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Use of Historical Data in Clinical Trials – A Practical Approach

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Disclosure

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Ivan Chan, Lanju Zhang, Zailong Wang, Li Wang are employees of AbbVie Inc.

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Outline

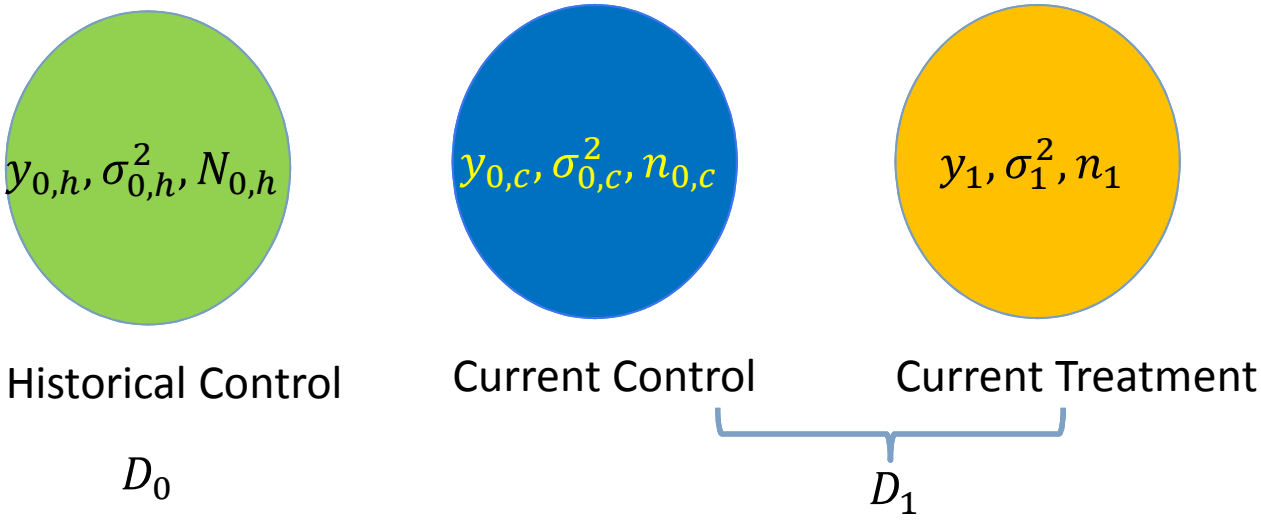
- Historical data borrowing in clinical trials – is this an acceptable approach in regulatory decision making?
- What needs to be considered in the design?
  - Source of historical data
  - Variability
  - How much to borrow
  - Evaluation of potential bias and efficiency gain
- A practical approach of borrowing data
  - A streamlined process
- An application
- Summary

Historical data borrowing methods review

- Pocock (1976) proposed guidelines of incorporating historical data (six criteria to be relevant); suggested a Bayesian approach
- Historical data summarization: Meta-analytic Predictive approach (Neuenchwander et al, 2010)
- Bayesian historical data borrowing
  - Power Prior (Ibrahim and Chen, 2000, Psioda and Ibrahim, 2018)
  - Commensurate prior (Hobbs et al, 2011)
  - Mixture Prior (Schmidli et al, 2014)

