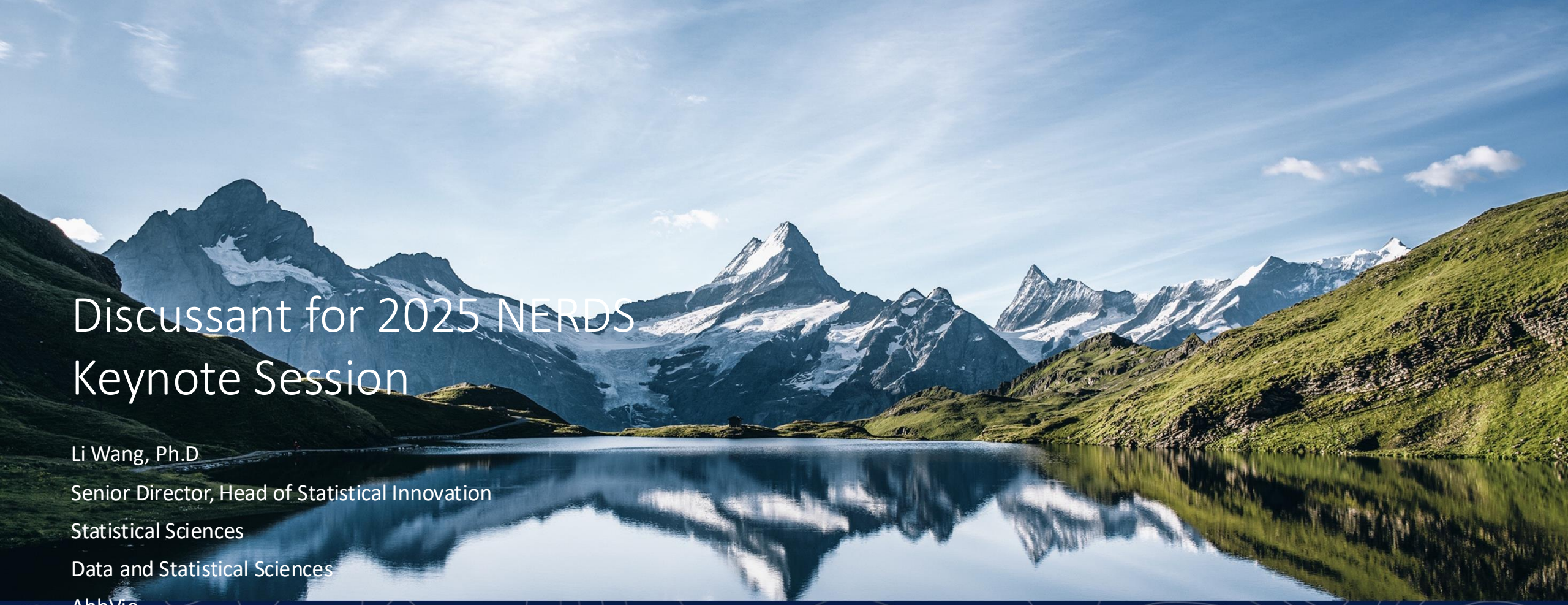


Discussant for 2025 NERDS Keynote Session

Li Wang, Ph.D

Senior Director, Head of Statistical Innovation

Statistical Sciences

Data and Statistical Sciences

AbbVie

10/10/2025

abbvie

Data & Statistical Sciences

Disclosure

- The support of this presentation was provided by AbbVie. AbbVie participated in the review and approval of the content.

- Li Wang is an employee of AbbVie Inc. and may own AbbVie stock.

