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# Incorporate External Control Data in New Clinical Trial Design and Analysis

Lanju Zhang
Abbvie Inc

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## Disclaimer

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# Outline

- Introduction to external control data incorporation in trial design and analysis
  - Regulatory landscape
  - Data
  - Incorporation spectrum
  - Statistical methodology
- Two Applications
  - Control substitution to augment in-trial control arm
  - Synthetic Control arm
- Conclusions

# Introduction: Incorporation into Trial Design and Analysis

- Traditionally
  - Trial design assumptions
  - Trial results contextualization
  - Non-inferiority trial margin

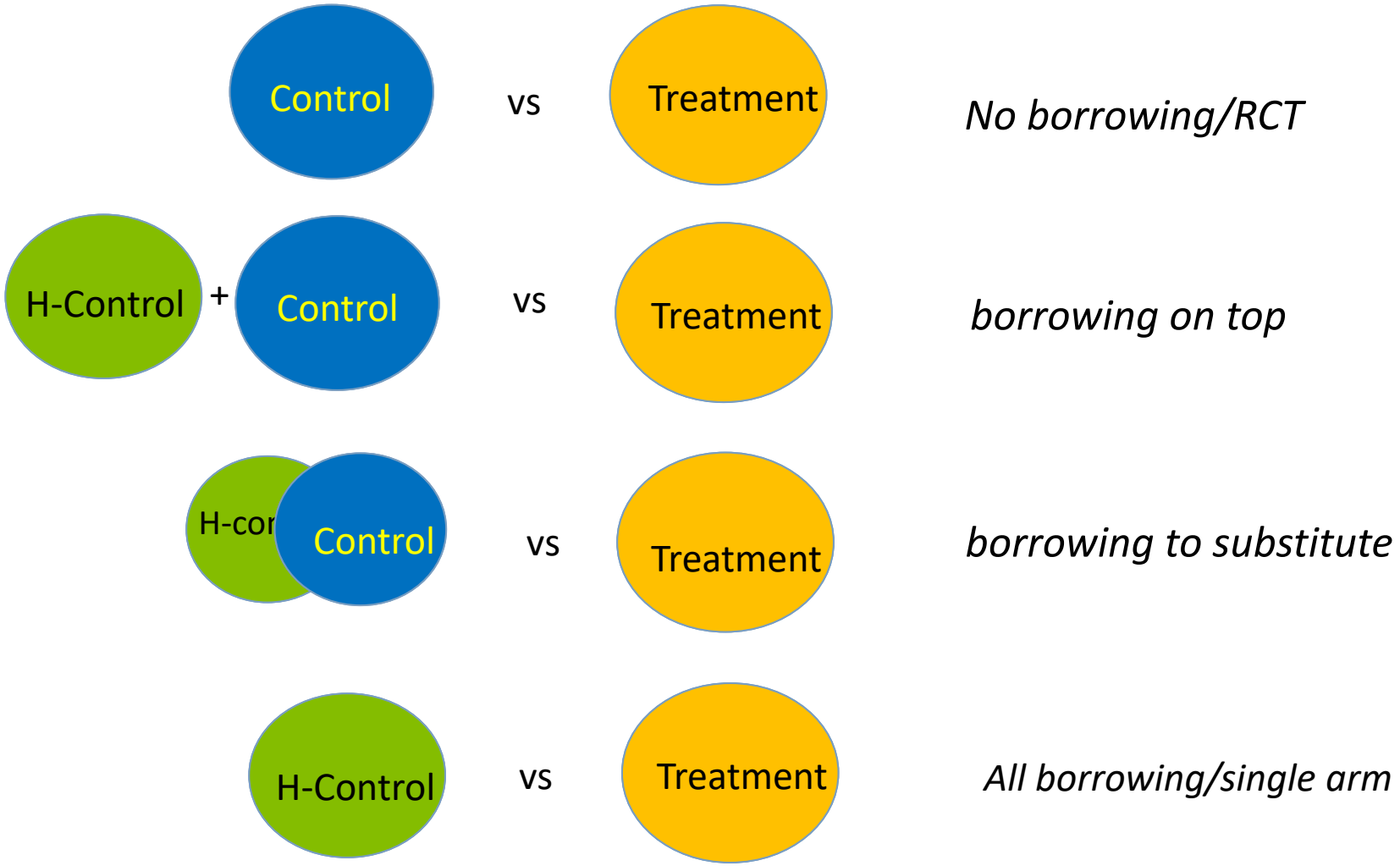
## Introduction: Regulatory Landscape

- Adaptive Design Guidance (FDA, 2019a)
  - Bayesian Adaptive Designs
    - Explicit borrowing of information from external sources, e.g., previous trials, natural history studies, and registries, via informative prior distributions to improve the efficiency of a trial.

## Introduction: Regulatory Landscape

- Complex and Innovative Design Guidance (FDA, 2019b)
  - When external information is explicitly borrowed into a design, such as in a Bayesian framework, a rationale for the borrowing and an explanation of how the prior distribution was formed from the prior information.
  - If prior information is being used, details about the source and choice of the prior information, its relevance to the proposed trial design, and an explanation of steps taken to ensure that all relevant prior information is accounted for, so that the prior information does not lead to misleading results.
  - For Bayesian inference, appropriate alternative trial characteristics should be considered, such as the maximum posterior probability of the null across values of the test statistic in the rejection region or the maximum posterior probability of a minimally clinically significant treatment effect across values of the test statistic outside of the rejection region (Ref. 5). It is also often informative to assess the sensitivity of trial operating characteristics to the choice of a prior distribution.