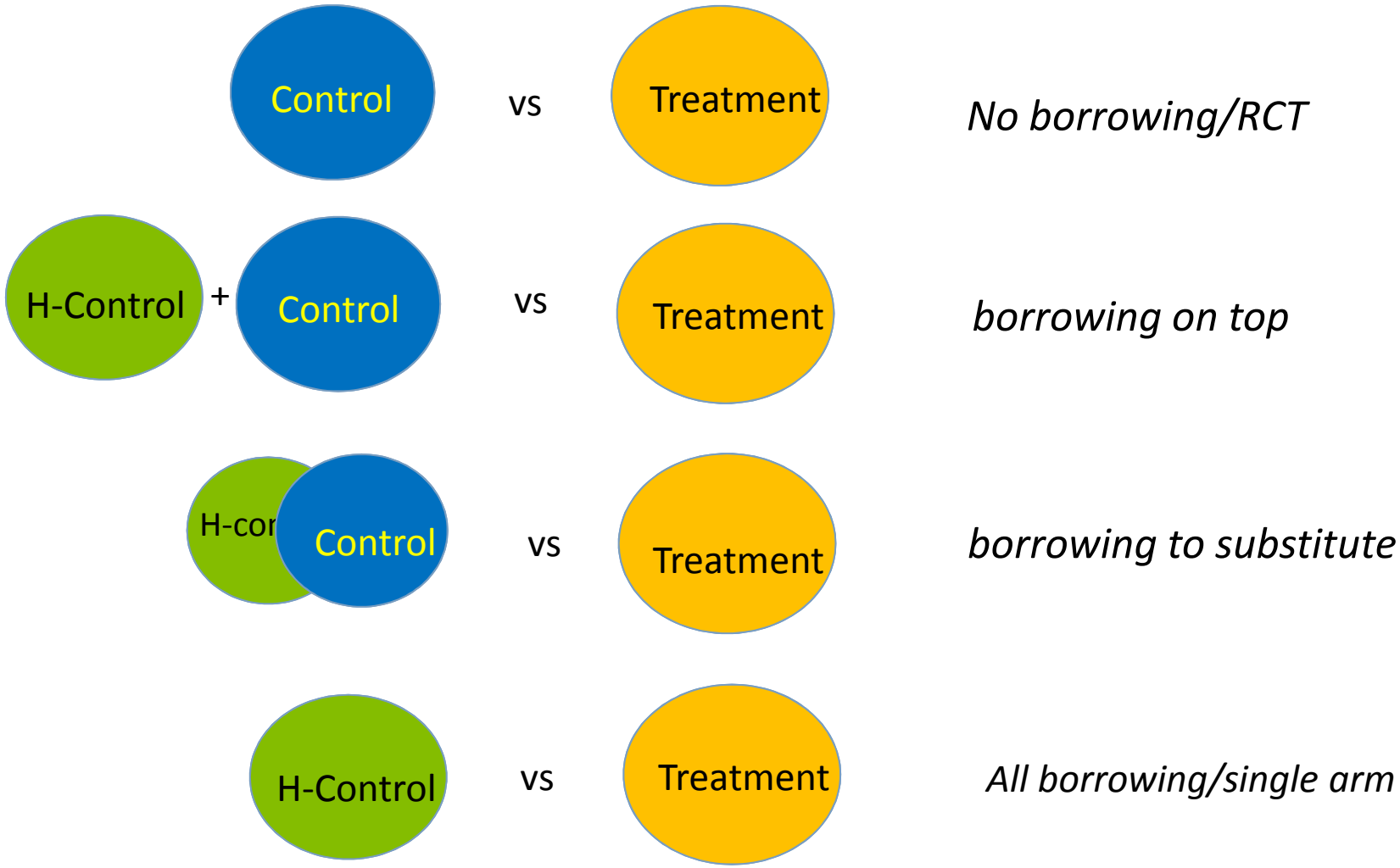
Notation

- Data



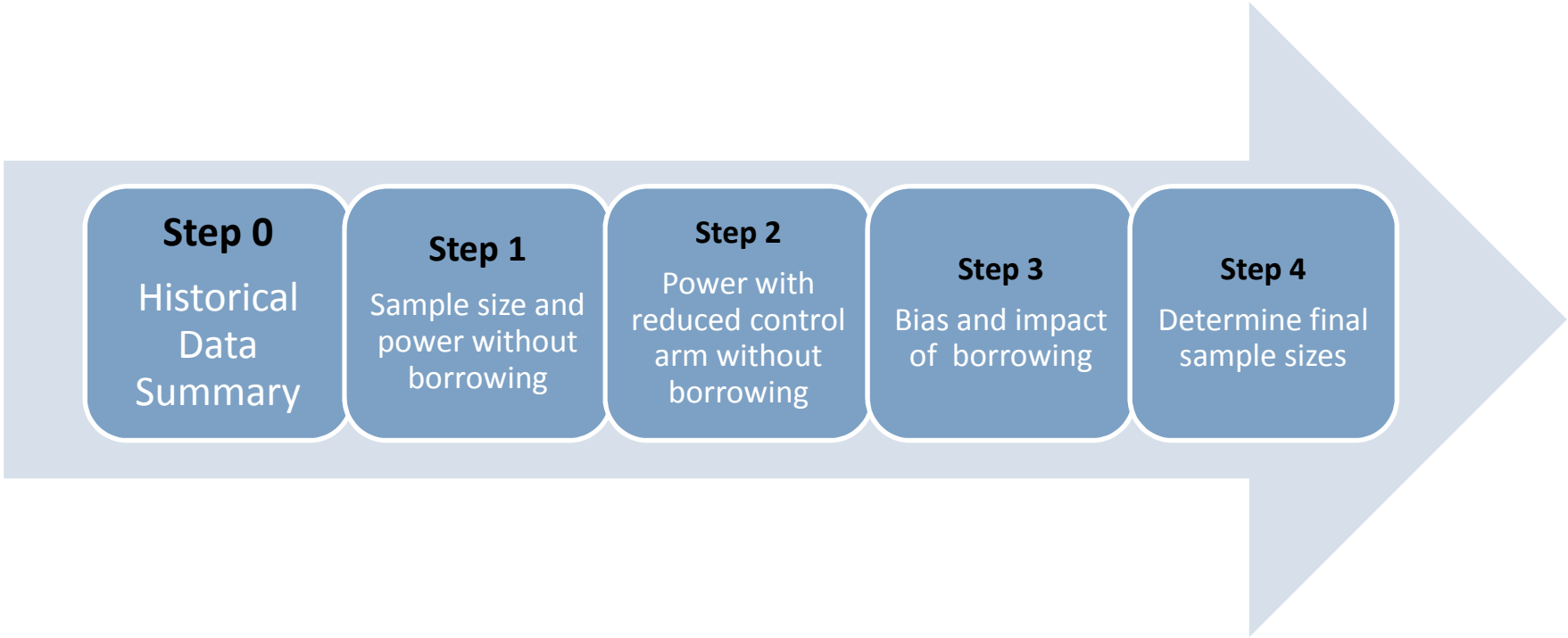
- Continuous endpoint
- Normally distributed, control mean μ_0, treatment mean μ_1, known variance
- Interest: comparing μ_0 and μ_1

Historical Data Borrowing – Full Spectrum of Possibilities



Historical Data Borrowing – A Practical Approach

- Select *comparable* historical control data
- Evaluate impact of bias
- Determine how much to borrow based on potential magnitude of bias
