Use of External Data for Efficient and Robust Evidence Generation:
A Case Study of Dynamic Borrowing with External Control for Overall Survival

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Objective

- Share experience of collaborating with the FDA on the design of a phase 3 randomised study in 1L Diffuse Large B-Cell Lymphoma (DLBCL) through the FDA's Complex Innovative Trial Designs (CID) Meeting Program

Why Innovative Design was needed

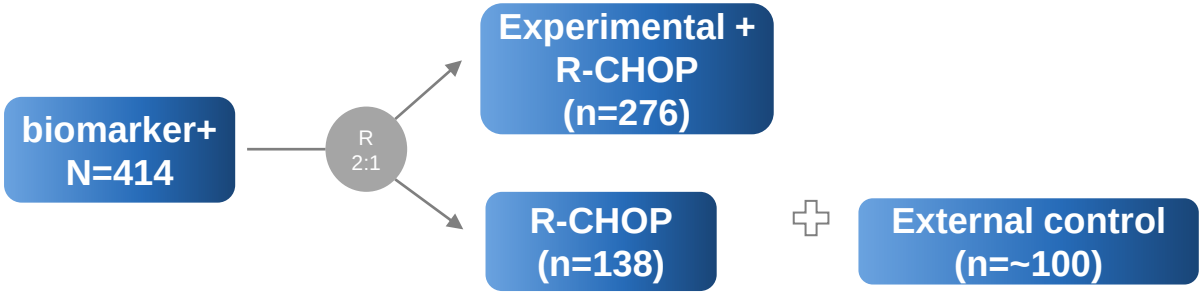
Unmet medical need in certain subgroup of DLBCL patients

- Diffuse large B-cell lymphoma (DLBCL) is the most common non-Hodgkin's lymphoma (NHL) worldwide, with 25,000 newly diagnosed patients in the United States (US) annually
- Standard of care for 1L DLBCL patients established over 20 years ago: it is well characterized and well understood
- Patients in certain subgroup of DLBCL have a poorer prognosis and consequently a high unmet medical need

"Borrowing" patients from the control arm of another study helps us

- Having fewer 'new' patients treated with a control regimen that is well established and that we know well
- **Shorten our study**
- Conducting **more efficient trials** by sharing control data between trials

Proposed Phase 3 Study Design in 1L DLBCL



Primary Endpoint:

- **PFS Investigator Assessed**

Key Secondary Endpoints

- **OS**, based on randomized patients & matched external control

- Analysis of primary endpoint (PFS) based on the randomized patients, designed to provide 80% power at the 5% significance level to detect a target HR of 0.6, one IA at 80% of events
- External control patients to be selected from a contemporary, ongoing internal clinical trial
- External control arm intended to support early OS analysis at the time of the primary PFS analysis
- Randomized study with external control arm using matched external controls through Bayesian dynamic borrowing

Rationale for Source of External Control Arm

- Prospective plan to select external controls from an ongoing, contemporary, internal randomized controlled clinical trial
- Consistent eligibility criteria planned
- Aim to target similar Sites and Investigators to aid similarity
- OS is a clear and clinically meaningful endpoint with minimal ambiguity in event determination
- 5 of the 6 proposed criteria outlined by Pocock* (1975) for selecting an external control source met

✓ Receiving a precisely defined standard treatment, the same as for randomized controls

✓ Part of a recent clinical study which contained the same requirements for patient eligibility

✓ Methods of treatment evaluation must be the same

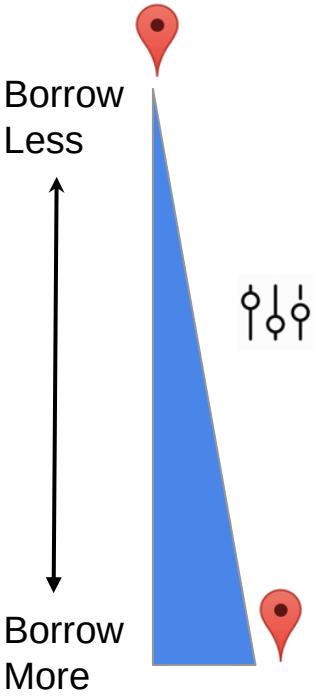
✓ Previous study must have been performed in the same organization with largely the same Investigators

✓ There must be no other indications leading one to expect differing results between the randomized and historical controls

- Distributions of important patient characteristics should be comparable to those in the new study

* Pocock SJ, Simon R. et al Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. Biometrics. 1975;31:103–115

