Randomized Clinical Trials with Hybrid Controls – Designs and Considerations

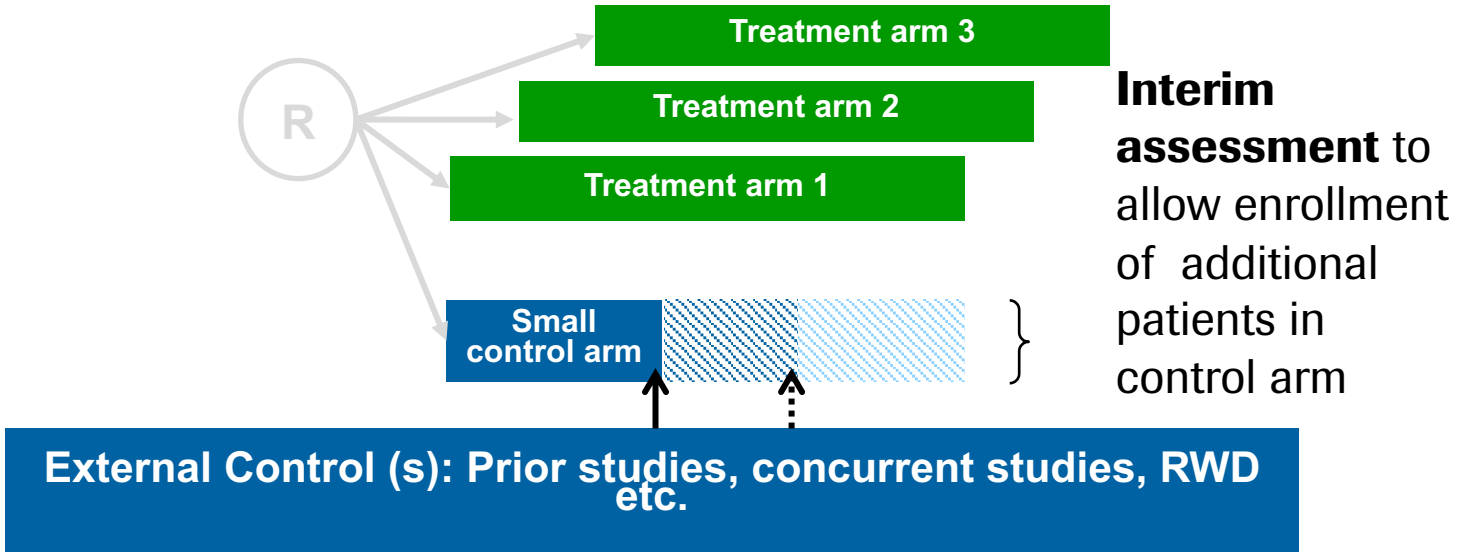
Jiawen Zhu

Principal Statistical Scientist, Genentech

BBSW, Nov. 7-8, 2019

Future trial design options

Utilize a hybrid control formed by both external and internal controls



Interim assessment to allow enrollment of additional patients in control arm

- **Opportunities**
  - the use of computers, mobile devices, wearables, and other biosensors
  - huge amounts of health-related data has been rapidly accumulated
  - development of sophisticated, new analytical capabilities
- **A way to get there…**
  - Validation on data quality and comparability
  - Right statistical methods
  - More challenges in trial operation

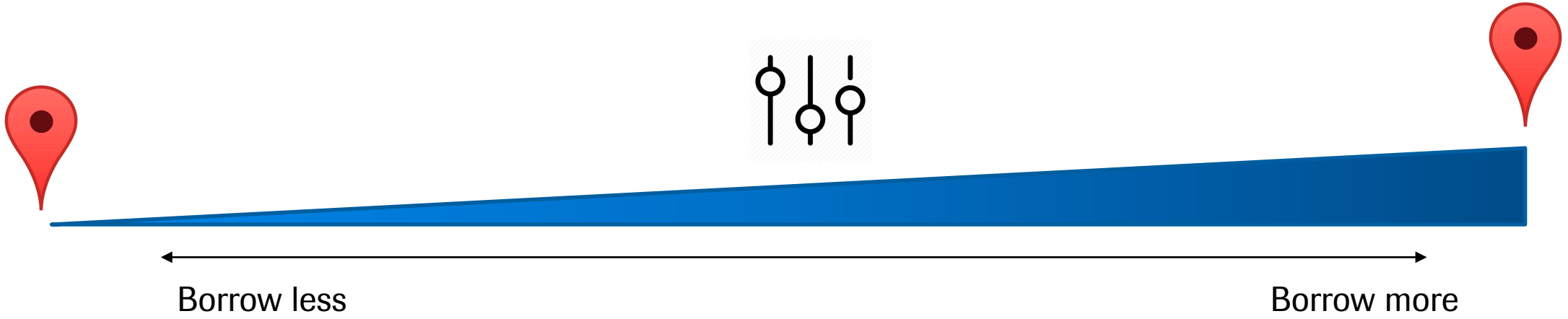
What are our choices?

1, Do not use historical/ external control

3, Dynamic borrowing

How much to borrow is updated with current data

2, Pooling



Dynamic borrowing methods (purple, green, blue) achieve similar power gains as full borrowing (red) with much less type I error inflation