- Analysis using a frequentist or Bayesian approach (equivalent with the normally distributed and priors specified)

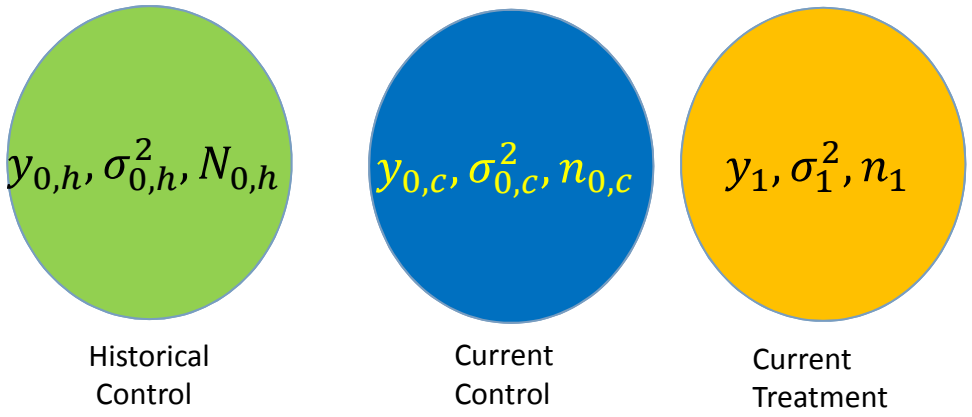


Bayesian Framework for Trial Design

- Bayesian: μ_0 and μ_1 are *random* quantities
- Priors
  - Control prior based on historical data
  - Treatment prior: noninformative
- Posteriors
  - $\mu_1,\ \ \mu_0$
  - Trial success criterion: $\Pr(\mu_1 - \mu_0 > \Delta | D_0, D_1) > p_0$