How to Mitigate Potential Biases: Borrowing approaches

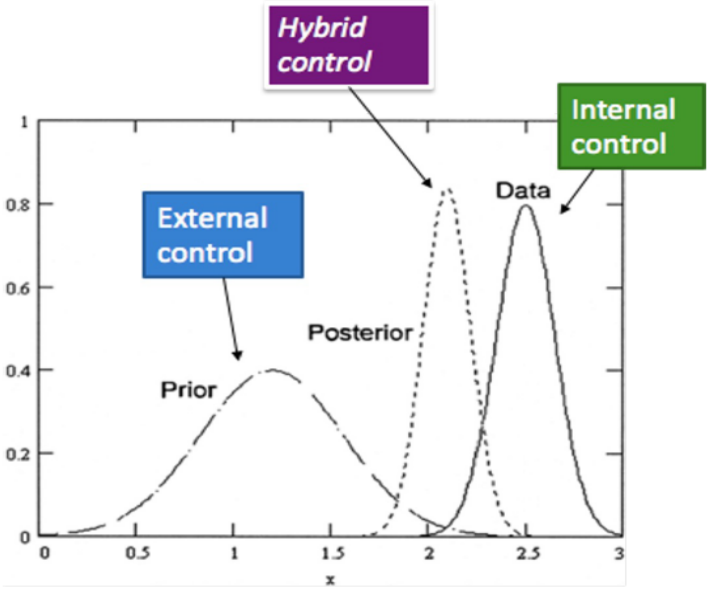


- **No borrowing**
  only RCT data is used to estimate treatment effect
- **Dynamic borrowing: Conservative prior**
  Sceptical on external control
- **Dynamic borrowing: Aggressive prior**
  Optimistic on external control
- **Full borrowing**
  Two controls are pooled together when estimating treatment effect

Dynamic borrowing mitigates risks of borrowing inconsistent external control if there are things that "we don't know we don't know"

Method reference: Lewis, CJ, Sarkar, S, Zhu, J, Carlin, BP et al. Borrowing from historical control data in cancer drug development: A cautionary tale and practical guidelines. Statistics in Biopharmaceutical Research, 11(1):67–78, 2019

How to Mitigate Potential Biases: Bayesian methods can be used to bring in external controls



Statistical distributions

- A natural way to borrow information from external or historical controls
  - External trial data can be used in setting up the study prior
- Impacts of informative prior
  - Potential for increased influence of the datasets with bias
- It is important to take into account the difference between internal/external control data
  - A **dynamic borrowing** framework

Figure adapted from "Methods for Assessing the Credibility of Clinical Trial Outcomes –Drug information journal; Robert A. Matthews (2001)"

CID Pilot Program Process & Our Experience

- Complex Innovative Trial Designs (CID) pilot Meeting Program lasts for 240 days counting from submitting meeting request and includes two 1.5hr meetings
- CID pilot program facilitated a collaborative scientific discussion with the FDA
- FDA required detailed proposals of the planned statistical methodology supported by extensive simulations
- The opportunity for 2 separate meetings helped to reach alignment on the statistical methodology
  - Preliminary method proposal: Propensity score covariate adjustment; key discussion at CID #1
  - FDA perceived the results may be difficult to interpret using this approach
  - FDA recommended methods that require minimal assumptions, allowing a straightforward interpretation of the treatment effect
  - Propensity score matching method proposed by Sponsor as an alternative
  - We were able to clarify design and analysis in CID #1 and provide updated analysis plan and simulation based on propensity score matching before CID #2
- FDA agreed that updated statistical methodology and new simulations were acceptable for the analysis of OS as the first secondary endpoint, which has the potential to be included in labelling
- Link to published case study on FDA website: https://www.fda.gov/media/155405/download

What was the FDA looking for?

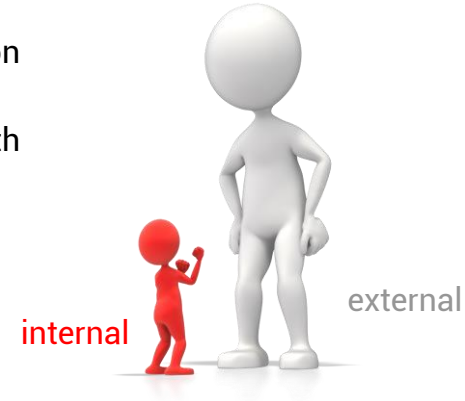
- **Model-assumptions assessment**
  - Standard analysis typically requires few assumptions
  - Borrowing: more assumptions and less standard; FDA provided valuable input on where and how to make assessments
- **Pre-specification**
- **What could hamper inclusion of OS in label (similar to traditional designs):** examples include
  - Whether the model assumptions appear to be met
  - Any outlying subgroup effects
  - Whether the endpoint was credibly captured or not
  - Overall conduct of the study
  - Missing data
  - Level of comparability of baseline characteristics
- **Non-statistical considerations:**
  - Is the summary of analysis clear?
  - Interpretable by clinicians?
  - Provides valuable information?