# Introduction: Incorporation Spectrum



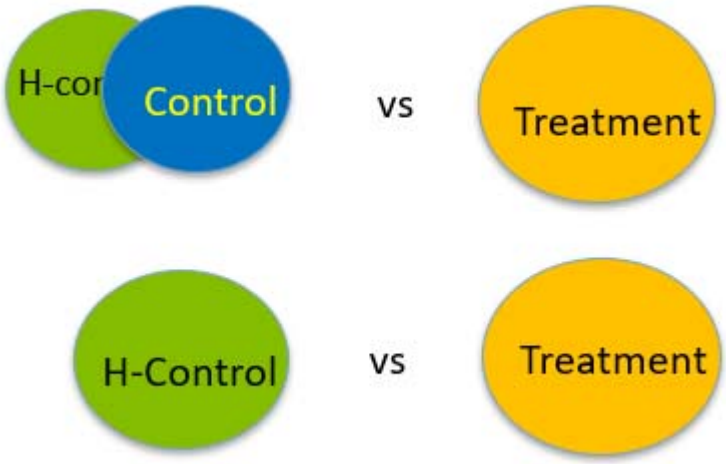
# Introduction: Data Selection

- Pocock (1976) proposed guidelines of incorporating historical data (six criteria to be relevant); suggested a Bayesian approach
  - Patient Population
  - Prior and Concomitant therapy
  - Control treatment
  - Endpoints/outcome measures
  - Regions
  - SOC/medical practice
  - Contemporaneity
  - Analysis methods

# Introduction: Control Data

| Control type | Concurrent | concurrent + external RCT data | external RCT data | RWD |
|---|---|---|---|---|
| **Evidence strength** | strongest | Strong when the results of the two control sources are similar | fair | fair |
| **Data quality for decision making** | best | Good when the results of the two control sources are similar | fair | fair |
| **Regulatory acceptance** | most acceptable | Acceptable | acceptable | negotiable |
| **Timeline** | longest | shorter | shortest | shortest |
| **Cost** | largest | lower | lowest | lowest |
| **Potential area of application** | diseases with SOC | diseases with SOC | rare diseases, life-threatening conditions, or pediatric trials | rare diseases, safety evaluation |
| **Statistical Methods** | standard | Bayesian/frequentist | Matching or other causal inference methods for confounding control | matching or other causal inference methods for confounding control |
| **Registration** | yes | potential | potential | potential |

# Introduction: Statistical Methodology



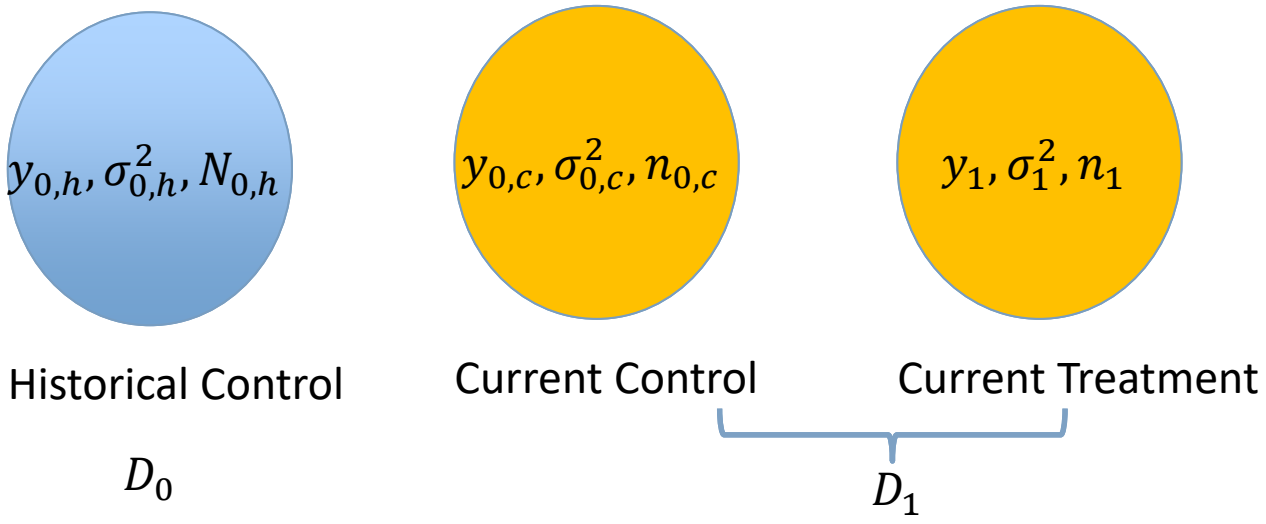

- Bayesian Methods
  - Data selection
  - Summary data
- Propensity Score
  - Data selection
  - Individual-level data

## Introduction: Statistical Methodology

- 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, 2019)
  - Commensurate prior (Hobbs et al, 2011)
  - Mixture Prior (Schmidli et al, 2014)
- Frequentist approach (reviewed in Viele et al 2014)

# Application 1: Control Substitution

- Data




- Continuous endpoint
- Normally distributed, control mean $\mu_0$, treatment mean $\mu_1$, known variance
- Interest: comparing $\mu_0$ and $\mu_1$