A Practical Approach for Historical Data Borrowing

- Priors
  - Meta-analytic Predictive Prior (MAP): $\mu_0 \sim N\left(y_{0,h}, \frac{\sigma_{0,h}^2}{n_{0,h}}\right)$
    - $n_{0,h}$: borrowing size defined by the borrowing fraction a_0
  - Treatment prior: noninformative
- Posteriors
  - Control: $\mu_0 \sim N\left(\frac{n_{0,h}\sigma_{0,c}^2}{n_{0,h}\sigma_{0,c}^2+n_{0,c}\sigma_{0,h}^2} y_{0,h} + \frac{n_{0,c}\sigma_{0,h}^2}{n_{0,h}\sigma_{0,c}^2+n_{0,c}\sigma_{0,h}^2} y_{0,c}, \frac{\sigma_{0,h}^2\sigma_{0,c}^2}{n_{0,h}\sigma_{0,c}^2+n_{0,c}\sigma_{0,h}^2}\right)$
  - Treatment: $\mu_1 \sim N\left(y_1, \frac{\sigma_1^2}{n_1}\right)$



Frequentist Design Properties for Historical Data Borrowing

- No borrowing ($a_0 = 0$)
  - Type I error rate is exactly α
  - Power and sample size are exactly as usual
- With borrowing ($a_0 > 0$)
  - When there is no bias, there is slight type I error rate deflation and power gain.
  - When there is bias, type I error rate and power change depends on the bias direction; its magnitude depends on borrowing fraction
  - If a_0=1, all control data are borrowed, a single arm trial

Determination of the Borrowing Size

- Evaluate the impact of bias and borrowing size on trial operating characteristics
  - Consider the frequentist properties of type I error control and power at design stage
  - Can also evaluate the bias and precision of the treatment effect estimate
- Select a borrowing fraction to optimize the operating characteristics

Example: Rheumatoid Arthritis POC trial

Design

- A proof of concept (POC) dose ranging trial in immunology (rheumatoid arthritis)
- 4 dose levels of a new treatment vs placebo
- Primary endpoint is change from baseline in disease activity score (DAS28) at week 12

Historical data

- Previous trials exist in similar disease setting
- Can we borrow some historical placebo data?
  - Reduce the number of concurrent placebo subjects
  - Increase the precision/power of study

Application: Rheumatoid Arthritis POC trial

- *Step 0: Historical data summary (MAP prior)*
  - Identify relevant historical trials (Pocock criteria, eg)

Historical Trial data on placebo control (DAS28-CRP)

study	n	mean	sd
1	176	-0.8	1.5
2	131	-0.6	1.5

  - Meta analysis
    - Mean: -0.71; 95% CI: (-0.919, -0.5); effective sample size: 151

Application: Rheumatoid Arthritis POC trial

- *Step 1*: Determine balanced sample size per group without borrowing

$$n_1 = \frac{2\left(\Phi^{-1}(1-\alpha) + \Phi^{-1}(1-\beta)\right)^2 \sigma^2}{\delta^2}$$

  - n_1=36 for treatment effect δ=-0.88, α=0.05, β=0.2, σ=1.5

- *Step 2*: Determine power without borrowing for different randomization ratio $k = n_1 : n_{0,c}$ (eg, k:1 randomization ratio).

$$1 - \beta_1 = \Phi\left[\sqrt{\frac{2}{1+k}}\left(\Phi^{-1}(1-\alpha) + \Phi^{-1}(1-\beta)\right) - \Phi^{-1}(1-\alpha)\right]$$

Randomization Ratio (k)	Power
1	80%
3/2	72%
2	65%
3	54%

Application: Rheumatoid Arthritis POC trial

- *Step 3*: Evaluate operating characteristics with historical data borrowing
- Assume bias is a proportion ***r*** of the treatment difference, ie, $|y_{0,h} - \mu_{0,f}| = r\delta$.
- Recall $a_0 = \frac{n_{0,h}}{n_{0,h}+n_{0,c}}$. Given k, r, and a_0,

