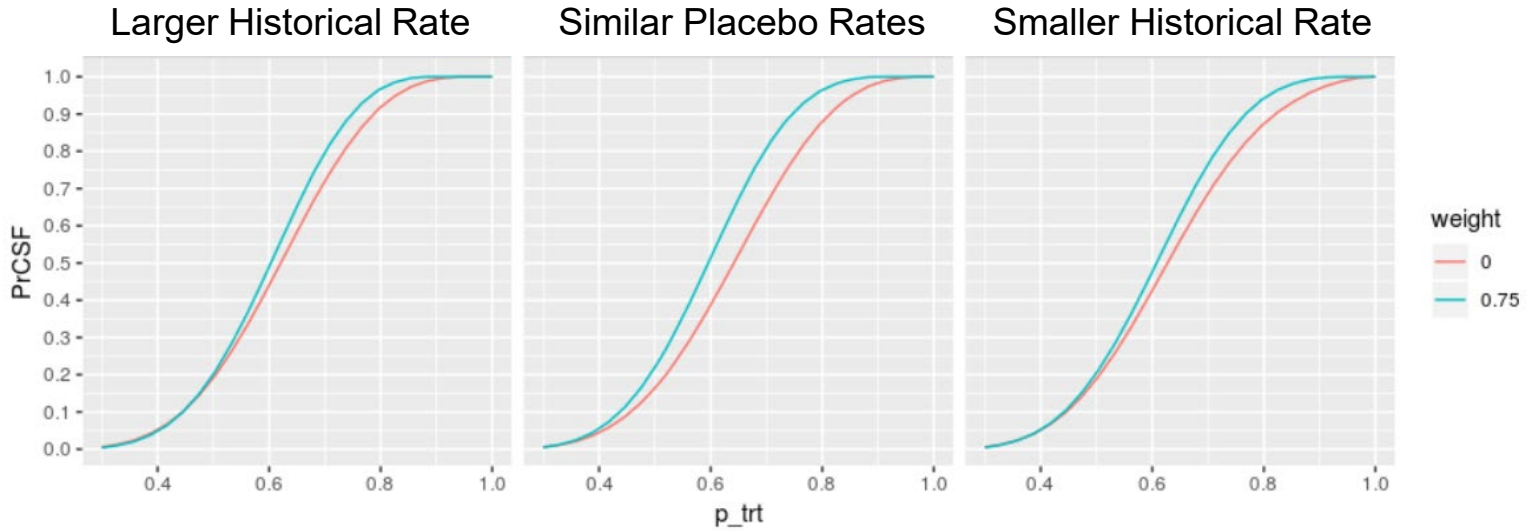
Dynamic borrowing models automatically decide how much information (paint) can be borrowed, depending on how similar the response rate (colors) are

Dynamic Borrowing (Dichotomous Mixture Prior)

$$
\begin{aligned}
y_{trt} &\sim \text{Bin}(n_{trt}, p_{trt}) \\
p_{trt} &\sim \text{Beta}(a_{trt}, b_{trt}) \\
y_{pbo} &\sim \text{Bin}(n_{pbo}, p_{pbo}) \\
p_{pbo} &\sim w_1 \text{Beta}(a_{pbo1}, b_{pbo1}) + (1 - w_1)\text{Beta}(a_{pbo2}, b_{pbo2})
\end{aligned}
$$

- Sum of a_{pbo1} and b_{pbo1} chosen to have an effective sample size equal to the number of desired borrowed patients
- Values of a_{pbo2} and b_{pbo2} often chosen to create a diffuse Beta distribution
- Weight parameter w_1 indicates sensitivity of borrowing, where $w_1 = 1$ indicates full borrowing and $w_1 = 0$ indicates never borrowing

Dynamic Borrowing (Example)