# Application 1: Control Substitution

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

## Application 1: Control Substitution

- Power Prior Approach (Ibrahim and Chen, 2000)
- Duan et al (2006) and Neuenschwander et al (2009)
  - Ibrahim and Chen (2000) violates likelihood principle
  - Proposed to normalize the prior
- Prior and posterior for $\mu_1 \; and \; \mu_0$
  - Posterior is proportion to the following
  - $$\alpha_0{}^{a-1}(1-\alpha_0)^{b-1}\frac{L(\mu_0|D_0)^{\alpha_0}\pi_0(\mu_0)}{\int L(\mu_0|D_0)^{\alpha_0}\pi_0(\mu_0)d\mu_0}\pi_1(\mu_1)L(\mu_0,\mu_1|D_1)$$

Prior for power $\alpha_0$ | Normalized Prior for $\mu_0$ | Prior for $\mu_1$ | Likelihood of $D_1$

    - a, b hyperparameters
  - $\alpha_0$ doesn't depend on in-trial data

## Application 1: Control Substitution

- Commensurate Power Prior Approach (Hobbs et al, 2011)
  - Assume different parameters for historical and current control data

- Prior and posterior for $\mu_1, \mu_0, and\ \mu_{0h}$
  - Posterior is proportion to the following

$$\frac{(L(\mu_{0h}|D_0)p(\mu_0|\mu_{0h},\tau))^{\alpha_0}}{\iint (L(\mu_{0h}|D_0)p(\mu_0|\mu_{0h},\tau))^{\alpha_0} d\,\mu_{0h} d\mu_0} p(\alpha_0|\tau)p(\tau)\pi_1(\mu_1)L(\mu_0,\mu_1|D_1)$$

    - $\mu_{0h}$: historical control mean
    - $\tau$: between historical trial variability, or commensurability
    - $p(\mu_0|\mu_{0h},\tau)$: control prior, eg, N($\mu_{0h}$, $\tau^2$)
    - $p(\alpha_0|\tau)$: prior of $\alpha_0$ depends on $\tau$, eg, beta($\frac{\alpha_0}{\tau^2}$, 1)

## Application 1: Control Substitution

- Robust Mixture Prior Approach (Schmidli et al, 2014)
  - Hierarchical modeling and meta-analytic predictive prior
- Prior $\mu_0$
  - $y_{0,h} \sim \mathrm{N}(\mu_{0h}, \sigma^2)\ , h = 1, 2, \ldots H$
  - $\mu_{01}, \ldots, \mu_{0H}, \mu_0 \sim \mathrm{N}(\theta, \tau^2)$
  - $\theta$, flat prior and $\tau$ half normal prior
  - Effective sample size:
  - Mixture based on Kullback-Leibler divergence
  - Robustize by adding a non-informative component
- Prior for $\mu_1$ noninformative
- R Package RBest

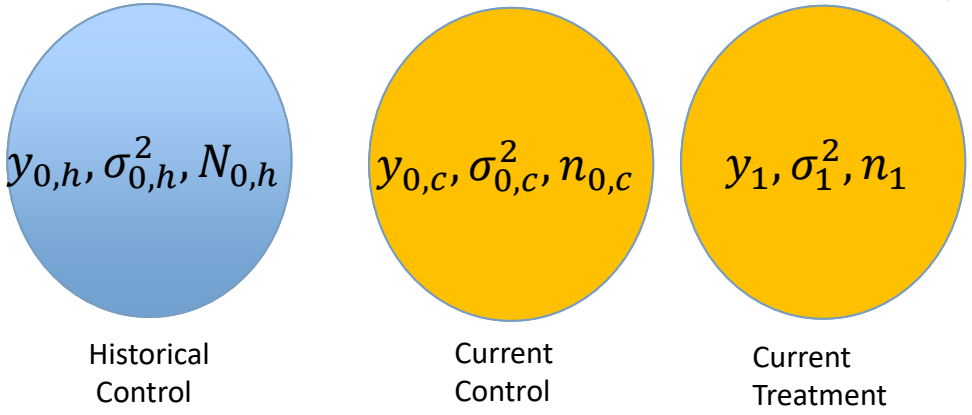
## Application 1: Control Substitution

- Proposed approach (L Zhang et al, 2020)
  - Build borrowing into design

- Basic ideas
  - Summary data, eg, mean, variance and between trial variability
  - Effective sample size as an upper bound for borrowing size
  - Conjugate prior
  - Commensurability depends on bias (=historical control –in trial control mean)
  - Explicit relationship between bias and error rates
  - Final borrowing size determined by control of error rate inflation
  - A streamlined process from data selection to design and analysis