K. Viele et al 2013

Type I error

Power

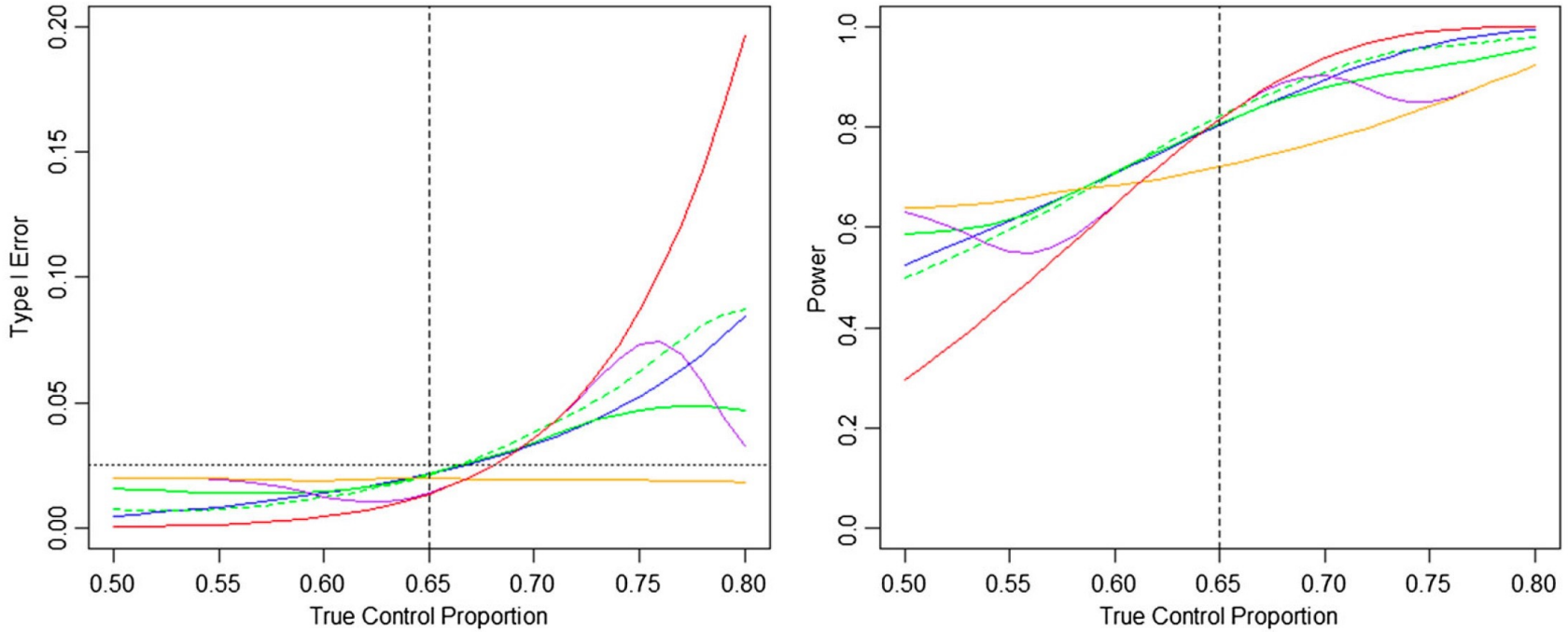
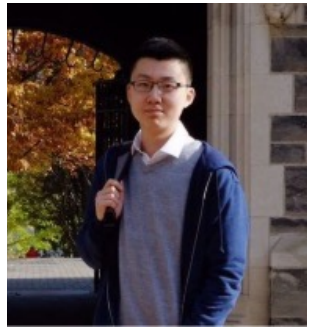


Figure 9. Type I error and power comparison for separate (orange), pooling (red), selected test-then-pool (size 0.10, purple), downweighted power prior (40% weight, blue), and hierarchical model (IGamma(1, 0.01) in dashed green, and IGamma(0.001, 0.001) in solid green). Generally, the test-then-pool approach has lower type I error and also lower power near a control rate of 0.65, but has reduced power compared to power priors and hierarchical models outside that range. For control rates near 0.65, all methods achieve similar power gains as pooling (red) with much less type I error inflation.

Dive in method operating characteristics

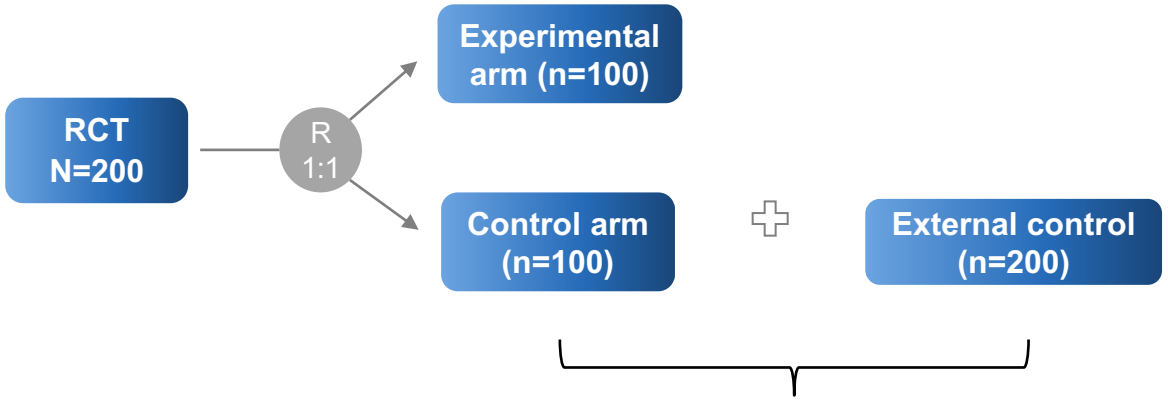
Simulation based on commensurate priors approach as an example



Ruilin Li

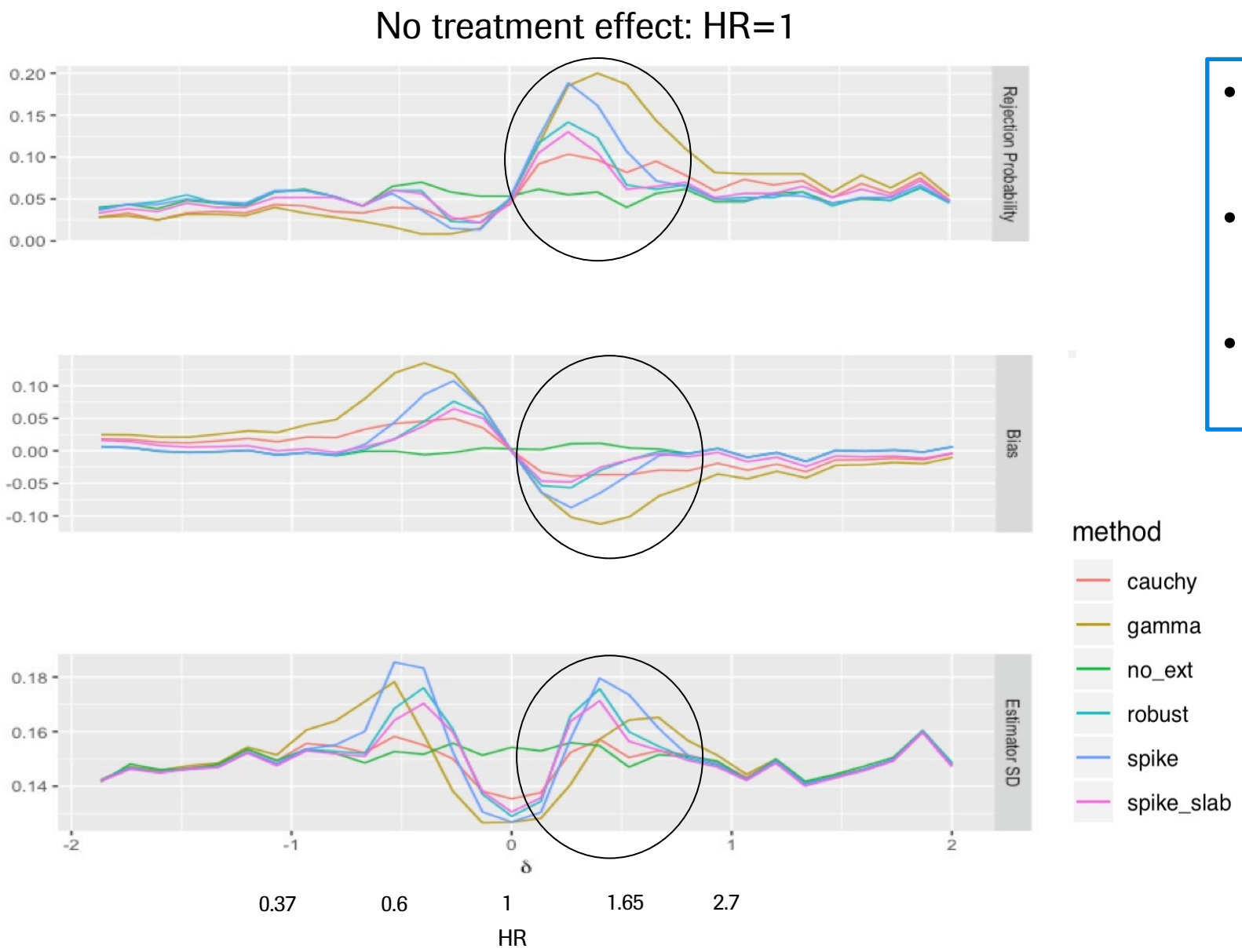
- Bias (δ) between internal/external control were assessed under a survival endpoint setting
- Aggressiveness level of borrowing were examined through Bayesian model with 5 different hyper-priors