Along with these considerations, ultimately, the FDA requires the final data from such a novel design to gain confidence in the ability to utilize external controls more readily

Final Analysis Flow Diagram

Control comparability evaluation | Propensity score matching | Bayesian dynamic borrowing

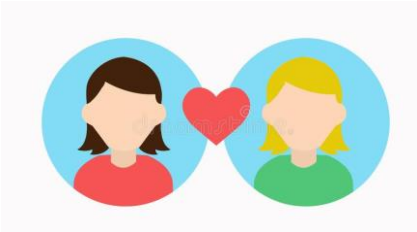
- Apply inclusion/exclusion criteria
- Flag baseline factors with significant difference between internal and external trials



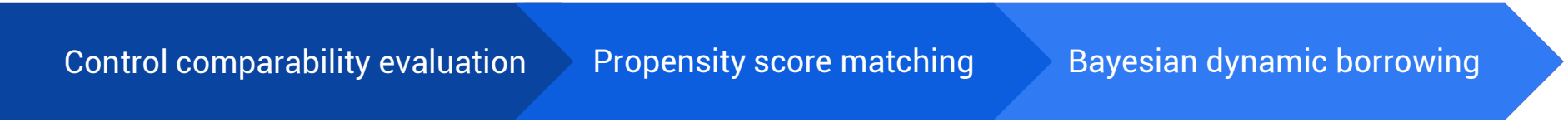
Final Analysis Flow Diagram

Control comparability evaluation | Propensity score matching | Bayesian dynamic borrowing

- Match patient population between internal and external trials using propensity score matching (PSM)
- Enhance covariates balance by filtering out unmatched patients



Final Analysis Flow Diagram



A method to:

- Automatically downweight external control data based on internal/external control agreement
- Provide inference of treatment effect with hybrid control (i.e. OS analysis)

Sensitivity analysis follows main analysis

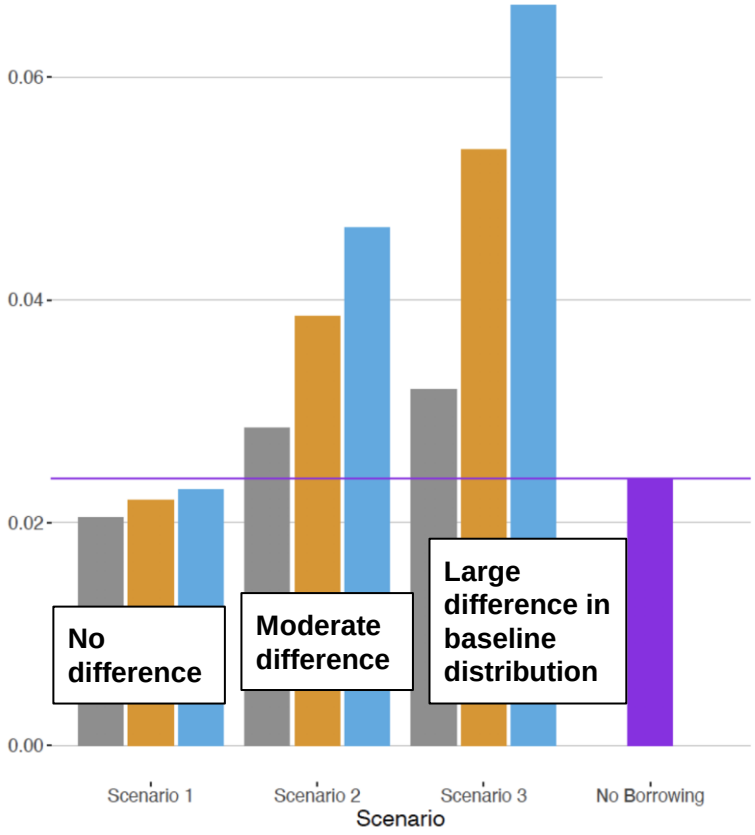
Simulation scope and objective

- Focused on the evaluation of the proposed statistical method (PS matching and the Bayesian commensurate prior approach)

- Examined the trial operating characteristics (OC) under:
  - Varying magnitude of ***differences in baseline characteristics***
  - Different ***choices of the commensurate prior*** which influences the degree of borrowing
  - ***Violation*** of various ***assumptions***