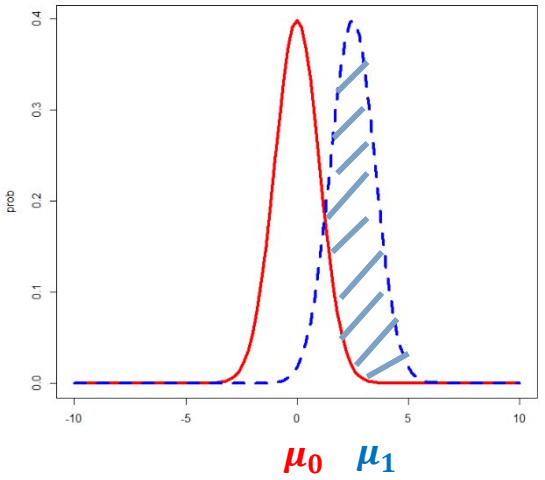
# Application 1: Control Substitution

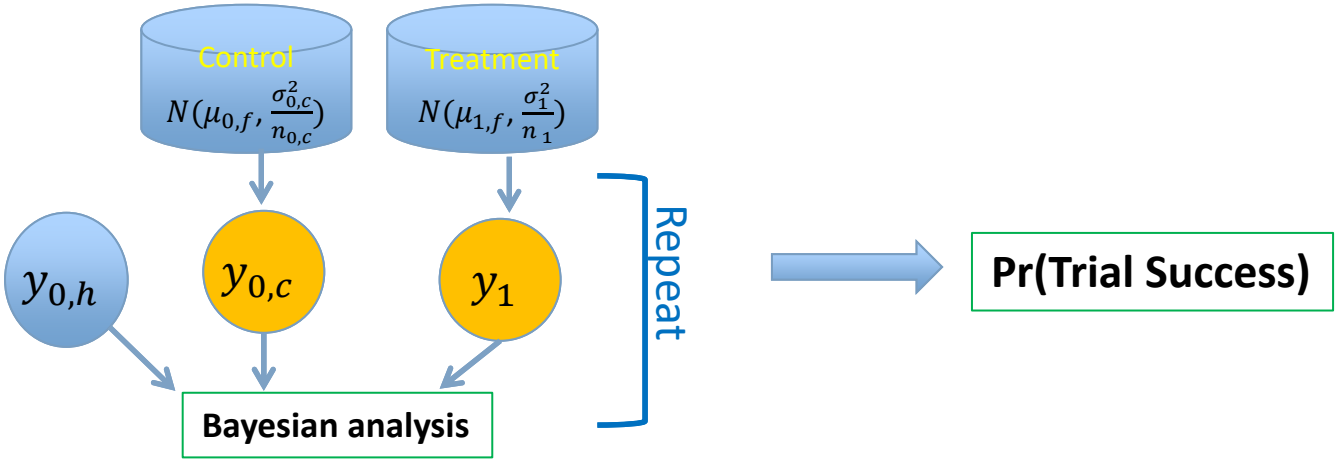
- Priors
  - MAP: $\mu_0 \sim N\left(y_{0,h}, \frac{\sigma_{0,h}^2}{n_{0,h}}\right)$ from meta analysis
    - o $n_{0,h}$: borrowing size
  - Treatment prior: noninformative
- Posteriors
  - Control: $\mu_0 \sim N\left(\frac{n_{0,h}\sigma_{0,c}^2}{n_{0,h}\sigma_{0,c}^2+n_{0,c}\sigma_{0,h}^2} y_{0,h} + \frac{n_{0,c}\sigma_{0,h}^2}{n_{0,h}\sigma_{0,c}^2+n_{0,c}\sigma_{0,h}^2} y_{0,c}, \frac{\sigma_{0,h}^2\sigma_{0,c}^2}{n_{0,h}\sigma_{0,c}^2+n_{0,c}\sigma_{0,h}^2}\right)$
  - Treatment: $\mu_1 \sim N\left(y_1, \frac{\sigma_1^2}{n_1}\right)$



# Application 1: Control Substitution

- Trial success: $\Pr(\mu_1 - \mu_0 > \Delta | Data) > p_0$
  - Assume $\Delta$=0, $p_0$=$1-\alpha$ =95% throughout
- Design properties



# Application 1: Control Substitution

## Design Properties

- Pr(trial success|true trt diff) depends on
  - treatment difference $\mu_{1,f} - \mu_{0,f}$
  - Bias of historical control data $(y_{0,h} - \mu_{0,f})$ commensurability
  - The proportion of historical control patients $a_0$ prior power
    - $a_0$=(#historical control patients)/(# combined control patients)

Pr(Trial success)=$\Pr(\Pr(\mu_1 - \mu_0 > 0|Data) > p_0)$

Effect size Bias

$$= \Phi\left(\frac{(\mu_{1,f}-\mu_{0,f})}{\sigma\sqrt{\frac{1}{n_1}+\frac{1-a_0}{n_{0,h}+n_{0,c}}}} - \frac{a_0(y_{0,h}-\mu_{0,f})}{\sigma\sqrt{\frac{1}{n_1}+\frac{1-a_0}{n_{0,h}+n_{0,c}}}} - \Phi^{-1}(p_0)\frac{\sqrt{\frac{1}{n_1}+\frac{1}{n_{0,h}+n_{0,c}}}}{\sqrt{\frac{1}{n_1}+\frac{1-a_0}{n_{0,h}+n_{0,c}}}}\right)$$