For each simulated trial

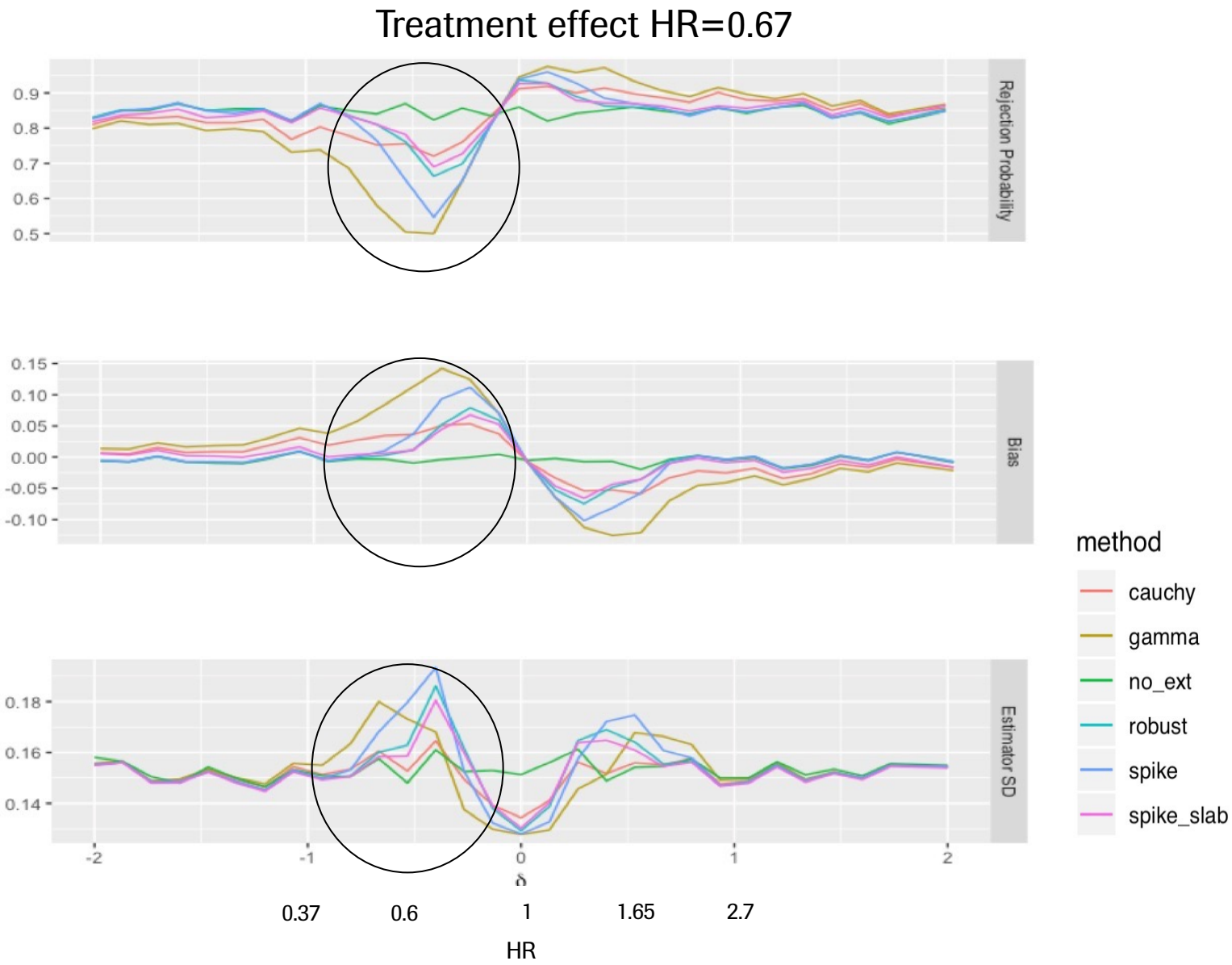


Bias (δ) were simulated from HR = 0.14 to 7.4

- Weibull distribution was assumed for time to event endpoint
  - RCT control median event time is 4 months
  - RCT treatment arm median event time is set to 4months and 7months