AbbVie in 2023

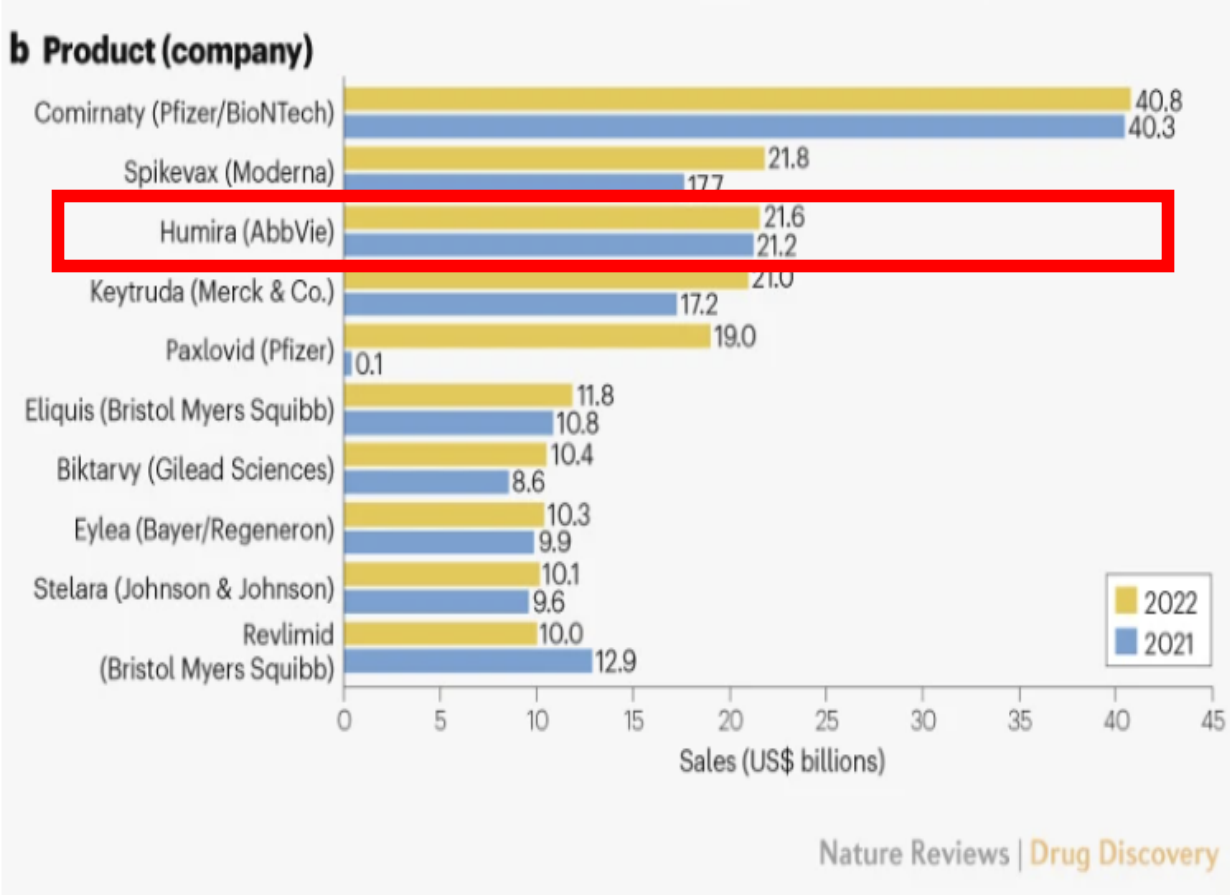


Fig. 1 | Top companies and drugs by sales in 2022. a, Top ten companies by sales of prescription and over-the-counter drugs. **b**, Top ten drugs by sales globally. Source: EvaluatePharma.

Source: https://www.proclinical.com/blogs/2023-7/the-top-10-pharmaceutical-companies-in-the-world-2023

Creating medicines and solutions that put impact first

- **50K+**
  - employees working in 70+ countries

- **$50B+**
  - invested in R&D since AbbVie's launch in 2013

- **~62MM**
  - **people are treated with AbbVie's products every year, including more than 21 million people in the United States**

- **175+**
  - countries where AbbVie products help people and patients including ~20 countries with R&D and/or manufacturing facilities

30 brands

and 60+ conditions treated across infants, adolescents, adults & seniors

Recognized for being a good corporate citizen and for our contributions to society and business performance

SIG Expertise and Publications/Manuscripts in Innovative Designs to Speed Up Clinical Development

Adaptive designs to make early or more informed decision

"Seamless phase II/III clinical trials with covariate adaptive randomization" (2022)

"Testing hypotheses of covariate-adaptive randomized clinical trials with time-to-event outcomes" (2023)

"Covariate-adjusted response-adaptive designs based on semiparametric approaches" (2023) and many more…