Type I error rates

$$\Phi\left[\frac{\pm\sqrt{2}ra_0\left(\Phi^{-1}(1-\alpha)+\Phi^{-1}(1-\beta)\right)-\Phi^{-1}(p_0)\sqrt{1+k(1-a_0)}}{\sqrt{1+k(1-a_0)^2}}\right]$$

Power

$$\Phi\left[\frac{\sqrt{2}(1\pm ra_0)\left(\Phi^{-1}(1-\alpha)+\Phi^{-1}(1-\beta)\right)-\Phi^{-1}(p_0)\sqrt{1+k(1-a_0)}}{\sqrt{1+k(1-a_0)^2}}\right]$$

- These formulae are general and don't depend on sample sizes, effect size, standard deviation etc.

Application: Rheumatoid Arthritis POC trial

- *Step 3*: Evaluate operating characteristics - Impact of bias and borrowing size on type I error rate and power;

  Type I error rate (Error) and power for **k=2**, α=0.05, 1-β=80%, δ =0.88
  Red cells for scenarios with power<70% or type I error rate >0.1.

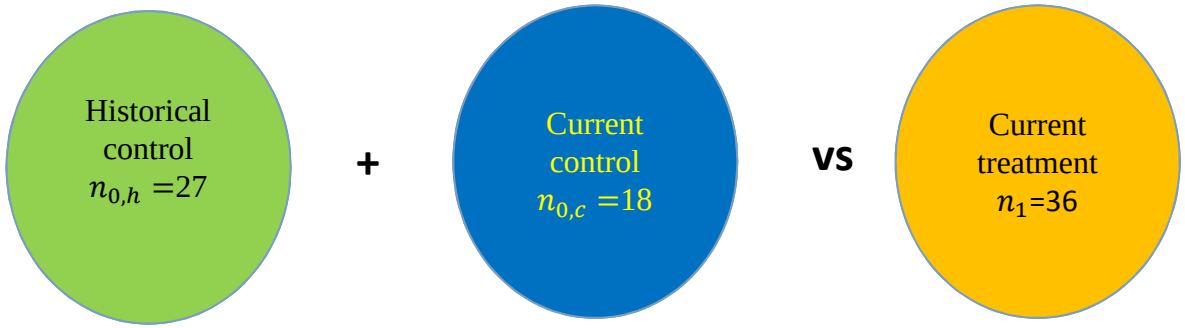
a_0\r	0		0.1		0.2		0.3		0.4		0.5	
	Error	Power	Error	Power	Error	Power	Error	Power	Error	Power	Error	Power
0.5	0.029	0.834	0.012 0.040	0.796 0.868	0.014 0.053	0.753 0.896	0.010 0.071	0.706 0.920	0.007 0.093	0.655 0.939	0.004 0.119	0.600 0.954
0.6	**0.027**	**0.873**	**0.018** **0.041**	**0.831** **0.907**	**0.011** **0.060**	**0.780** **0.934**	**0.007** **0.085**	**0.722** **0.955**	0.004 0.118	0.657 0.970	0.002 0.158	0.588 0.980
0.7	0.028	0.907	0.016 0.046	0.863 0.939	0.009 0.072	0.807 0.962	0.005 0.108	0.740 0.977	0.002 0.156	0.661 0.987	0.001 0.217	0.575 0.993
0.8	0.031	0.935	0.016 0.055	0.893 0.963	0.008 0.092	0.834 0.980	0.004 0.144	0.758 0.990	0.002 0.215	0.666 0.995	0.001 0.302	0.563 0.998

Note: In each cell the top value is for bias favoring null and the bottom is for bias favoring alternative
a_0: fraction of historical control patients among all control patients;
r: bias/(treatment difference); k: randomization ratio

Application: Rheumatoid Arthritis POC trial

- *Step 4*: Determine sample size for borrowing
  - Recall n_1 =36
  - Select k=2:1 and a_0=0.6 to maintain power while controlling type I error
    - $n_{0,c} = n_1/k$=18, $n_{0,h}=\frac{n_{0,c}\, a_0}{1-a_0}$=27
  - Ensure $n_{0,h}$ <=n_max=151