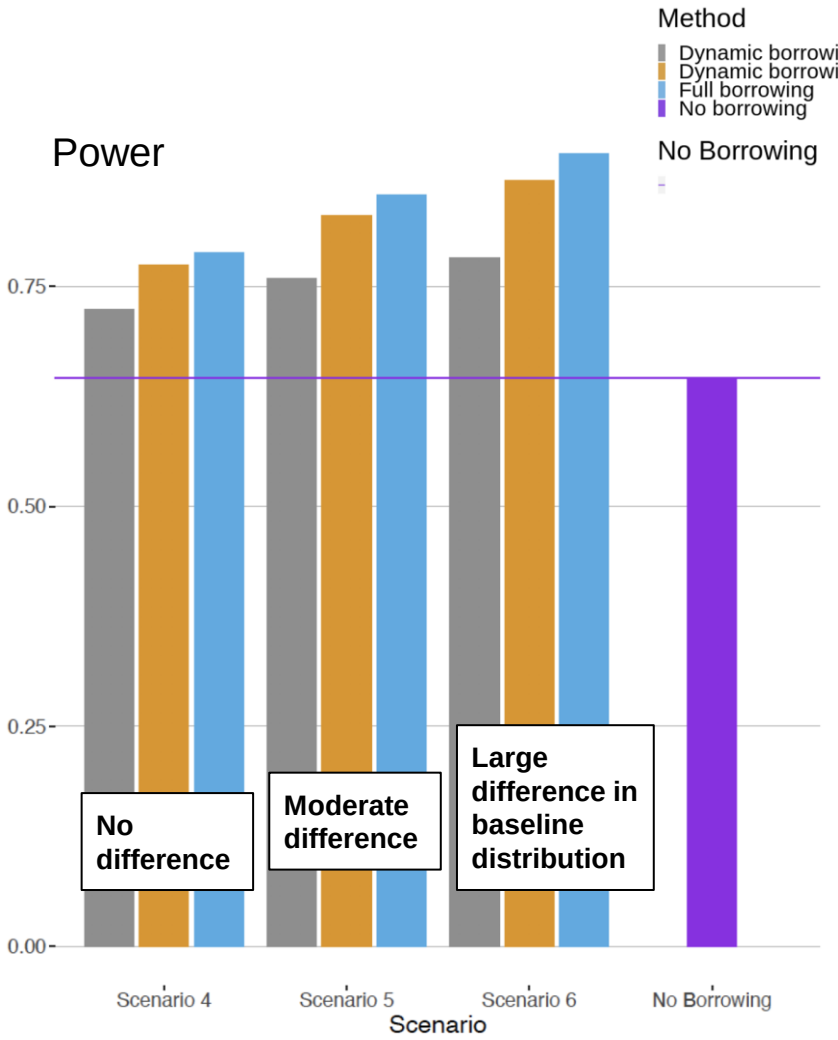
Simulation results highlights

Type I error



HR=hazard ratio; OS=overall survival.

Power



HR=hazard ratio; OS=overall survival.

Simulation results discussion

Table 19 Summary Table to Compare Method Performance for Differences in Baseline Characteristics Investigations

Approaches		Average Error Rate	Weighted Type I Error Rate*	Max Type I Error Rate
No borrowing (only RCT data)		0.024	0.024	0.024
Dynamic borrowing (with external control)	Conservative prior	0.023	0.023	0.032
	Aggressive prior	0.028	0.026	0.054
Full borrowing (pooling two control arms)		0.033	0.029	0.067

RCT= randomized controlled trial

* Weighted Type I Error Rate is calculated based on the assumed probability on the various scenarios: The probability for “The same” is assumed to be 62.5%, “moderate”, 20%, “large” 5%, “moderate reverse” 10%, and “large reverse” 2.5%.

Simulation Summary

- Consistent findings on the operating characteristics observed across all simulations covering a range of scenarios and assumptions

- The dynamic borrowing following by PS matching with a conservative prior method (half-Cauchy) has the most promising operating characteristics

Future Considerations for External Controls

- Disease setting is a key consideration in determining the suitability of a study design for external borrowing
  - Studies evaluated on a case-by-case basis
  - Studies in which we historically treat patients in the same way (eg. DLBCL) potentially strong candidates for innovative borrowing approaches
- External control arm source an important aspect
  - Our proposal met 5/6 Pocock criteria – other RWD sources will likely fulfil less
  - Aligning between trials on control treatments, endpoint definitions and other operational aspects will improve the quality of available control data for borrowing
- FDA showed an openness to our design with external controls for the secondary OS endpoint, although approvability remains a review issue
  - An important step towards the future and an ideal state of borrowing for a primary endpoint
- Early sponsor and Health Authority engagement is paramount when considering novel trial designs
- Successful adoption of novel innovative designs requires a collaborative effort between HA, academia and industry

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