Borrowing fraction $a_0$

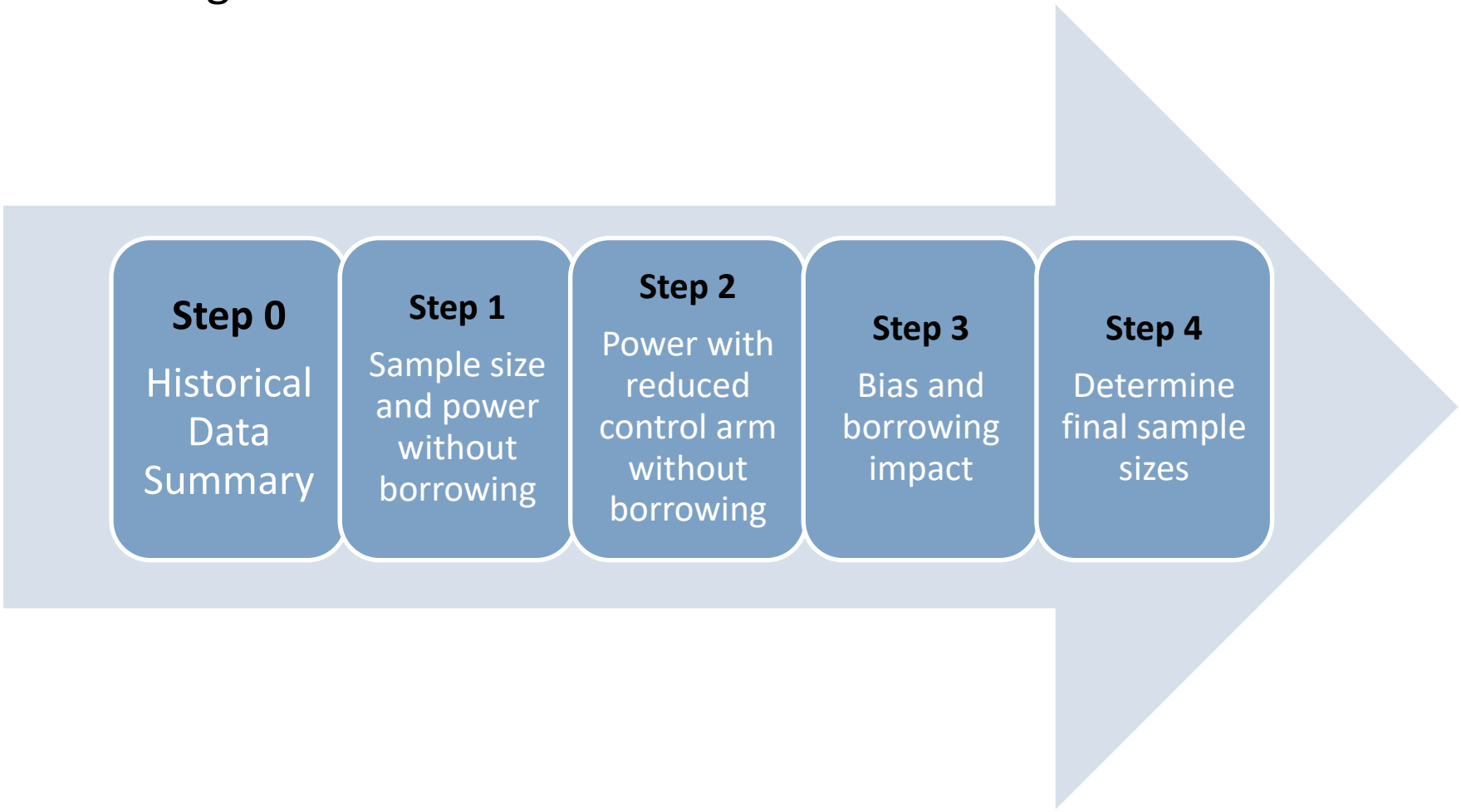
## Application 1: Control Substitution

Design Properties

- No borrowing ($a_0 = 0$)
  - Type I error rate is exactly $\alpha$
  - 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 is historical, a single arm trial

# Application 1: Control Substitution

Trial Design Process



# Application 1: Control Substitution

Application: Rheumatoid Arthritis POC trial

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

**Historical Trial data (DAS28-CRP)**

| Phase | n | mean | sd |
|---|---|---|---|
| 2 | 176 | -0.8 | 1.5 |
| 3 | 131 | -0.6 | 1.5 |

  - Meta analysis
    - Mean: -0.71; 95% CI: (-0.919, -0.5); effective sample size: 116

# Application 1: Control Substitution

- *Step 1*: determine balanced sample size without borrowing

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

  - $\delta$=-0.88, $\alpha$=0.05, $\beta$=0.2, $\sigma$=1.5, $n_1$=36

- *Step 2*: for different randomization ratio $k = n_1 : n_{0,c}$ (eg, k=2, 3, 4 means randomization ratio 2:1, 3:1, 4:1), determine power without borrowing.

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

Power using different randomization ratio k with $\alpha$=0.05 and 1-$\beta$=80% without borrowing

| k | $1-\beta_1$ |
|---|---|
| 1 | 80% |
| 3/2 | 72% |
| 2 | 65% |
| 3 | 54% |

# Application 1: Control Substitution

- *Step 3*: 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*

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

- $\delta$=-0.88, r=0.24
- These formulae are general and don't depend on sample sizes, effect size, standard deviation etc.

# Application 1: Control Substitution

- *Step 3*: select parameters based on impact on type I error rate and power;

  Type I error rate (Error) and power for **k=2**, $\alpha$=0.05, 1-$\beta$=80%
  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<br>0.040 | 0.796<br>0.868 | 0.014<br>0.053 | 0.753<br>0.896 | 0.010<br>0.071 | 0.706<br>0.920 | 0.007<br>0.093 | 0.655<br>0.939 | 0.004<br>0.119 | 0.600<br>0.954 |
| **0.6** | 0.027 | 0.873 | 0.018<br>0.041 | 0.831<br>0.907 | 0.011<br>0.060 | 0.780<br>0.934 | 0.007<br>0.085 | 0.722<br>0.955 | 0.004<br>0.118 | 0.657<br>0.970 | 0.002<br>0.158 | 0.588<br>0.980 |
| **0.7** | 0.028 | 0.907 | 0.016<br>0.046 | 0.863<br>0.939 | 0.009<br>0.072 | 0.807<br>0.962 | 0.005<br>0.108 | 0.740<br>0.977 | 0.002<br>0.156 | 0.661<br>0.987 | 0.001<br>0.217 | 0.575<br>0.993 |
| **0.8** | 0.031 | 0.935 | 0.016<br>0.055 | 0.893<br>0.963 | 0.008<br>0.092 | 0.834<br>0.980 | 0.004<br>0.144 | 0.758<br>0.990 | 0.002<br>0.215 | 0.666<br>0.995 | 0.001<br>0.302 | 0.563<br>0.998 |

