Bristol Myers Squibb®

Digital Twins in Clinical Trials: Concepts, Applications, and Future Directions

What are digital twins

How can digital twins be used in clinical trials?

Construction of digital twins

Examples of digital twins in trials and simulations

History of digital twins

- The term **"Digital Twin"** formally coined by **Dr. Michael Grieves (~2002)**, transitioning from physical replicas to fully **data-driven virtual models**
- Rapidly adopted in manufacturing and aerospace before migrating into **healthcare**
- The EU's **DISCIPULUS Project (2011–2013)** pioneered virtual patient avatars to simulate clinical interventions
- Now being evaluated in **clinical trials** to model patient responses and reduce costs
- Used to **optimize trial design** and predict patient dropout risk and performance
- Exploring replacement of real **control-arm patients** with virtual counterparts

Digital Twins for Clinical Trials

Digital twins: ***AI/ML-generated baseline projections of outcome trajectories under placebo or standard-of-care for all trial participants***

Prognostic Covariates

Twin-derived prognostic scores reduce unexplained variability, improving statistical power and enabling smaller, more efficient trials.

Patient Enrichment & Smart Selection

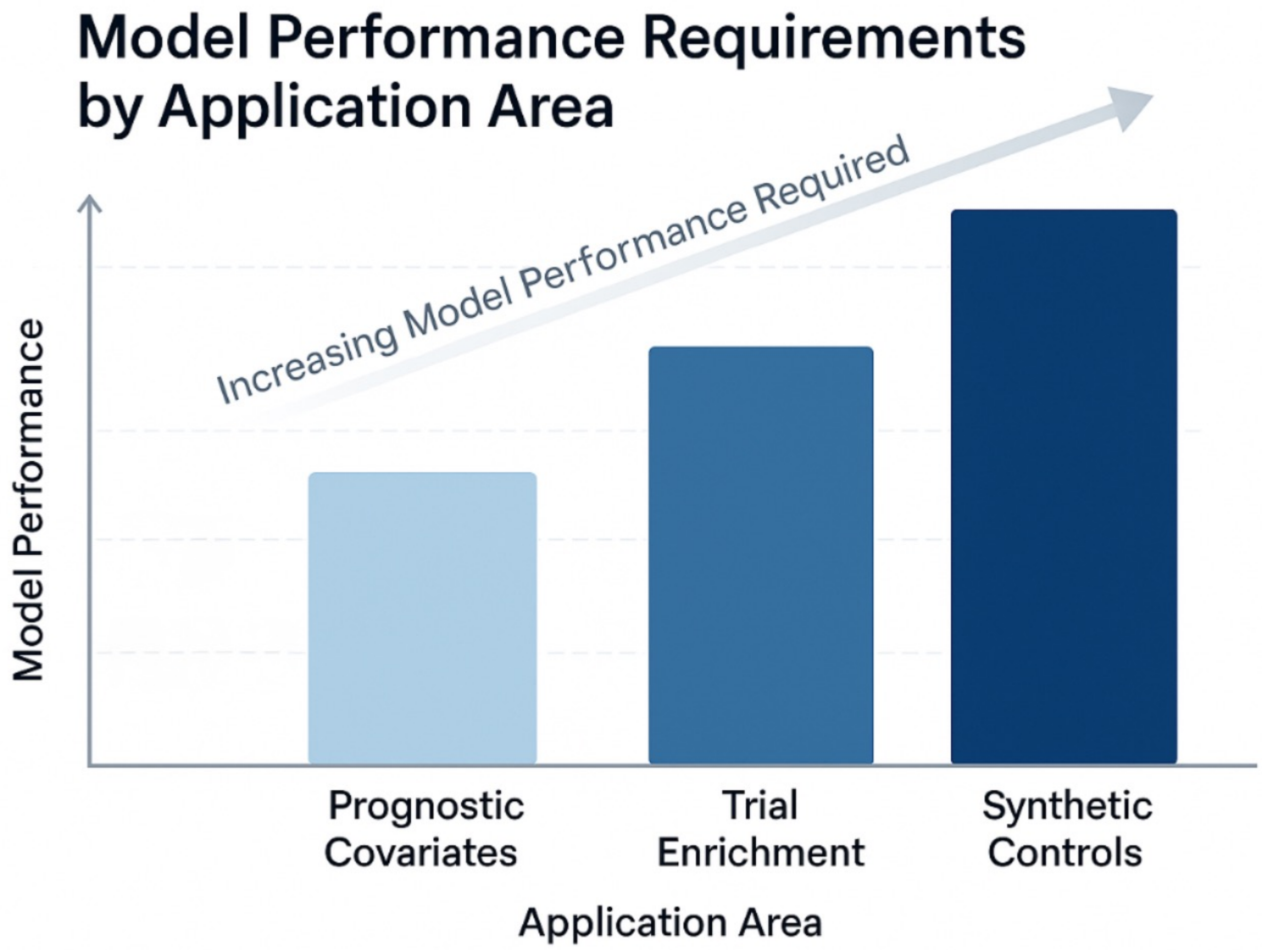
Identify individuals likely to exhibit measurable progression under SOC, improving treatment-effect detectability and accelerating trials.

Synthetic/Hybrid Controls

Use predicted control-trajectories to replace or augment control arms—reducing control-arm size, patient burden, and timelines while maintaining rigor.

Examples of DT development and application in pivotal clinical trials:

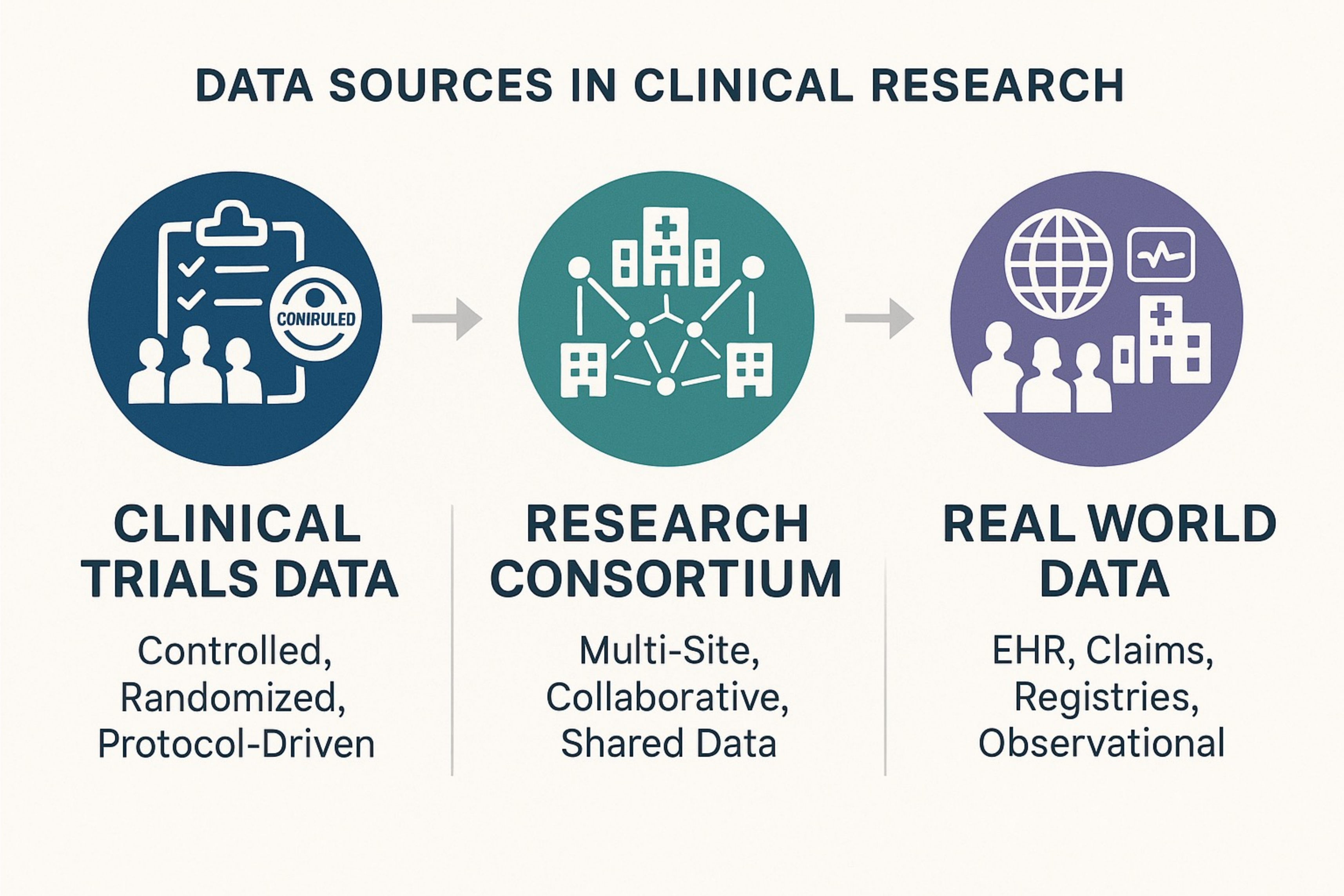
1. https://doi.org/10.1002/alz.70045; 2. https://doi.org/10.1002/alz.70702; 3. https://doi.org/10.1002/alz.13565



Model performance can be affected by analysis method/algorithm or type of training data

Models trained on populations that are different than the target trial population will be less accurate in their performance

Potential training data



Bristol Myers Squibb®

Clinical trial populations evolve over time

Contemporary Clinical Trials
Volume 116, May 2022, 106740

Inclusion and diversity in clinical trials: Actionable steps to drive lasting change

Michelle D. Kelsey [a,b], Bray Patrick-Lake [c], Raolat Abdulai [d], Uli C. Broedl [e], Adam Brown [f], Elizabeth Cohn [g], Lesley H. Curtis [b,h], Chris Komelasky [i], Michael Mbagwu [j], George A. Mensah [k], Robert J. Mentz [a,b], Amesika Nyaku [l], Stephanie O. Omokaro [m], Judy Sewards [n], Kendal Whitlock [e], Xinzhi Zhang [o], Gerald S. Bloomfield [a,b]

Show more

Add to Mendeley Share Cite

https://doi.org/10.1016/j.cct.2022.106740 Get rights and content

Abstract

Background

Improving diversity in clinical trials is essential in order to produce generalizable results. Although the importance of representation has become increasingly recognized, identifying strategies to approach this work remains elusive. This article reviews the proceedings of a multi-stakeholder conference about the current state of diversity in clinical trials and outlines actionable steps for improvement.

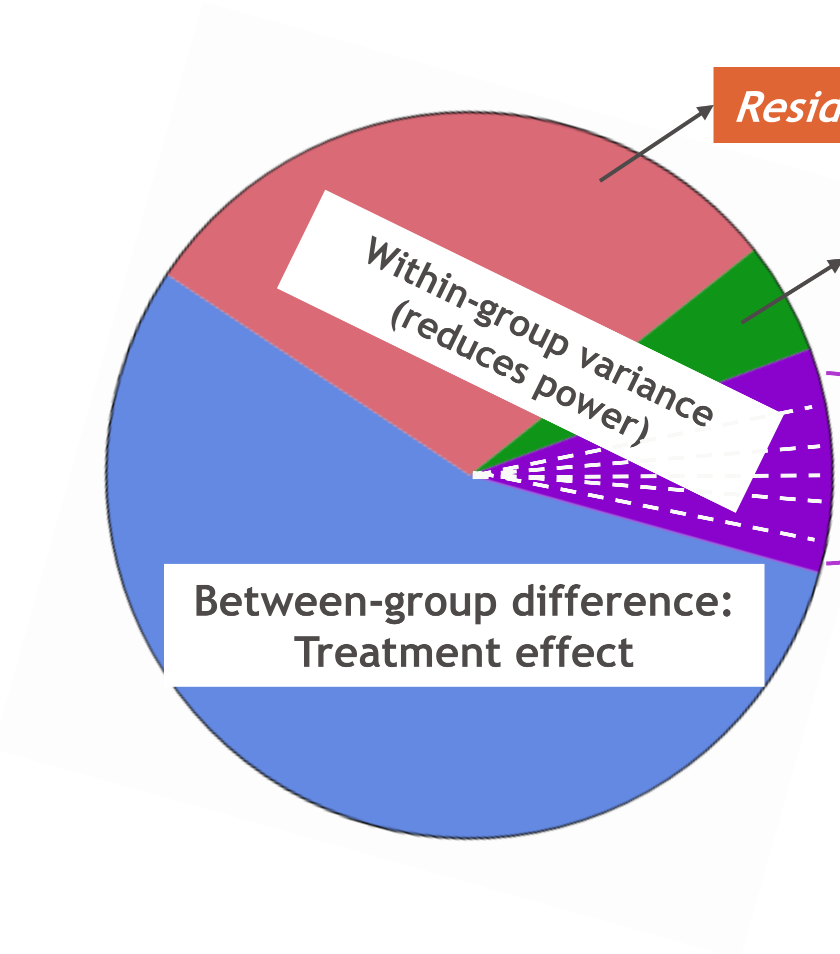
Methods

Populations can change over time in terms of demographics or clinical profile, including:

- **Diagnosis criteria and rates** — how patients are identified and how frequently diagnoses are made
- **Standards of care** — evolving clinical guidelines and best practices for treatment
- **Treatment regimens** — changes in drug combinations, dosing, or therapeutic approaches
- **Stage of disease at presentation** — shifts in how early or advanced the condition is at the time of diagnosis

Digital twins as a prognostic covariate

$$\textit{Test statistic} \sim \frac{\textit{Between group difference}}{\textit{Unexplained within group variance}}$$



Residual unexplained variance

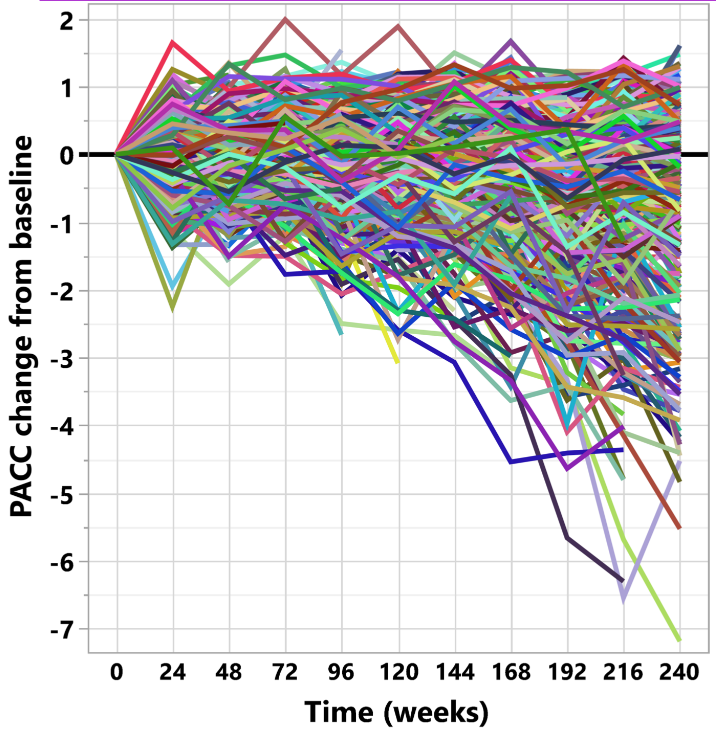
Explained by standard baseline covariates in statistical models (e.g., MMRM)

Variance due to heterogeneity in PACC progression

Use the digital twin progression trajectories as prognostic covariate in the statistical model for assessing treatment effect (e.g., MMRM)

dashed lines are digital twins from different AI/ML models

Heterogeneity in clinical progression

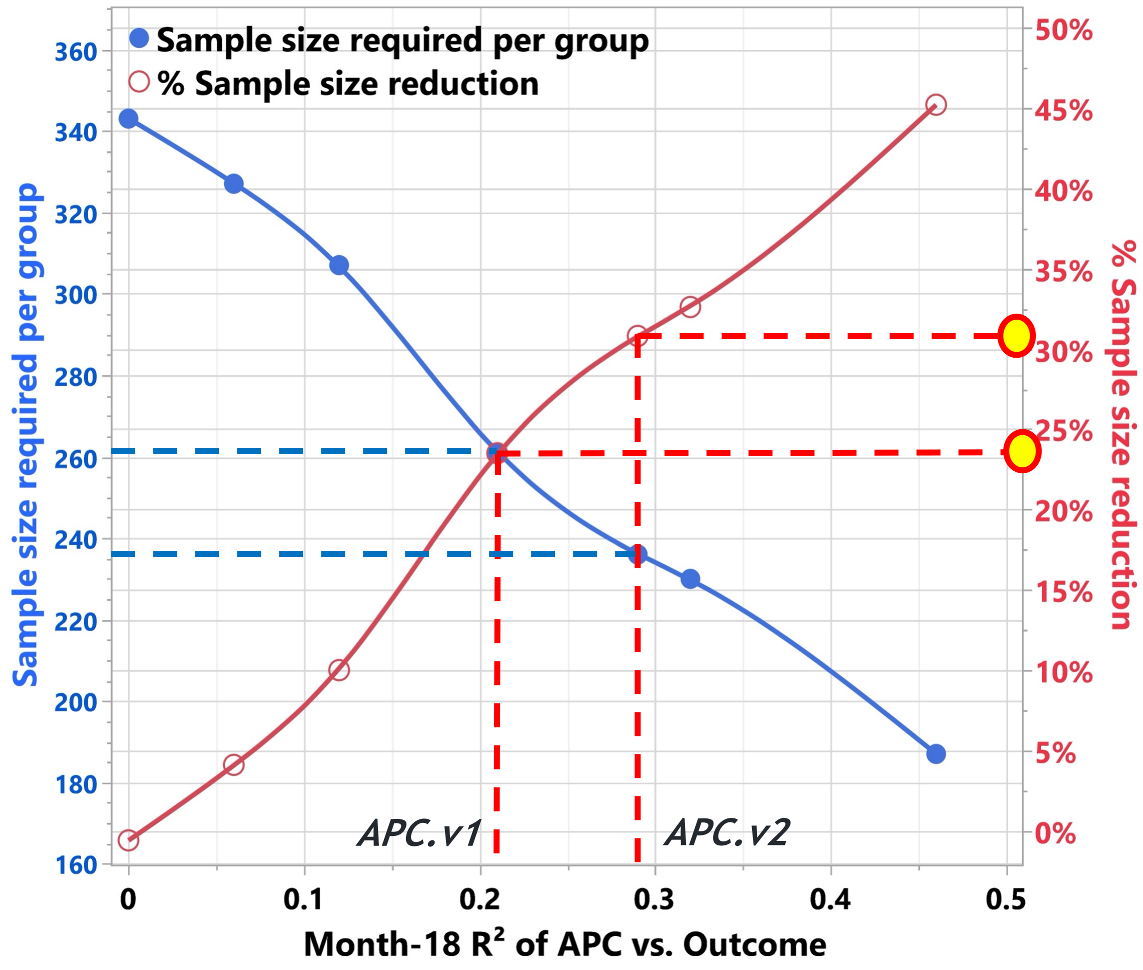


Adapted from Devanarayan et al. 2025, Alz & Dem.