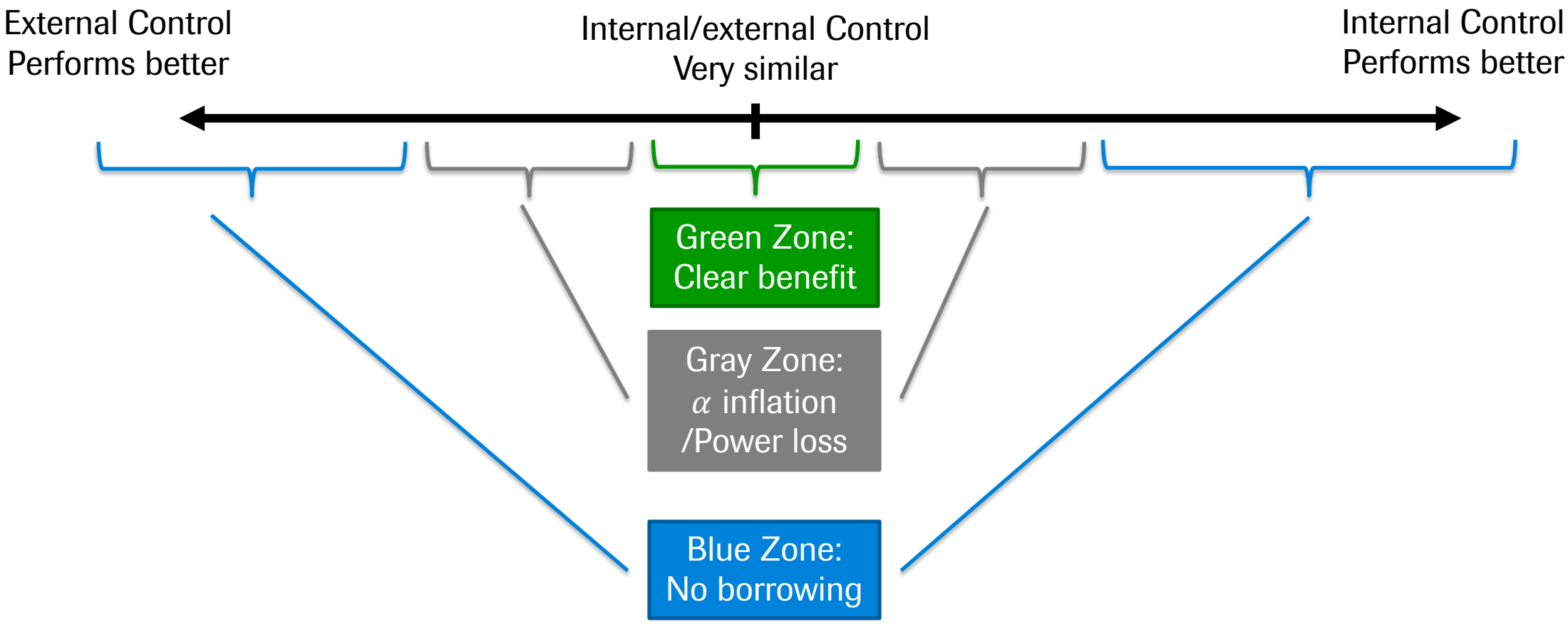


- Good type I error control at $\delta = 0$ and $\delta > 1$
- Global maximum of type I error happened at $\delta \in (0,0.5)$
- How models are set-up impacts to the area of type I error inflation



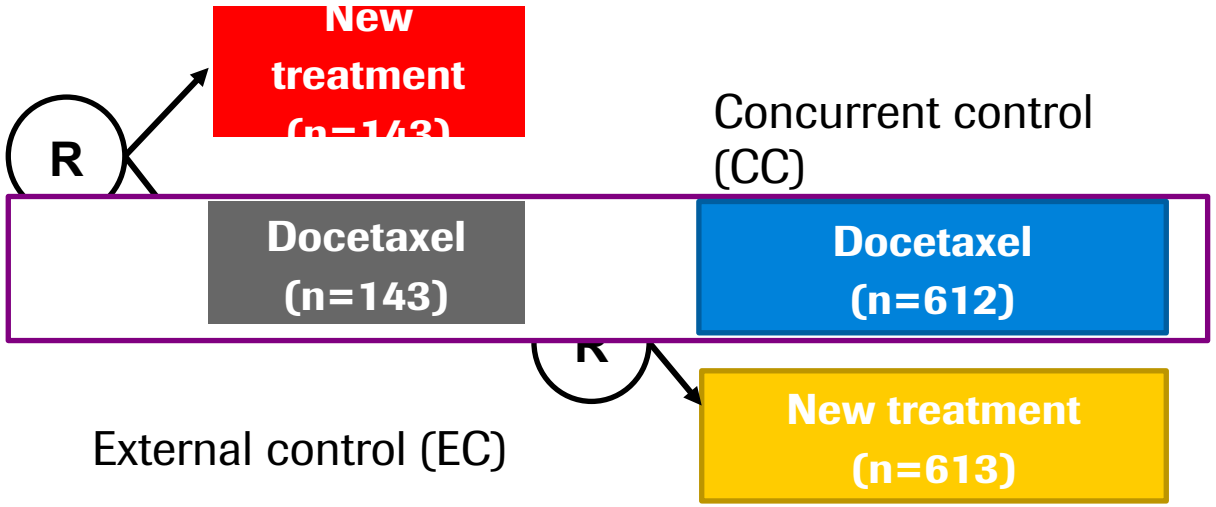
- Power gain at range $\delta > -0.1$
- Global minimum of power loss happened at range $\delta \in (-0.5, 0)$ or $(-1, 0)$ up to model set-up
- How models are set-up impacts to the area of power loss

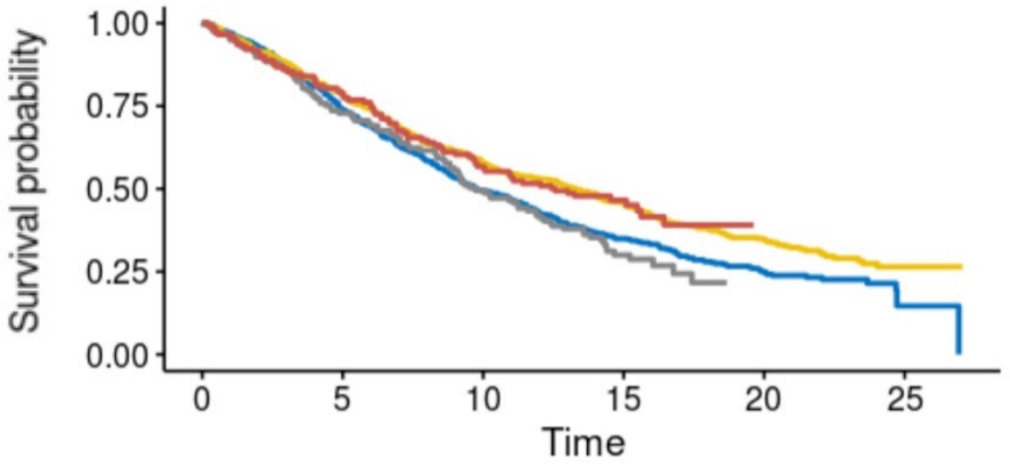
New design variable to consider: *Control comparability*