More Powerful Designs (Optimal Design)

"Bayesian optimal phase II design for randomized clinical trials" (2022)

"BOP2-DC: Bayesian optimal phase II designs with dual-criterion decision making" (2023)

"Bayesian Optimal Power Multi-Arm-Multi-Stage Design with Survival Endpoint" (in prep) and many more

Run trials in parallel rather than sequentially

"A Bayesian platform trial design to simultaneously evaluate multiple drugs in multiple indications with mixed endpoints" (2023)

"A Bayesian Predictive Platform Design for Proof of Concept and Dose Finding Using Early and Late Endpoints" (submitted) and many more

Leverage out-of-trial data sources to Augment or Replace in-trial Data

"Addressing statistical issues when leveraging external control data in pediatric clinical trials using Bayesian dynamic borrowing" (2022)

"The targeted virtual control approach for single-arm clinical trials with external controls" (2022)

"Leveraging external evidence using Bayesian hierarchical model and propensity score in the presence of covariates" (2023) and many more

SIG Expertise and Publications/Manuscripts in ML/DL and Advanced Analytics

Natural Language Processing (NLP)

"Natural language processing to identify lupus nephritis phenotype in electronic health records" (2023)

"Bertsurv: Bert-based survival models for predicting outcomes of trauma patients" (2023)

"Characterizing design patterns of EHR-driven phenotype extraction algorithms" (2023) and many more…

Imaging Deep Learning

"A one-step deep learning framework for psoriasis area and severity prediction trained on interventional clinical trial images" (2024)

"Unlocking the Potential of Proprietary Clinical Development Datasets for Image-Based Machine Learning Models" (submitted) and many more

Enrollment Prediction

Leveraging Deep Learning and NLP to Co-build an **End-to-End Platform** to Predict Trial Duration and Site Enrollment for different stages from Portfolio Planning, Protocol Design to Trial Execution

"Real time monitoring and prediction of time to endpoint maturation in clinical trials" (2022) and many more

Rare Event Prediction and Novel Digital Endpoint

"A Machine Learning Case Study to Predict Rare Clinical Event of Interest: Imbalanced Data, Interpretability and Practical Considerations" (2024)

"Quantifying Nocturnal Scratch in Atopic Dermatitis: A Machine Learning Approach Using Digital Wrist Actigraphy" (2024)