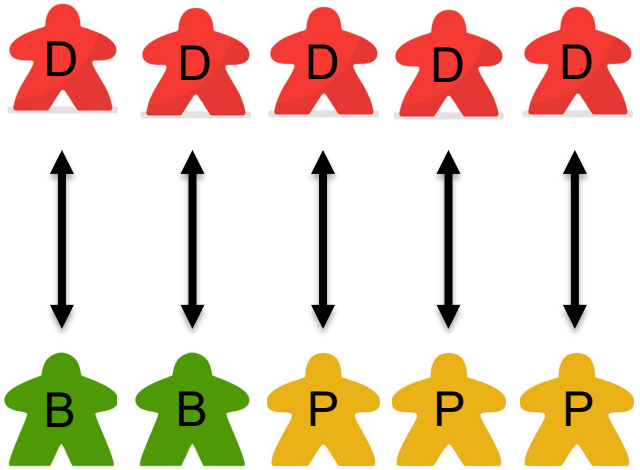


- Consider a scenario where we want to randomize 40 patients and borrow 20
- Power (based on a critical success factor) is greater for the mixture model (weight = .75) than no borrowing (weight = 0) even when the control placebo response rate is different than historical control, with similar type I error rates.

Borrowing by Propensity Score Matching

Introduced by Lin et al (2018)

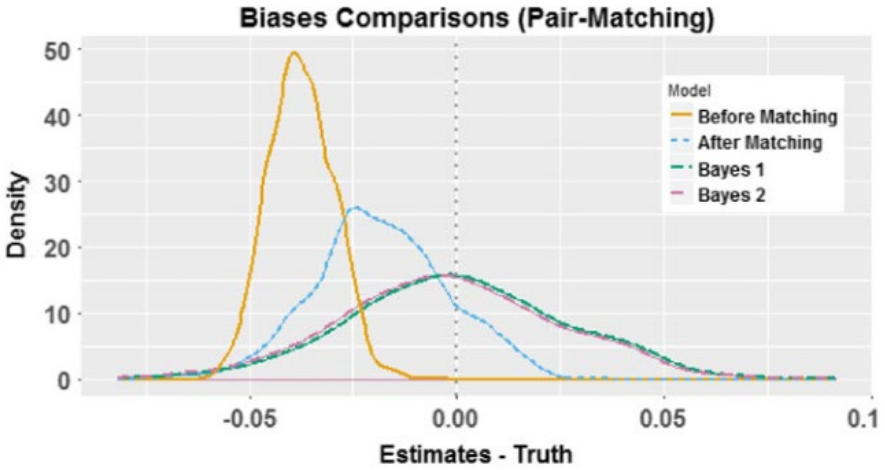
- Utilizes patient-level data
- Propensity scores based on fully known covariates are computed for each patient, enrolled and historical
- Patients on active drug in the prospective study are pair-matched with patients on placebo, with enough historical patients chosen to achieve 1:1 matching
- The estimated propensity scores of the borrowed historical patients are used as the weights in a power prior model



D = Drug, P = Placebo, B = Borrowed

Borrowing by Propensity Score Matching

- Liu et al assessed this method using a bootstrap simulation study from two studies
- Bias is greatly reduced by using the propensity scores in the power prior model, with great coverage in capturing the original treatment effect



Binomial-logistic
Beta-Binomial

	Trt. Eff. Mean (SD)	Trt. Eff. SD Mean (SD)	Bias Mean (SD)	Coverage	Power	Cr.I. Width
Before matching	-0.0169 (0.0078)	—	-0.0376 (0.0078)	—	—	—
After matching	-0.0012 (0.0166)	—	-0.0219 (0.0166)	—	—	—
Bayes 1	0.0213 (0.0261)	0.0423 (0.001)	0.0005 (0.0266)	0.996	0.997	0.1657
Bayes 2	0.0190 (0.0263)	0.0422 (0.001)	-0.0017 (0.0263)	0.995	0.995	0.1655

Conclusions

- Early Phase Development is getting exceedingly tricky due to competition and interest in rare diseases
- We have a multitude of historical data sources from which we can leverage placebo data for inference
- There are also multiple published methods for incorporating historical data into new studies that have positively impacted operating characteristics
- To maximize benefit, great care is needed to determine what data, and how much of it, to use

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References

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