Post-hoc hybrid control example 1

Borrowing data from an almost identical trial in NSCLC

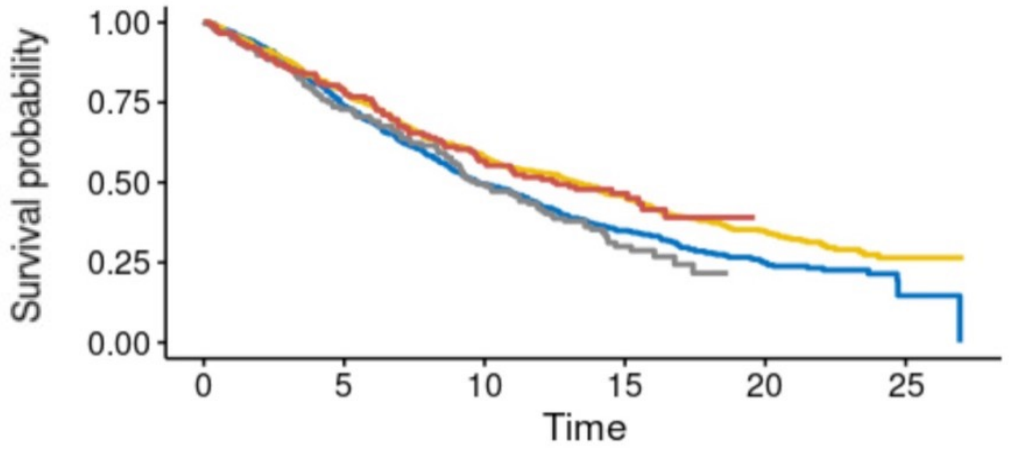




Number at risk

Trial A control	612	415	266	177	70	6
Trial A new trt	613	464	332	250	116	15
Trial B control	143	97	65	24	0	0
Trial B new trt	144	110	78	33	0	0

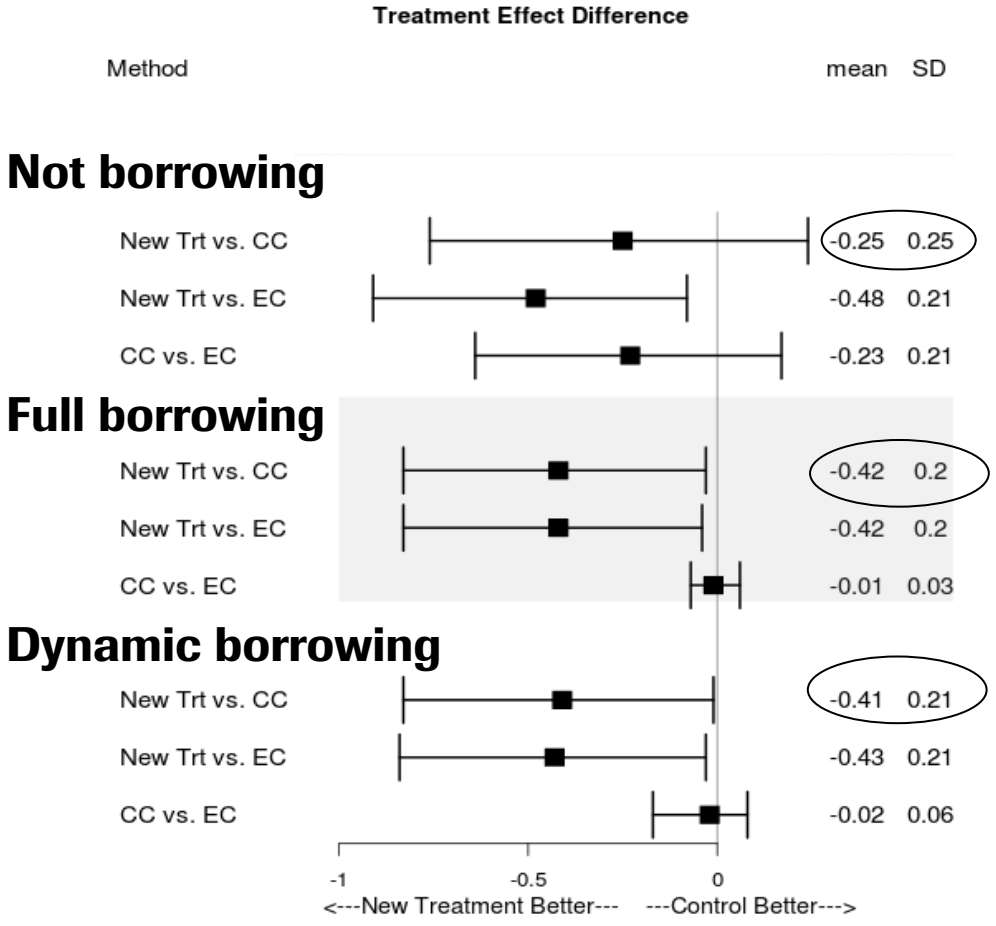
Dynamic borrowing objectively accepts external control when controls are comparable



Number at risk

Trial A control	612	415	266	177	70	6
Trial A new trt	613	464	332	250	116	15
Trial B control	143	97	65	24	0	0
Trial B new trt	144	110	78	33	0	0

resample 50 pt/arm from trial A and borrow control from trial B (n=143)