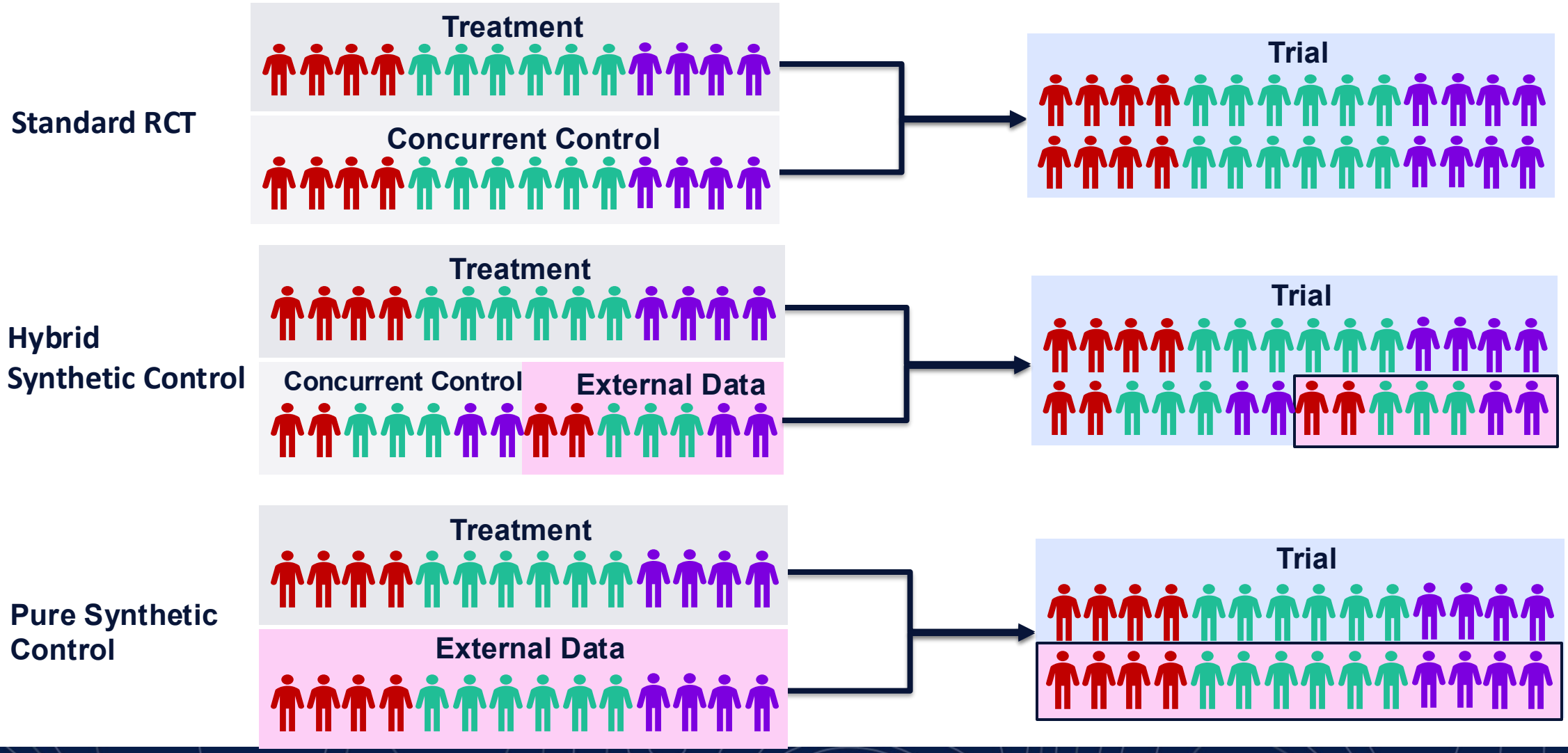
"HIV-AICare: An AI Tool for Optimizing Antiretroviral Therapy in People with HIV" (submitted) and many more

Business Need for Innovation in Rare Diseases

- Small population: < 200,000 patients in US
- Hard to enroll
- May not have existing medicine to treat
- Often times, it is not ethical or practical to enroll a control arm
- Need more innovative ways to establish “substantial evidence of the drug effectiveness”

Credit: Chris Williamson Getty Images

Innovative Trial Designs with Synthetic Control Arm



Synthetic Control Arm

- A Control Arm with Synthesized External Information
  - Hybrid Synthetic Control Arm (With Concurrent Control)
  - Pure Synthetic Control Arm (No Concurrent Control/Pure External Control)

- Advantage: Reduced sample size and shortened timeline

- Requires serious methodology consideration to ensure scientific rigorousness and validity

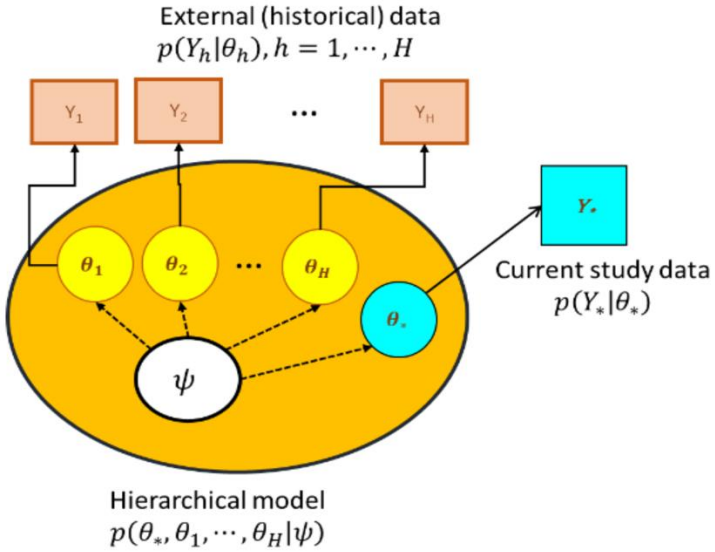
- Regulatory authority buy-in is crucial

Key Points to Consider for Synthetic Control Arm

- Available data sources
  - Natural history studies
  - Previous conducted clinical trials
  - Published data
  - Claims
  - Electronical medical records
  - Disease registries
- Careful choice of data with a good understanding of benefit and risks
- Similarity assessment of external data
- Statistical methodology to control potential bias and to achieve satisfactory design operating characteristics
- Detailed statistical analysis plan for design and analysis

Statistical Methodologies for Hybrid Synthetic Control Arm

- Bayesian Dynamic Borrowing (BHM, RMAP)



> Biometrics. 2014 Dec;70(4):1023-32. doi: 10.1111/biom.12242. Epub 2014 Oct 29.