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

# Application 1: Control Substitution

- *Step 3*: select parameters based on impact on type I error rate and power

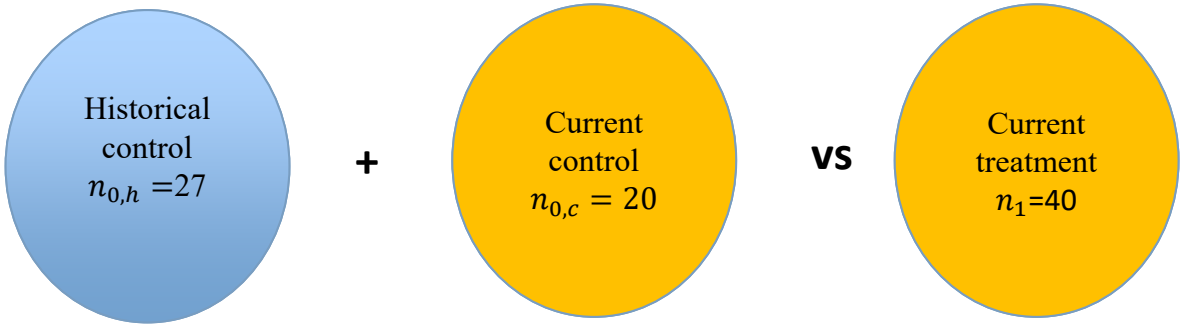
Type I error rate (Error) and power for **k=3**, $\alpha$=0.05, 1-$\beta$=80%
Red cells for scenarios with power<70% or type I error rate >0.1.

| $a_0$\r | 0 | | 0.1 | | 0.2 | | 0.3 | | 0.4 | | 0.5 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Error | Power | Error | Power | Error | Power | Error | Power | Error | Power | Error | Power |
| 0.6 | 0.022 | 0.812 | 0.015<br>0.033 | 0.762<br>0.855 | 0.009<br>0.049 | 0.705<br>0.891 | 0.006<br>0.069 | 0.642<br>0.920 | 0.003<br>0.095 | 0.576<br>0.943 | 0.002<br>0.127 | 0.507<br>0.960 |
| 0.7 | 0.022 | 0.866 | 0.013<br>0.036 | 0.813<br>0.908 | 0.007<br>0.058 | 0.749<br>0.939 | 0.003<br>0.087 | 0.675<br>0.961 | 0.002<br>0.128 | 0.593<br>0.976 | 0.001<br>0.179 | 0.507<br>0.986 |
| 0.8 | 0.025 | 0.913 | 0.013<br>0.045 | 0.862<br>0.948 | 0.006<br>0.076 | 0.795<br>0.970 | 0.003<br>0.121 | 0.712<br>0.984 | 0.001<br>0.183 | 0.615<br>0.992 | 0.000<br>0.262 | 0.511<br>0.996 |

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

# Application 1: Control Substitution

- *Step 4*: determine sample sizes
  - $n_1$ =36
  - $k$=2:1 and $a_0$=0.6
  - $n_{0,c} = n_1/k$=18, $n_{0,h}=\frac{n_{0,c}\, a_0}{1-a_0}$=27
  - Ensure $n_{0,h}$ <=n_max=117
- In the data analysis, evaluate $\Pr(\mu_1 - \mu_0 > \Delta | Data)$ and check whether it is $> p_0$.



## Application 1: Control Substitution

- *Step 4*: determine sample sizes
  - $n_1$ =36
  - $k$=2:1 and $a_0$=0.6
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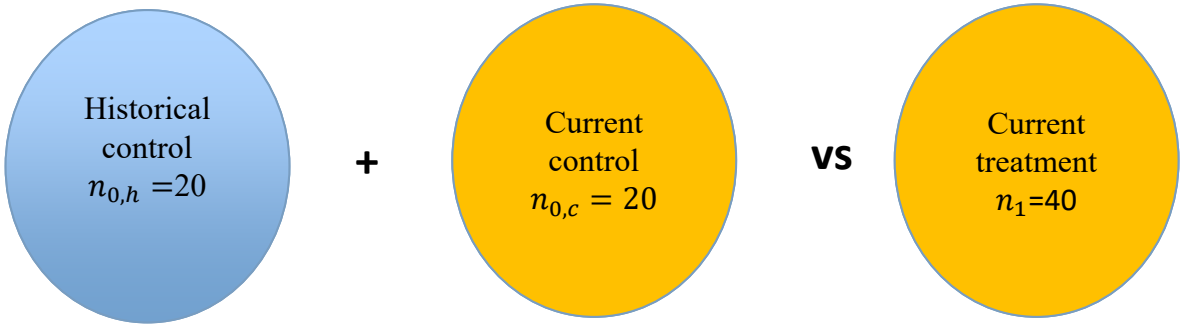
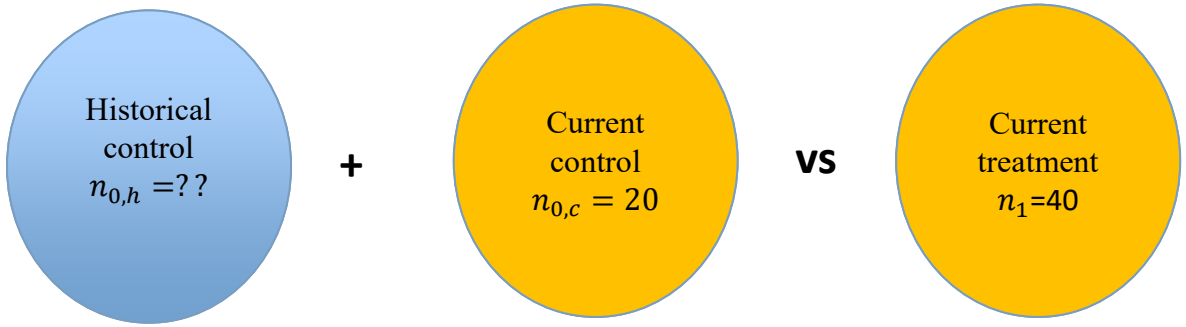
  and check whether it is $> p_0$.