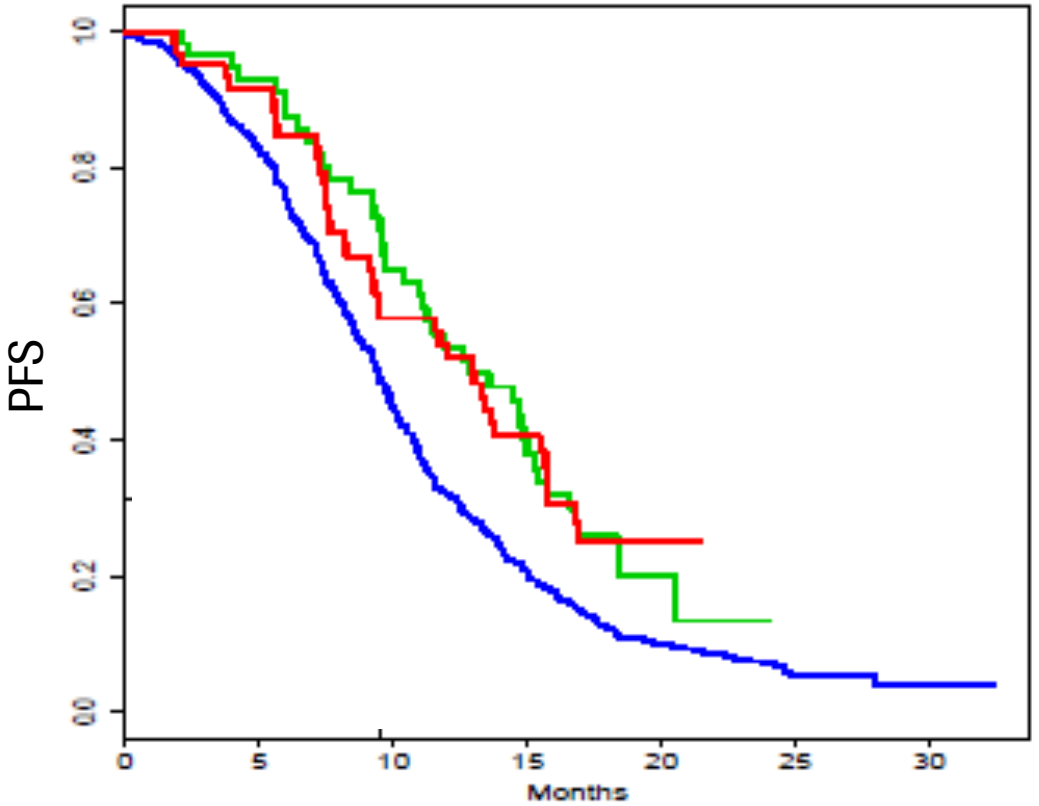


Notations: CC: concurrent control from trial A
EC: external control from trial B

Post-hoc hybrid control example 2

Borrowing data from historical studies in mCRC

Study	EC1 (2008)	EC2 (2012)	More Recent: Trial C	
Treatment	Folfox+Bev (n=349)	Folfox+Bev (n=64)	Folfox+Bev (n=62)	New treatment (n=63)
ORR(%)	47	47	64	58.7
Median DoR(mo)	8.3	9.9	11.1	10.8
Median PFS (mo)	9.5	9.9	12.8	13.1

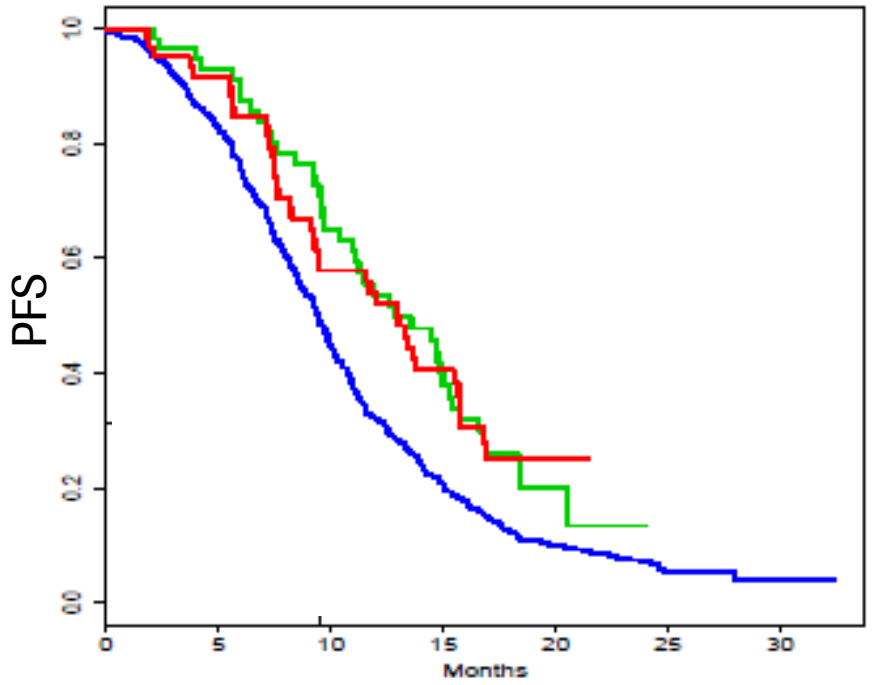


Green: control data from trial C (n=62)

Red: New treatment from trial C (n=63)

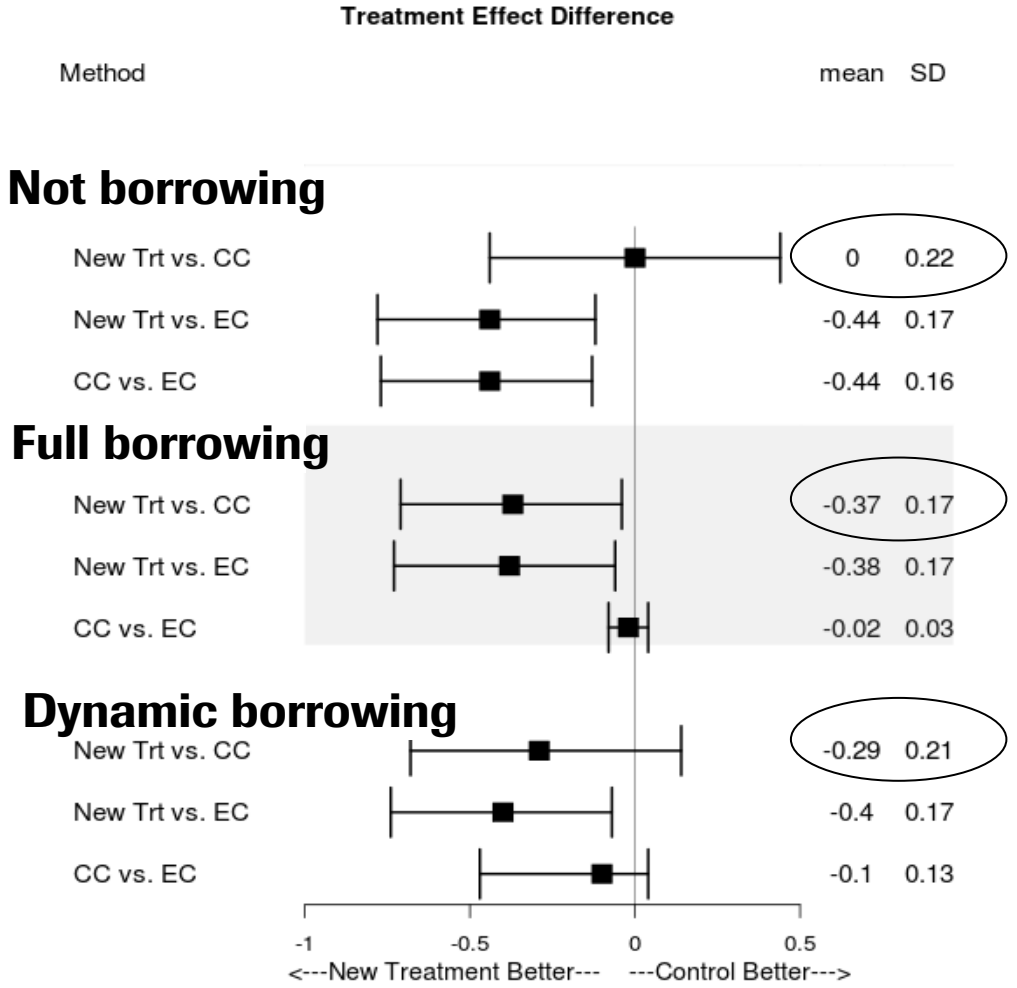
Blue: control data from pooled historical/external trial D and E (n=413)