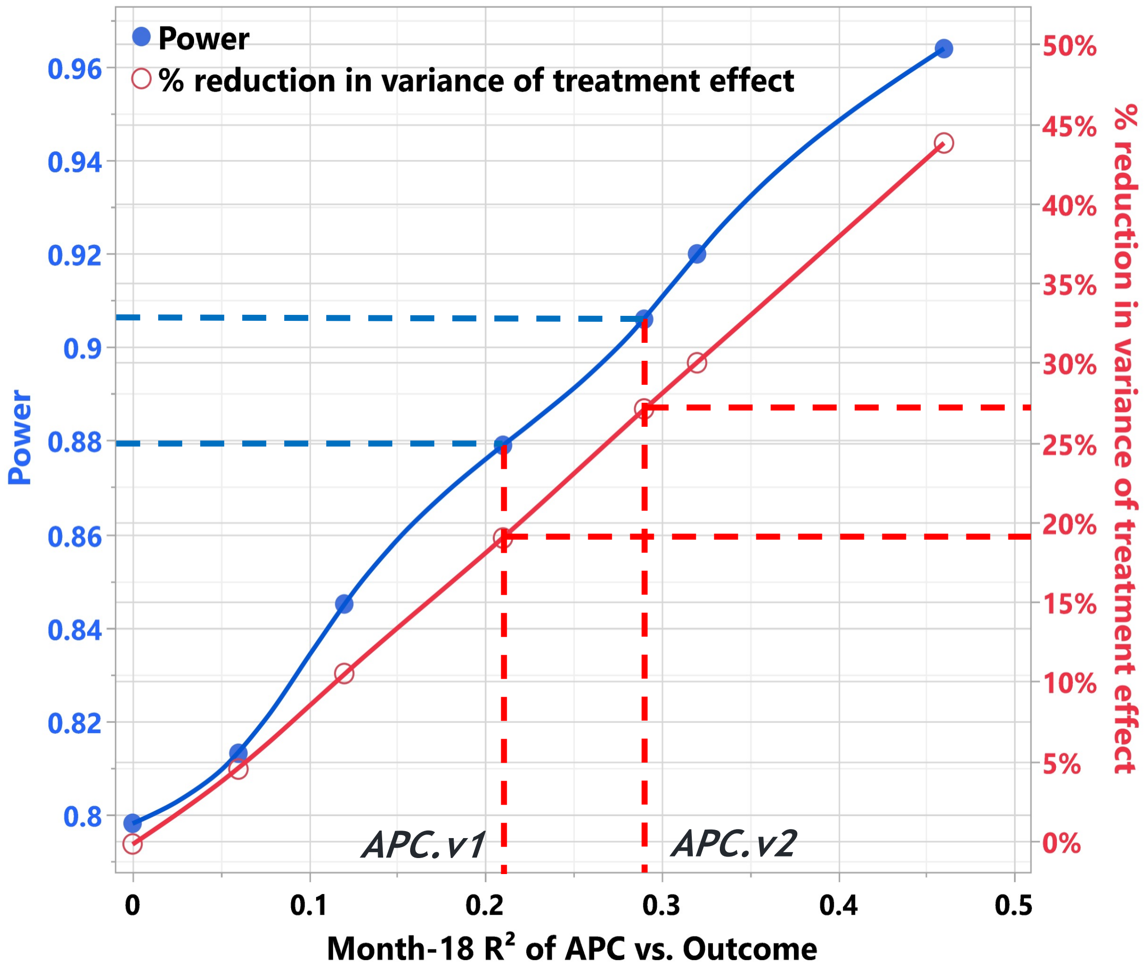
Bristol Myers Squibb®

Digital twins as prognostic covariate (simulation)

Reduces sample size by 31%



Increases power from 80% to 91%



APC.v1: DT model using baseline clinical features
APC.v2: DT model using baseline clinical & MRI features

Devanarayan et al., 2025, Alz & Dem.

Bristol Myers Squibb®

. APC, Alzheimer's disease prognostic covariate. MMRM, mixed models for repeated measures. MRI, magnetic resonance imaging.

FDA Guidance (May 2023) recommends the use of prognostic covariates for improving trial efficiency

Adjusting for Covariates in Randomized Clinical Trials for Drugs and Biological Products

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Oncology Center of Excellence (OCE)