# Application 1: Control Substitution

- Dynamic borrowing
  - Determine actual borrowing size depends on observed difference between controls
    - Larger difference, borrowing less



# Application 1: Control Substitution

## Regulatory Interaction

- Teleconference with FDA
  - Initial feedback
    - Only in-trial data will be considered
  - Meeting minutes
    - Depending on the data selection and stat methods, can be considered
  - SAP submission
    - No comments received

# Application 1: Control Substitution

## Regulatory Interaction

- Teleconference with FDA
  - Initial feedback
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    - No comments received

## Application 1: Control Substitution

Results

- Planned borrowing ($n_{0,h} = 20$)
  - Posterior prob > 95%
- Dynamic borrowing ($n_{0,h} = 60$)
  - Posterior prob was very similar

# Application 2: Synthetic Control Arm

- Subject-level data available
  - Similar trial settings
  - Covariate data
  - Outcome data
- Propensity score approach
  - Matching
  - Stratification
  - Inverse probability weighting
  - Regression

# Application 2: Synthetic Control Arm

- Process for integrity
  - Independent team doing matching
  - Prespecified rules
  - Masked from outcome
  - Matching was done after enrollment complete and before unblinding
  - A secure location for covariate data

# Application 2: Synthetic Control Arm

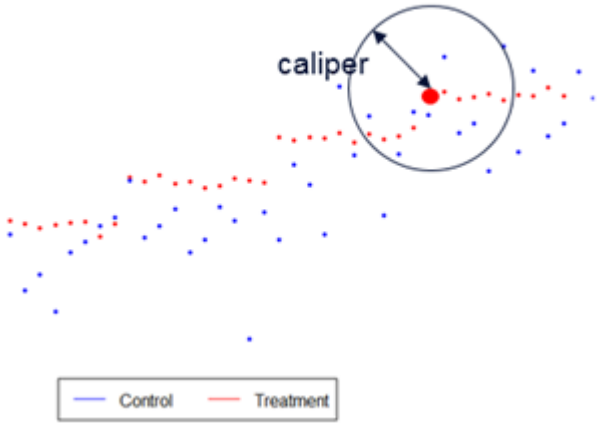
- A POC study comparing a new drug X to Adalimumab for RA
  - 2:1 randomization ratio: X 30; Ada: 15
- Created a synthetic placebo arm as common control
  - Placebo patients available from 3 recently completed clinical trials
  - Used individual level data matched by baseline characteristics
  - Propensity score matching based on baseline covariates

# Application 2: Synthetic Control Arm

- Comparing to a synthetic placebo arm with Propensity Score Matching

PS analysis → Matching → Analysis: pairwise comparison

| PS analysis | Matching | Analysis: pairwise comparison | |
|---|---|---|---|
| T: 45 | T: 45 | X: | 30 |
| P: | P: 45 | ADA: | 15 |
| | | Placebo: | 45 |




Propensity score matching

| Matching Ratio (Treated: Placebo) | N_X: N_ADA: N_PBO | Two-Group Comparison Power (ADA vs. PBO) |
|---|---|---|
| 1:1 | 30:15:45 | 82% |
| 1:2 | 30:15:90 | 87% |
| 1:3 | 30:15:135 | 88% |

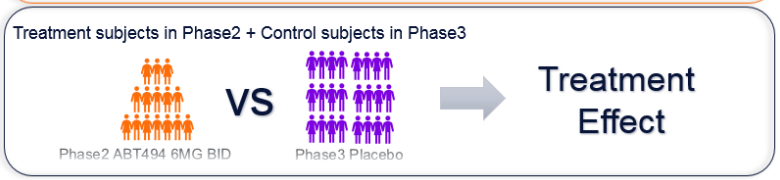
# Application 2: Synthetic Control Arm

## A Pilot study

- Comparing Ph2 trial result versus Ph2 treatment + Ph3 Placebo with of 4 PS-methods