Dynamic borrowing objectively downweighs external control when controls are not comparable



Green: control data from trial C (n=62)
Red: New treatment from trial C (n=63)
Blue: control data from pooled EC1 and EC2 (n=413)

Trial C borrow control from trial EC1 and EC2

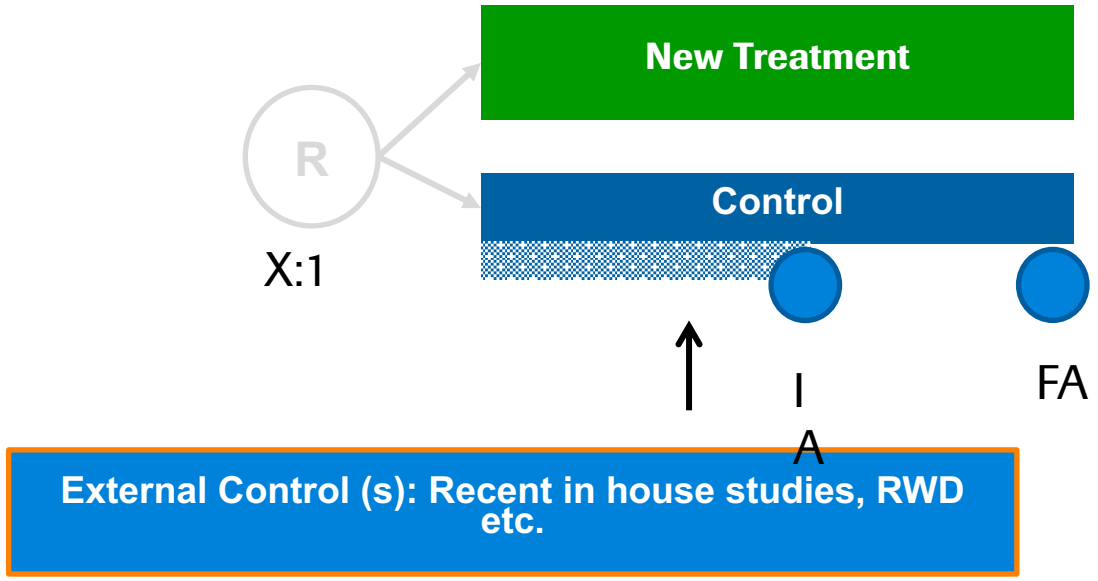


Notations:
CC: concurrent control, EC: external control

When design a hybrid control trial

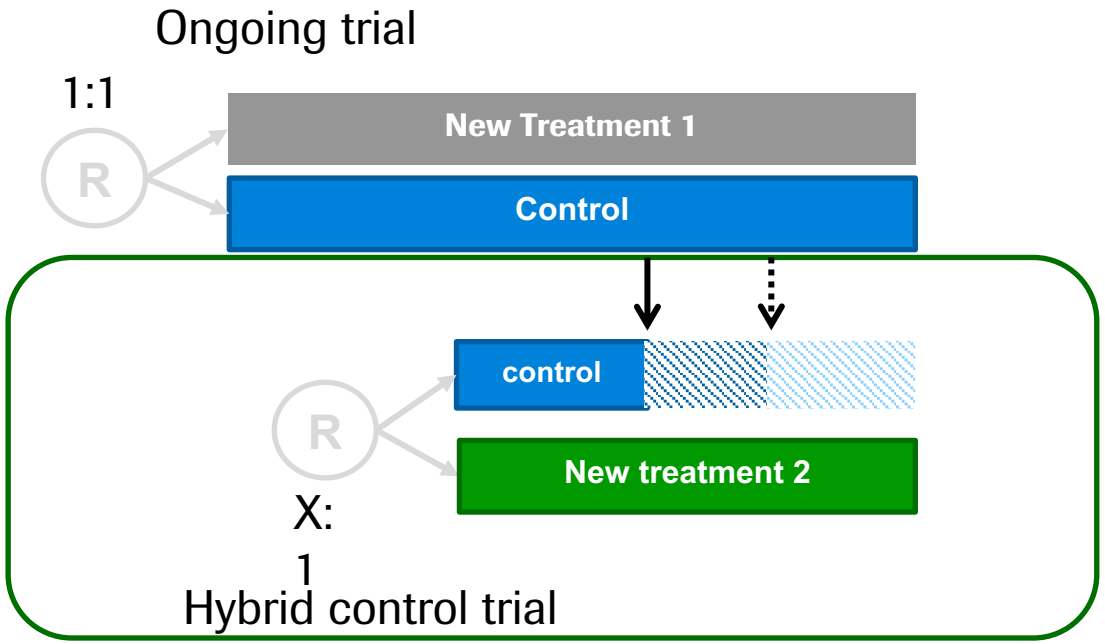
- New design variable: Internal/external control comparability (δ)
  - Make assumptions (SOC are fully established and well known)
  - Plan for the “worst” scenario
- To quantify the external control
  - Effect historical sample size $EHSS \approx n_{hist}\{(\text{Prec}(\theta|\text{D}, D_0))/(\text{Prec}(\theta|\text{D})) - \mathbf{1}\}$
  - Numerical approach
- Adaptive design
  - To insure sufficient study power
  - Better fits in trials with long enrollment period
- To support *selected* analysis/objectives
  - e.g. interim analysis, subgroup analysis etc.