- This design can save 18 concurrent placebo subjects
  - Reduce >$5 million cost and 2 months enrollment time



R-Shiny Tool for Historical Data Borrowing

Historical Borrowing -- Continuous Endpoint

Step 1: Historical Information:

(A) Number of Historical Trials:

2

(B) Number of Control Subjects in Each Historical Trial(comma delimited, same length as number of trials)

176,131

(C) Control Mean Value in Each Historical Trial(comma delimited, same length as number of trials)

0.8,0.6

(D) Standard Deviation for Control Group in Each Historical Trial(comma delimited, same length as number of trials)

1.5, 1.5

(E) Level of Confidence Interval for Pooled Mean Estimates

0.95

Step 2: Current Study Assumptions:

(F) Treatment Effect (TRT-PBO)

0.88

(G) Common Standard Deviation

1.5

(H) One-sided Alpha Value

0.05

(I) Target Power

0.8

Step 3: Bayesian Criteria:

(J) Treatment vs Control Ratio in Current Trial

2:1

(K) Target Difference(TD)

0

(L) Target Probability(TP)

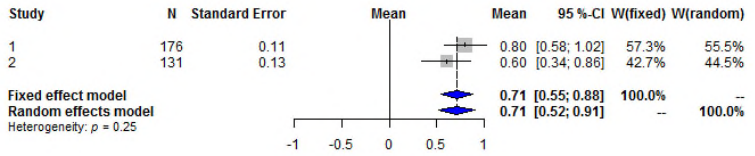
0.95

Step 4: Conclusions:

Step1 | Step2 | Step3 | Step 4 | Guidance

Meta Analysis of Historical Control Data [Please input (A) - (E) in left panel]

Forest Plot of Historical Data Meta Analysis



Effective Sample Size from Historical Data

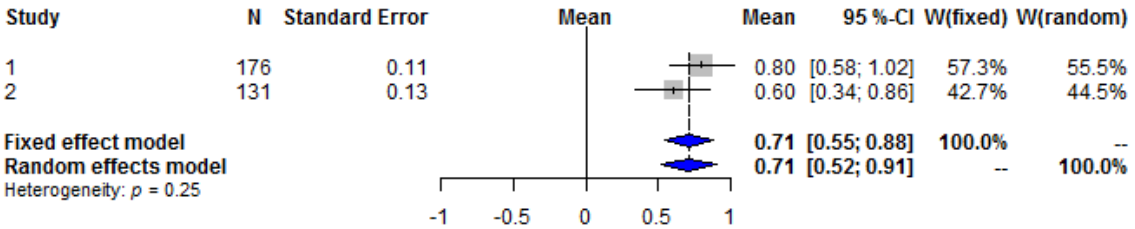
Method	Between Study Variation: tau^2	Meta Mean	Pooled Standard Deviation	95%-Confidence Interval	Effective Sample Size
REML	0.01	0.71	1.50	(0.52, 0.91)	151

Step 1: Meta Analysis Predictive Prior

Step1 | Step2 | Step3 | Step 4 | Guidance

Meta Analysis of Historical Control Data [Please input (A) - (E) in left panel]