Phase 2 Study


PS Analysis

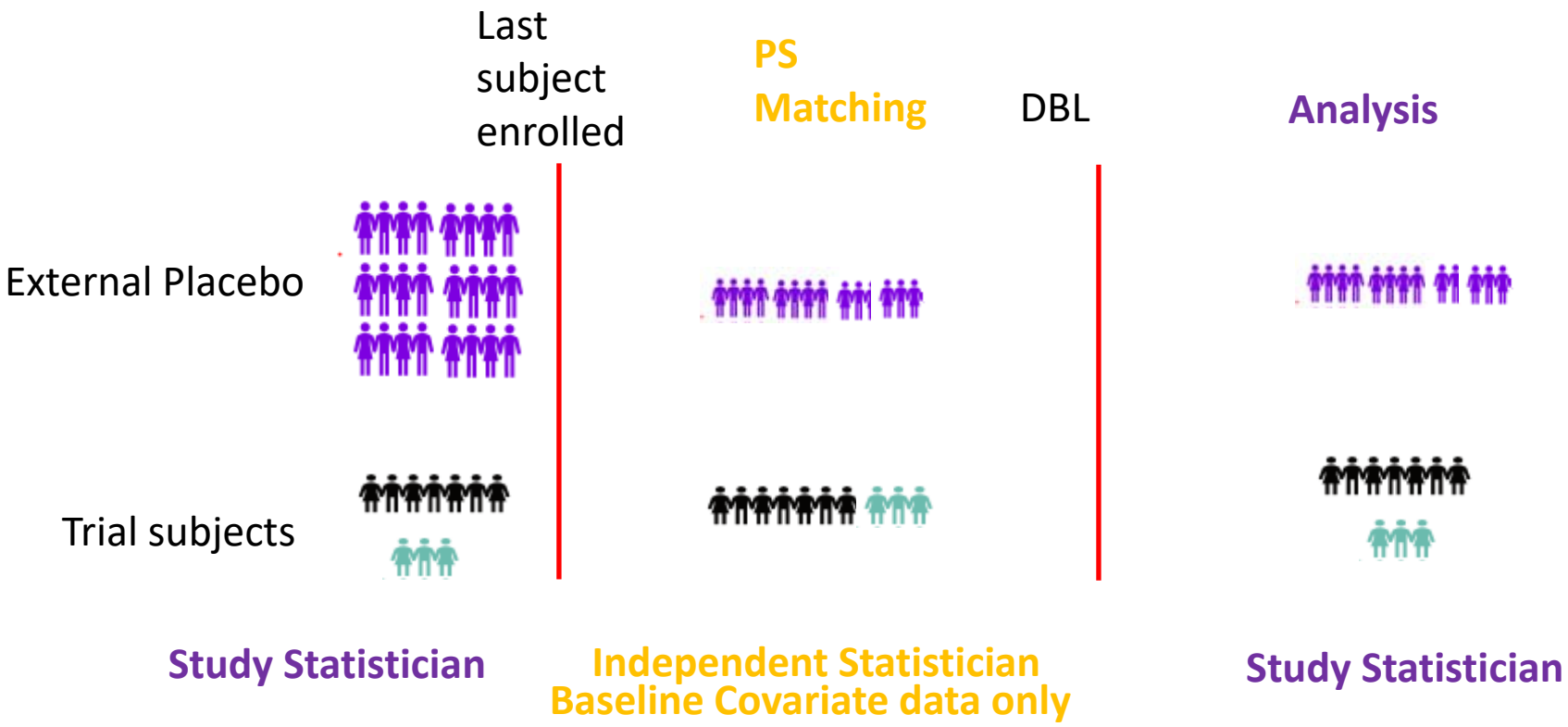



## Summary of results: ACR20 (Binary)

| Approach | $N_{trt}$:$N_{pbo}$ | Absolute Difference | | Odds Ratio | |
|---|---|---|---|---|---|
| | | Estimate 95% CI | P-value | Estimate 95% CI | P-value |
| **Original Study550** | **55:55** | **0.236 (0.037, 0.436)** | **0.022** | **2.636 (1.218, 5.705)** | **0.014** |
| **Combined Dataset** | | | | | |
| Stratifying by PS | 54:159 | 0.276 (0.102, 0.449) | 0.002 | 3.151 (1.483, 6.695) | 0.005 |
| **Matching by PS** | **38:38** | **0.270 (0.034, 0.506)** | **0.025** | **3.160 (1.217, 8.204)** | **0.018** |
| Weighting by PS | 54:159 | - | - | 2.596 (1.051, 6.413) | 0.039 |
| Logistic regression adjusting for PS | 54:159 | - | - | 3.354 (1.580, 7.118) | 0.002 |

# Application 2: Synthetic Control Arm

- Used Independent Statistician to select matching controls prior to database lock



# Application 2: Synthetic Control Arm

- Plan
  - Six demographic and 11 baseline disease characteristic covariates
  - Total eight scenarios
    - PS modeling: logistic with or without Firth penalty
    - Matching algorithm: greedy and optimal with different caliper
    - Matching ratio: 1:1 or 2:1
  - Criteria: standardized mean difference (SMD) of covariates and number of matched treatment subjects
- Data
  - Enrolled 48 subjects
  - More than 700 external placebo subjects

## Application 2: Synthetic Control Arm

- Results
  - Final model: logistic with Firth, greedy (caliper=0.8), 2:1 ratio
    - all matched
    - SMD: mean=0.036, max=0.09
  - Alternative models
    - When using caliper=0.2, three subjects cannot be matched
    - Balancing was similar in terms of SMD
- Data analysis
  - Matched data set incorporated into database
  - Comparison of drug X and Ada to synthetic placebo arm
  - Tables created through the same TFL production

## Conclusions

- Drug development cost is skyrocketing and timeline is protracting.
- Data is accumulating in many disease areas
- Incorporating external data to new trial can help to accelerate drug development
- External control data has high quality
- Incorporating to substitute a control arm or create a synthetic control arm
- No free lunch
  - A smaller in-trial control arm leading to high variability
  - A synthetic control arm may bias comparison

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