May 2023
Biostatistics

Contains Nonbinding Recommendations

III. RECOMMENDATIONS FOR COVARIATE ADJUSTMENT IN CLINICAL TRIALS

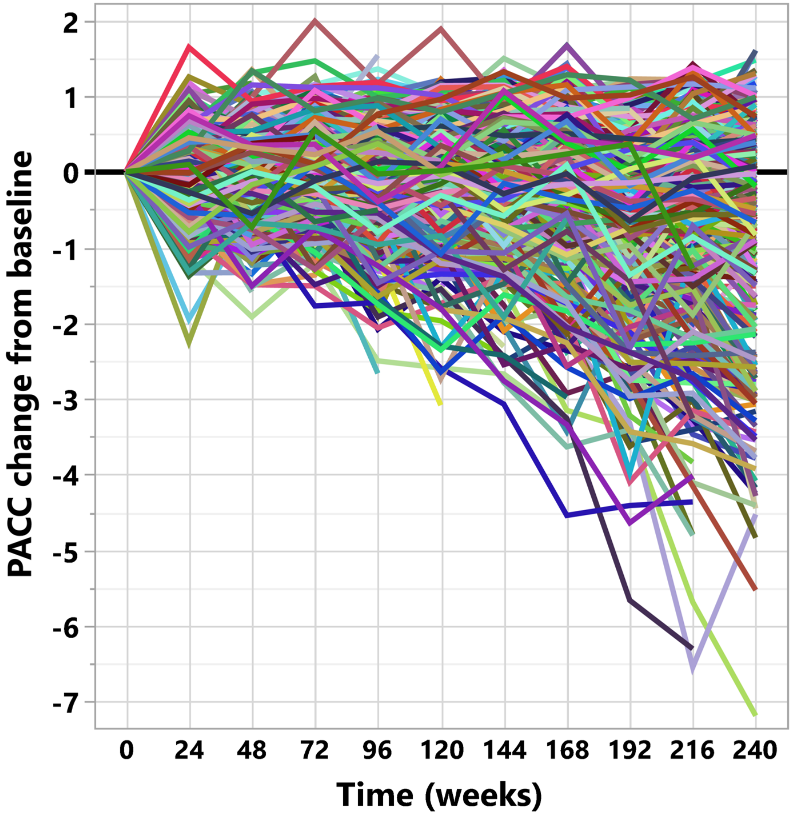
A. General Considerations

- An unadjusted analysis is acceptable for the primary analysis of an efficacy endpoint.
- Sponsors can adjust for baseline covariates in the analyses of efficacy endpoints in randomized clinical trials. Doing so will generally reduce the variability of estimation of treatment effects and thus lead to narrower confidence intervals and more powerful hypothesis testing.
- Sponsors should prospectively specify the detailed procedures for executing covariate-adjusted analysis before any unblinding of comparative data. FDA review will emphasize the prespecified primary analysis rather than post-hoc analyses using different models or covariates.
- Covariate adjustment leads to efficiency gains when the covariates are prognostic for the outcome of interest in the trial. Therefore, FDA recommends that sponsors adjust for covariates that are anticipated to be most strongly associated with the outcome of interest. In some circumstances these covariates may be known from the scientific literature. In other cases, it may be useful to use previous studies (e.g., a Phase 2 trial) to select prognostic covariates or form prognostic indices.
- Covariate adjustment can still be performed with covariates that are not prognostic, but there may not be any gain in precision (or may be a loss in precision) compared with an unadjusted analysis.
- Covariate adjustment is acceptable even if baseline covariates are strongly associated with each other (e.g., body weight and body mass index). However, adjusting for less correlated baseline covariates generally provides greater efficiency gains.
- Randomization is often stratified by baseline covariates. A covariate adjustment model should generally include strata variables and can also include covariates not used for stratifying randomization. In some cases, incorrect stratification may occur and result in actual and as-randomized baseline strata variables. A covariate adjustment model can use either strata variable definition as long as this is prespecified.
- Sponsors can conduct randomization/permutation tests with covariate adjustment (Rosenbaum 2002).
- In a trial that uses covariate adjustment, the sample size and power calculations can be based on adjusted or unadjusted methods. The latter will often lead to a more conservative sample size.

- Covariate adjustment leads to efficiency gains when the covariates are prognostic for the outcome of interest in the trial. Therefore, FDA recommends that sponsors adjust for covariates that are anticipated to be most strongly associated with the outcome of interest. In some circumstances these covariates may be known from the scientific literature. In other cases, it may be useful to use previous studies (e.g., a Phase 2 trial) to select prognostic covariates or form prognostic indices.

Digital twins as prognostic covariate for clinical trials: Process

Historical control data used to model variability in disease progression



Develop progression model
Use external data and baseline features to model natural progression.

Apply the model at baseline
to forecast each trial participant's *natural progression trajectory (digital twins)* before randomization.

Include digital twins as time-varying prognostic covariate
in models assessing treatment effect.

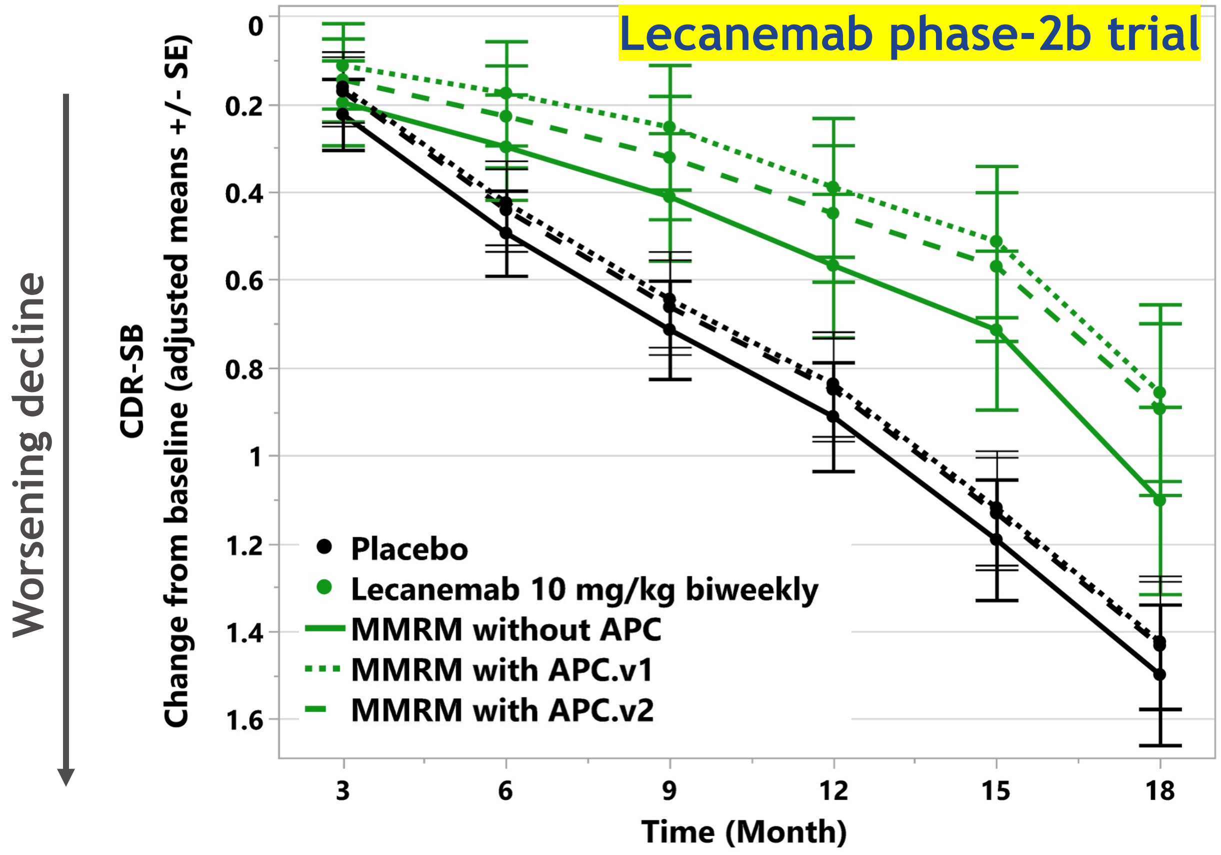
Impact:

- *Enhances precision and power*
- *Reduces required sample sizes*
- *Adjusts baseline imbalances*

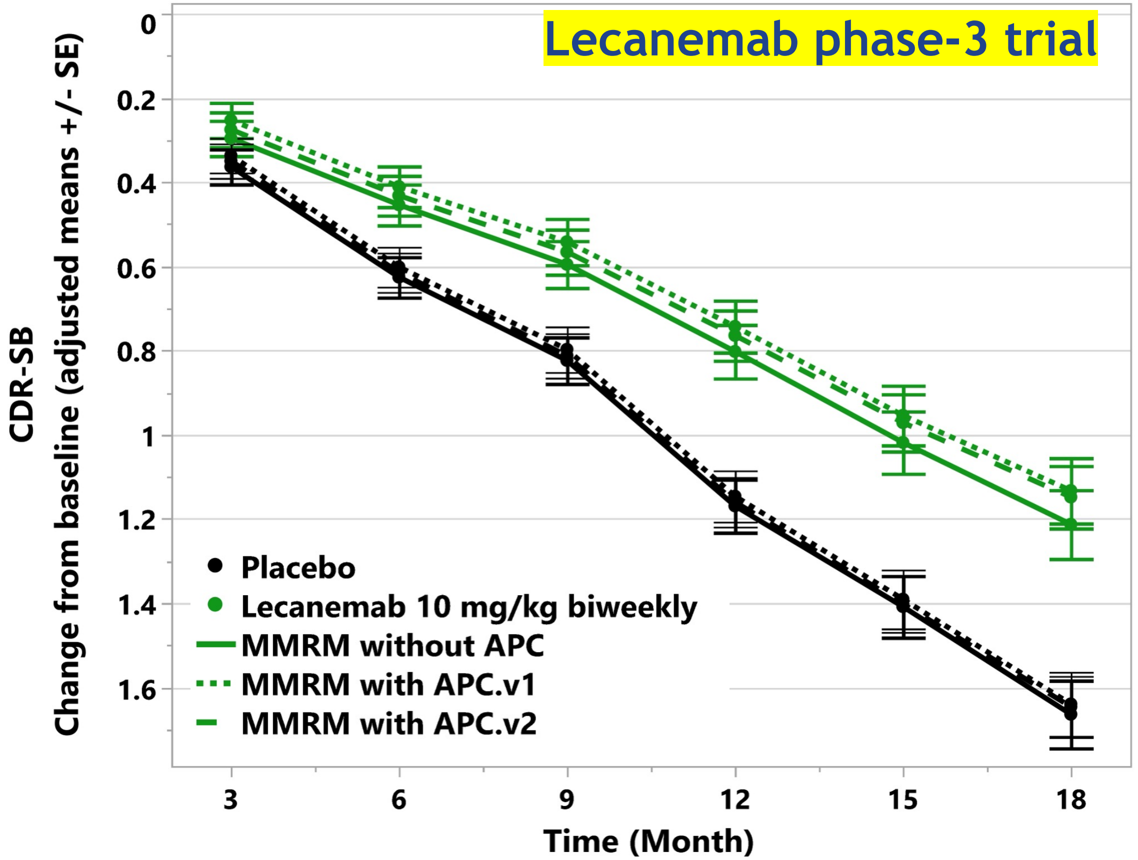
Adapted from Devanarayan et al. 2025, Alz & Dem.

Digital twins as prognostic covariate (real example)

Variance of treatment effect estimate reduced by 17% (p-value changes from 0.13 to 0.02)



Variance of treatment effect estimate reduced by 19%



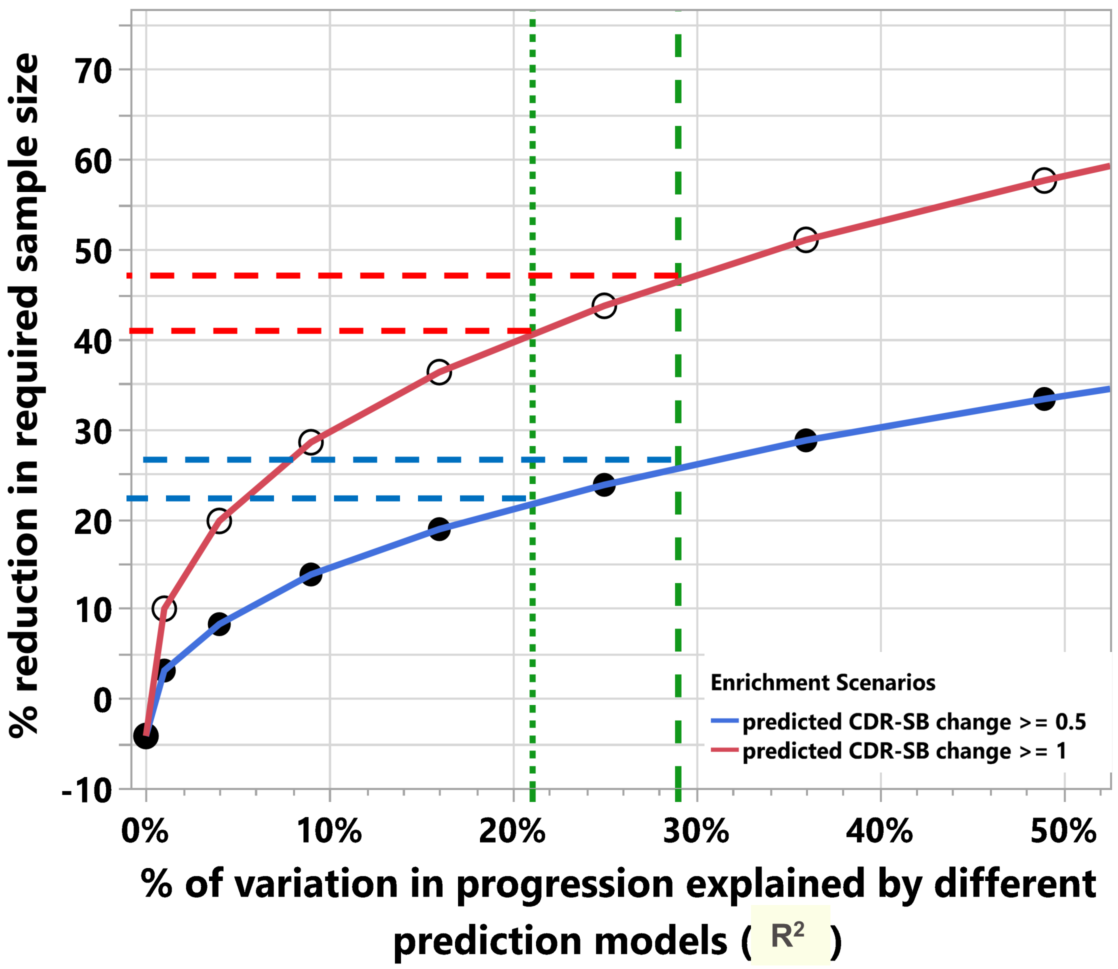
APC.v1: DT model using baseline clinical features
APC.v2: DT model using baseline clinical & MRI features