Forest Plot of Historical Data Meta Analysis



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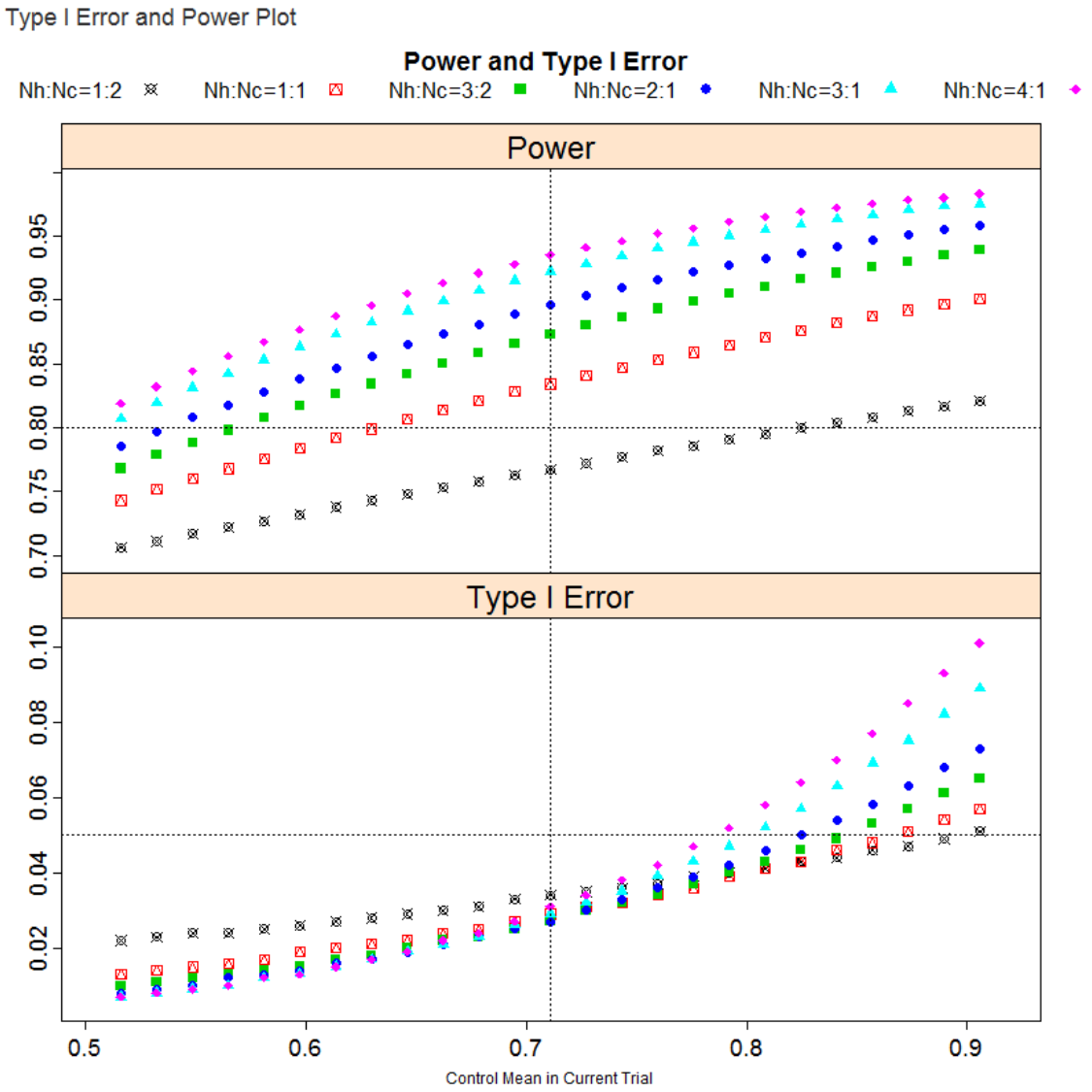
Step 3: Operating Characteristics (Type I Error and Power)



Step 4: Overall Design

Step1 | Step2 | Step3 | Step 4 | Guidance

Conclusion [Please input (M) - (P) in left panel]

Bayesian Criteria:

P(Treatment Mean - Control Mean > 0 | Data) > 0.95

Historical Trials Data:

Study No.	Sample Size N	Mean	Standard Deviation
1	176	0.80	1.50
2	131	0.60	1.50

Current Trial Design:

Assumed Treatment Difference	Assumed Common Standard Deviation	Number of Subjects in Treatment Group	Number of Subjects in Current Control Group	Number of Subjects in Historical Control Group	Number of Saved Control Subjects
0.88	1.50	36	18	27	18

Summary

- Relevant and “good” historical control data can
  - Reduce type I error rate with slight power gain when there is no prior-data conflict
  - Control type I error rate inflation and power loss to a desired degree in general

- We propose a systemic way to design and analyze trials with historical data borrowing
  - Bayesian framework with good frequentist properties
  - **No simulation is needed**!
  - Explicit assessment of impact of bias and borrowing size on operating characteristics
  - Emphasis on design stage

Key References

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