Robust meta-analytic-predictive priors in clinical trials with historical control information

Heinz Schmidli [1], Sandro Gsteiger, Satrajit Roychoudhury, Anthony O'Hagan, David Spiegelhalter, Beat Neuenschwander

- Prognostic Modeling (PROCOVA)

Increasing the efficiency of randomized trial estimates via linear adjustment for a prognostic score

Alejandro Schuler, David Walsh, Diana Hall, Jon Walsh, Charles Fisher, for the Critical Path for Alzheimer's Disease, the Alzheimer's Disease Neuroimaging Initiative and the Alzheimer's Disease Cooperative Study

From the journal The International Journal of Biostatistics
https://doi.org/10.1515/ijb-2021-0072

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

16 March 2022
Case No.: EMA/SA/0000059571
Committee for Medicinal Products for Human Use (CHMP)

DRAFT Qualification opinion for Prognostic Covariate Adjustment (PROCOVA™)

Draft agreed by Scientific Advice Working Party (SAWP)	10 February 2022
Adopted by CHMP for release for consultation	24 February 2022[1]
Start of public consultation	22 March 2022 [2]
End of consultation (deadline for comments)	03 May 2022[3]

Comments should be provided using this template. The completed comments form should be sent to ScientificAdvice@ema.europa.eu

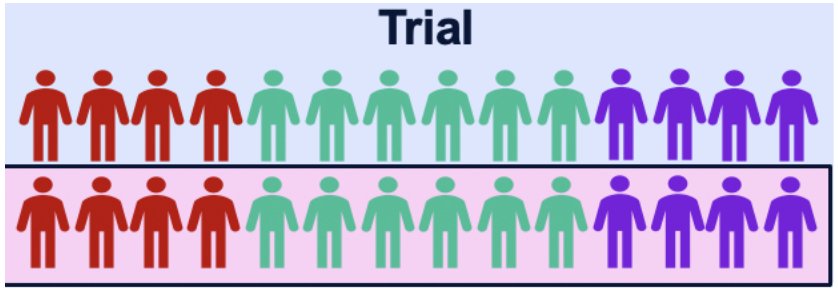
Keywords	Qualification of Novel Methodology, Statistical methodology, Prognostic Covariate Adjustment, Sample size estimation

Statistical Methodologies for Pure Synthetic Control Arm

- Propensity Score Based:
  - Matching
  - Stratification
  - Covariate Adjustment
  - Inverse Probability of Treatment Weighting (IPTW)

- Targeted Learning Based Virtual Controls
  - Super learner (ensemble learning)
  - Targeted Maximum Likelihood Estimator (TMLE)

$$\hat{\theta}_{VC-TMLE} = \theta(\hat{\mathcal{P}}^*) = \frac{1}{N}\sum_{i=1}^{N}\{Y_{ei} - \hat{Q}^*(0, X_{ei})\}$$



The targeted virtual control approach for single arm clinical trials with external controls, Yixin Fang and Sheng Zhong, AbbVie

Target Learning

- Very powerful and rigorous analysis method
- Motivated by RWE
- Two models:
  - Outcome model (predict y given treatment + covariates)
  - Treatment model (predict treatment assignment given covariates)
- Double Robustness
  - When either model is correctly specified, estimate is consistent (unbiased in large samples)
  - When both models are correctly specified, estimate is asymptoticly most efficient and consistent (in large samples)

Target Learning in Small Samples

- Needs to very cautious
- Very powerful R-packages: TMLE and LTMLE
- Super learner (ensemble modeling) can be applied to both models
- Lots of parameters to consider
- Be careful of overfit