Devanarayan et al., 2025, Alz & Dem.

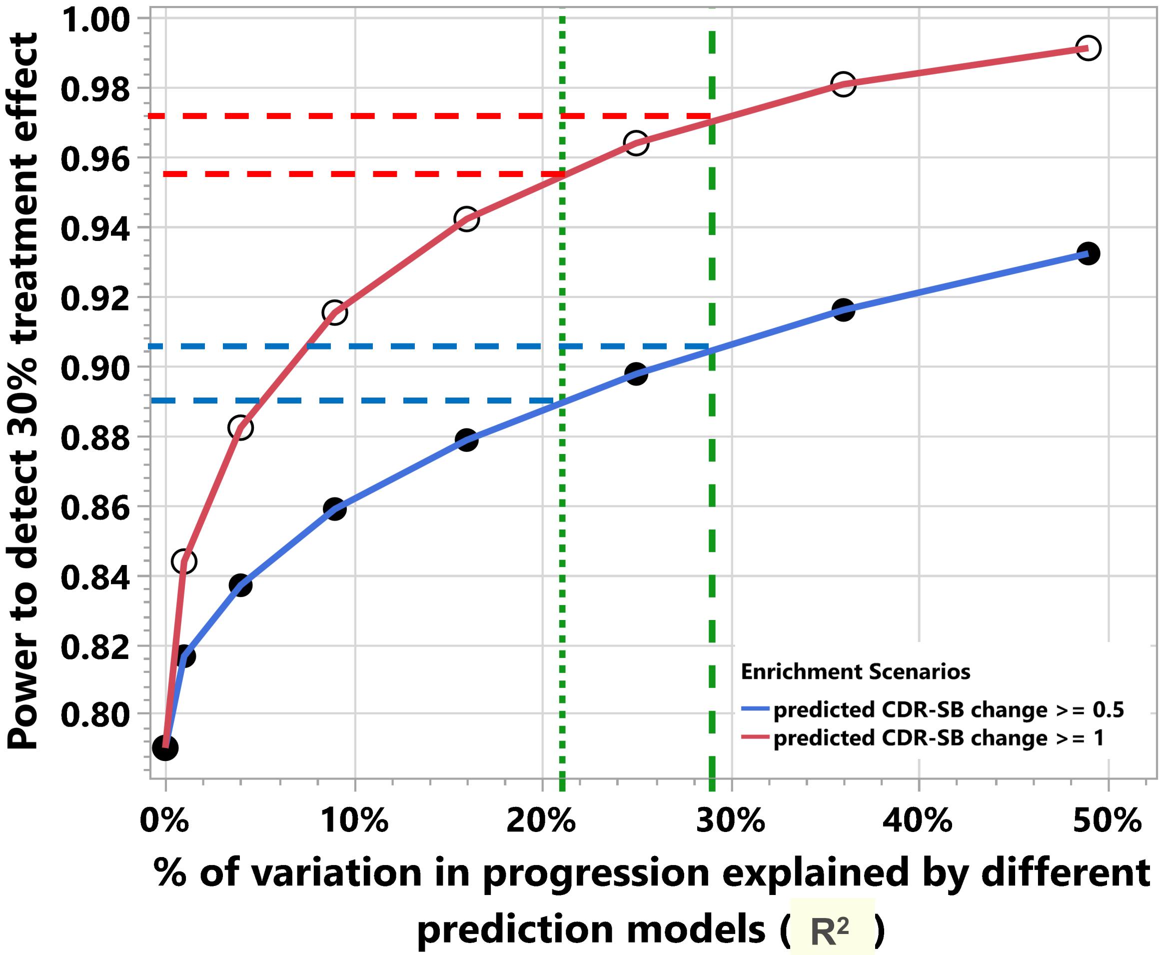
Bristol Myers Squibb

Digital twins for patient enrichment (simulation)