Design example 1: a “Minimally invasive” hybrid control trial



- Design study with planed power at final analysis
- Enables more informative decision making at interim analysis
- Possibility to bring in decision timeline
- Minimal modification
- No sample size saving
- Potential place to employ:
  - POC trials, confirmatory trial with HA buy-in

Design example 2: an adaptive hybrid control trial



➢Design study with X:1 randomization ratio

➢Design interim look(s) for control comparability assessment

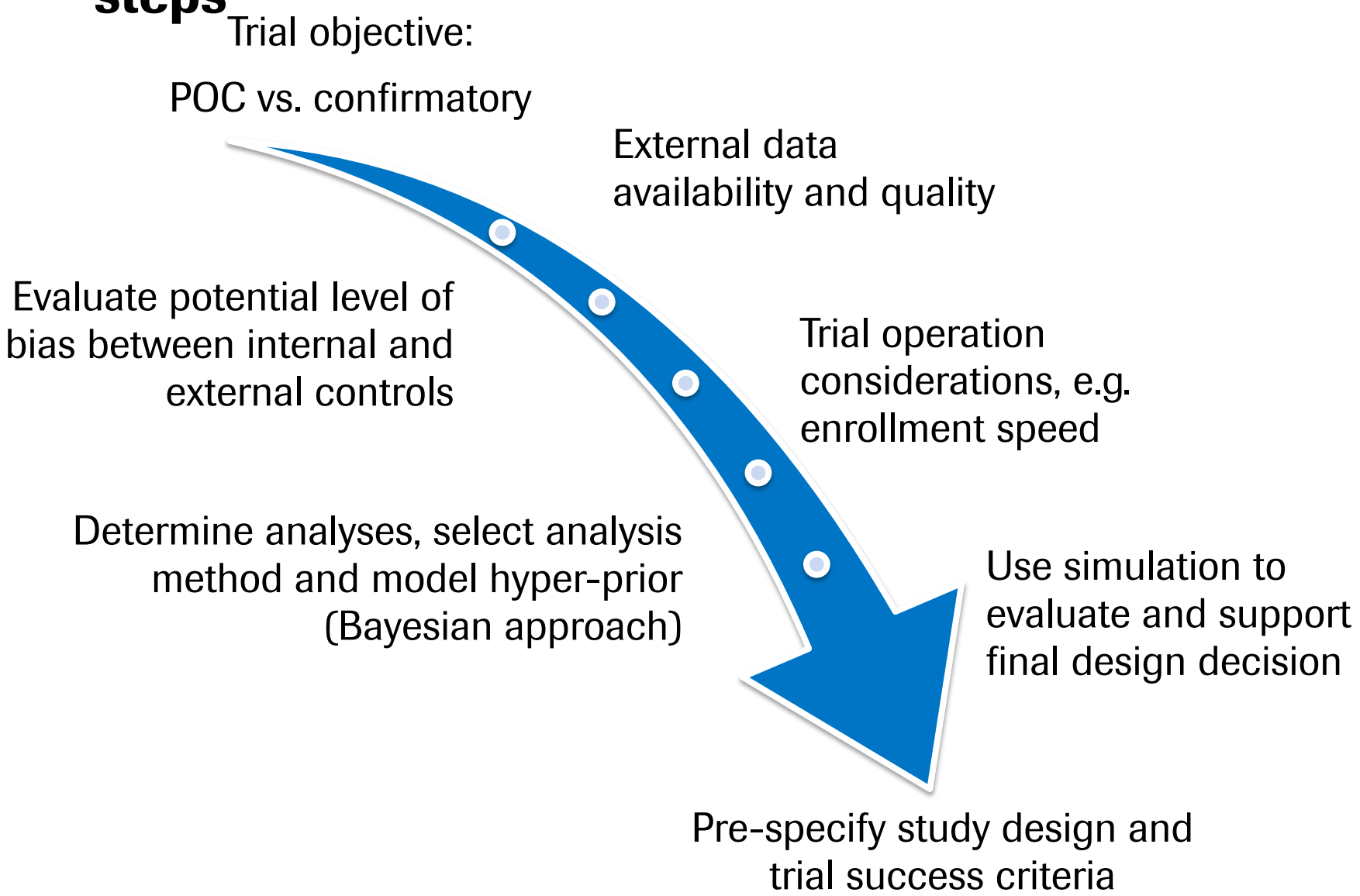
➢ Adjust the randomization ratio when the interim indicates commensurable sets of controls

➢Operational-wise is more challenging

➢Potential place to employ:

➢confirmatory trials in rare disease

Hybrid control trial design decision flow: 7 steps



Summary

- It is an emerging field, a lot of opportunities for industry- industry, industry-academia collaborations
- It's critical to assess control data quality and potential bias before designing a study
- More fine tunings and planning are required than standard trial
- Trial OC simulation will be needed for each trial design
- Pre-specify method and analysis plan in SAP and be transparent!

Acknowledgement

External collaborators:

Somnath Sarkar, Brad Carlin, Ruilin Li, James Normington, Connor Jo Lewis

Roche/Genentech Biostatistics colleagues:

Cornelia Irl, Qi Xia, Jane Fridlyand, Imola Fodor,
Federico Mattiello, Ray Lin, Joseph N. Paulson

Roche/Genentech real world data scientist colleagues:

Natalia Sadetsky, Angela Hsieh

Reference

- TransCelerate PSoC Workshop outline, 11-12 Oct 2016, Jersey City
- Pocock SJ. The combination of randomized and historical controls in clinical trials. J Chron Dis 1976;29:175–88.
- Viele K, Berry S, Neuenschwander B, Amzal B, Chen F, Enas N, et al. Use of historical control data for assessing treatment effects in clinical trials. Pharmaceut Statist 2014;13:41–54.
- Lim, J., R. Walley, J. Yuan, J. Liu, A. Dabral, N. Best, A. Grieve, L. Hampson, J. Wolfram, P. Woodward, et al. 2018. Minimizing patient burden through the use of historical subject-level data in innovative confirmatory clinical trials: Review of methods and opportunities. *Therapeutic Innovation & Regulatory Science* 52:546–559
- Lewis, C.J., Sarkar, S., Zhu, J., and Carlin, B.P. (2018) Borrowing from Historical Control Data in Cancer Drug Development: A Cautionary Tale and Practical Guidelines, accepted by Statistics in Biopharmaceutical Research
- Normington, J., Zhu, J., Mattiello, F. Sarkar, S., and Carlin, B.P. An effective Bayesian platform trial design for borrowing adaptively from historical control data in lymphoma, submitted to CCT
- Pennello, G. and Thompson, L. (2008). Experience with reviewing Bayesian medical device trials. J. Biopharmaceutical Statistics, 18, 81(115).
- Hobbs, B.P., Carlin, B.P., and Sargent, D.J. (2013). Adaptive adjustment of the randomization ratio using historical control data. Clinical Trials, 10, 430 440.
- Chen, N., Carlin, B.P., and Hobbs, B.P. (2017). Web-based statistical tools for the analysis and design of clinical trials that incorporate historical controls. Research report, Division of Biostatistics, University of Minnesota. Submitted to J. Statistical Software.
- Irony, T. (2019) Regulatory Perspectives when Leveraging Complex Innovative Trial Designs. DIA/FDA Biostatistics Industry and Regulator Forum, Bethesda, April 8-10, 2019

Doing now what patients need next