Reduces sample size by 23% to 49%



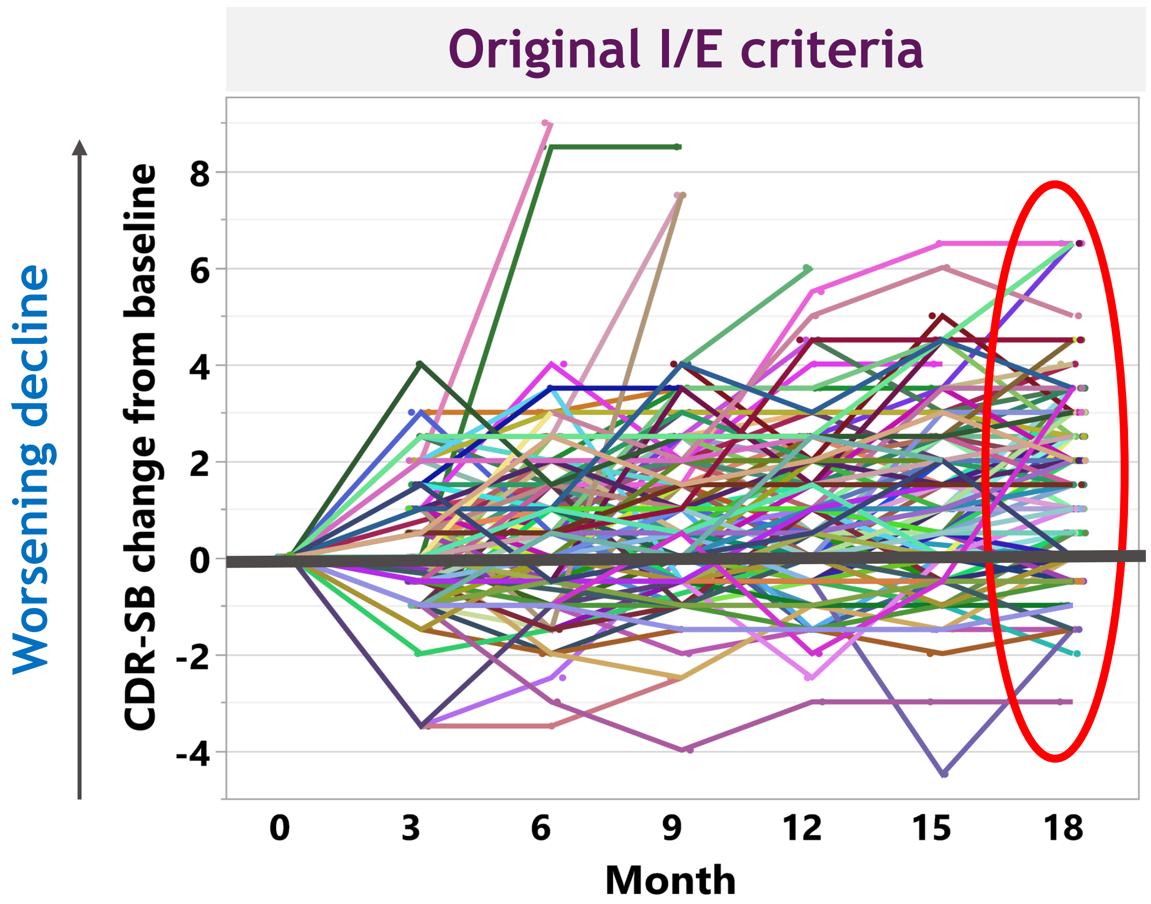
Increases power from 80% to 89% - 97%

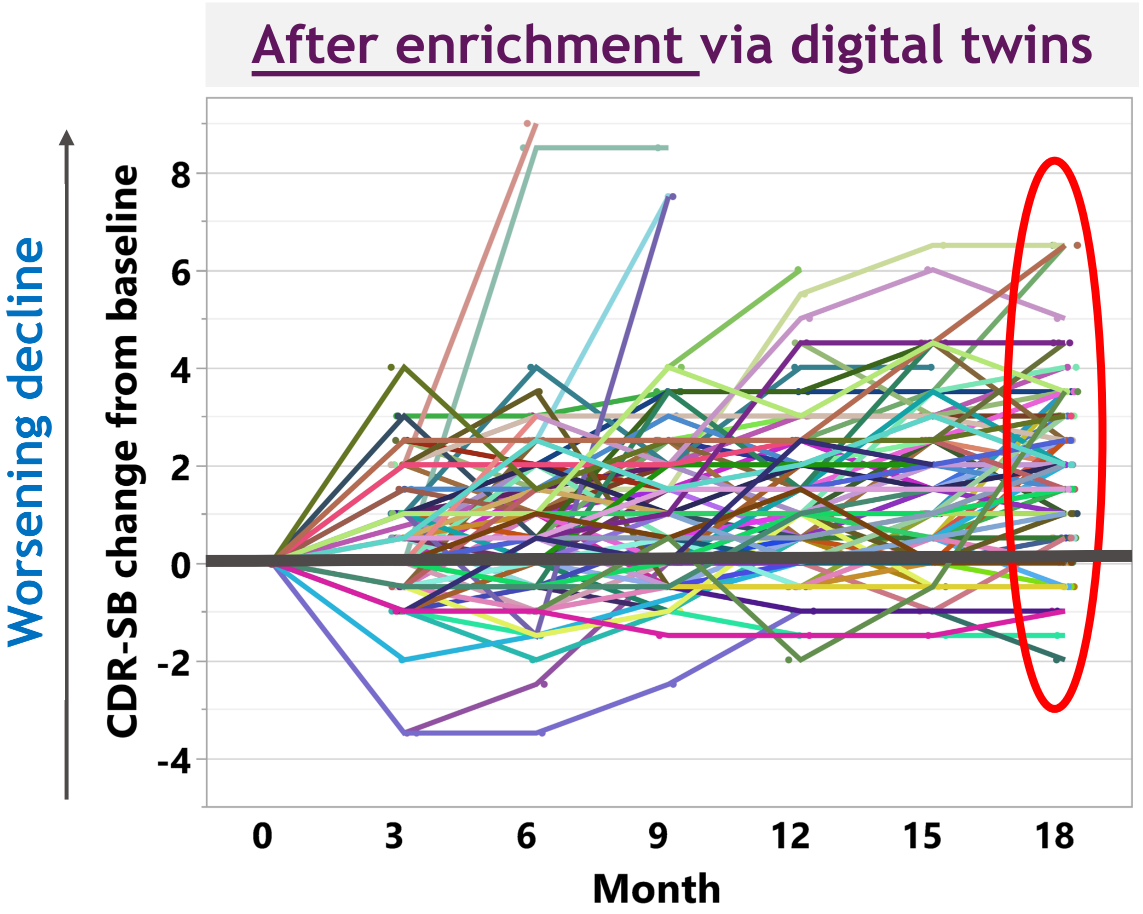


Devanarayan et al., 2024, Alz & Dem.

Bristol Myers Squibb®

Digital twins for patient enrichment (real example)





- *Digital twin enrichment increases the % of progressors from 60% to 80%.*
- *Inter-subject variance reduced by 50%*

Devanarayan et al., 2024, Alz & Dem.

Key takeaways

Digital twins can be applied to clinical trials in a number of ways; prognostic covariates, patient enrichment/selection and synthetic controls

Data for model training can be obtained from multiple sources but should be matched to the trial population

Simulation can provide insights on how different implementations affect trial design and expected outcomes

Continued engagement with regulatory agencies to understand requirements, standards and best practices

Thank you!