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Applying prognostic scoring adjustments to enhance clinical trial efficiency in neurodegenerative diseases

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Covariate Adjustment

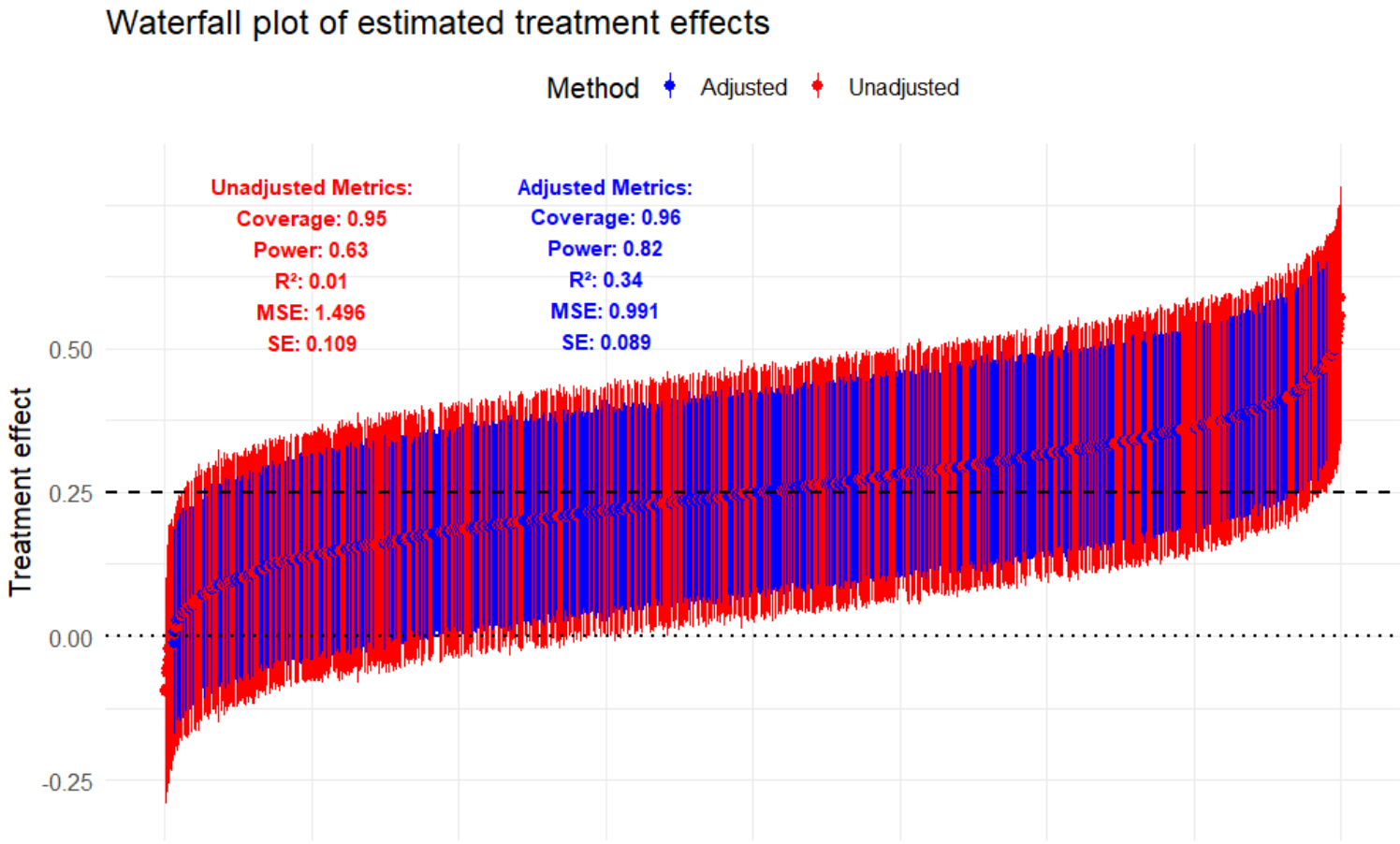
$$Y|X,T \sim N(\mu = 0.25 \times \text{Treatment}_1 + 0.5X_1 + 0.3X_2 + 0.2X_3, \sigma^2 = 1)$$

Simulation (repeated x1000)

Standard RCT design considerations:

- Provide high power to test whether a treatment effect exists
- Provide reasonable precision to characterize the treatment effect

- Outcome = treatment or control ± prognostic covariate(s)



$$Y_i = \beta_0 + \beta_1 \times \text{Treatment}_{0 \text{ or } 1} + \epsilon_i$$

or

$$Y_i = \beta_0 + \beta_1 \times \text{Treatment}_{0 \text{ or } 1} + \beta_2 \text{Age}_i + \ \ldots + \beta_n \text{PC}_{\text{ni}} + \epsilon_i$$

Digital Twin Workflow

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Step 1

Use observed patient characteristics (e.g., demographics, biomarkers) from external data sources.

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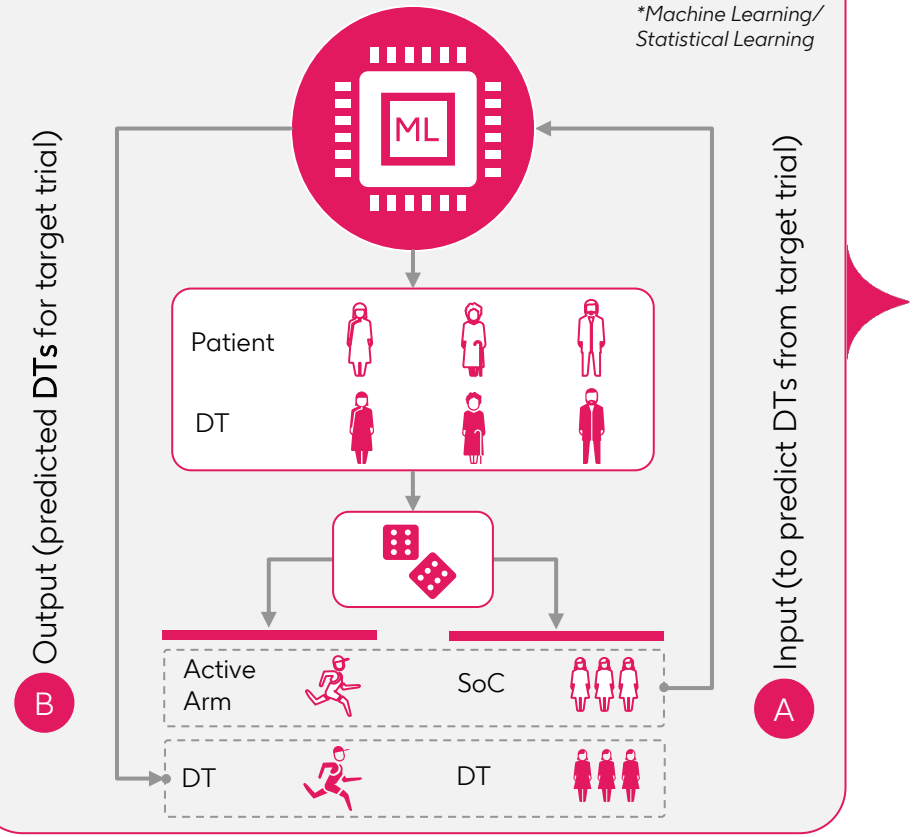
Step 2

Train an ensemble of ML/SL* models on external data to predict outcomes based on standard of care. Apply these models to baseline characteristics of trial patients to create a personalised digital twin for each patient, predicting their likely outcome.



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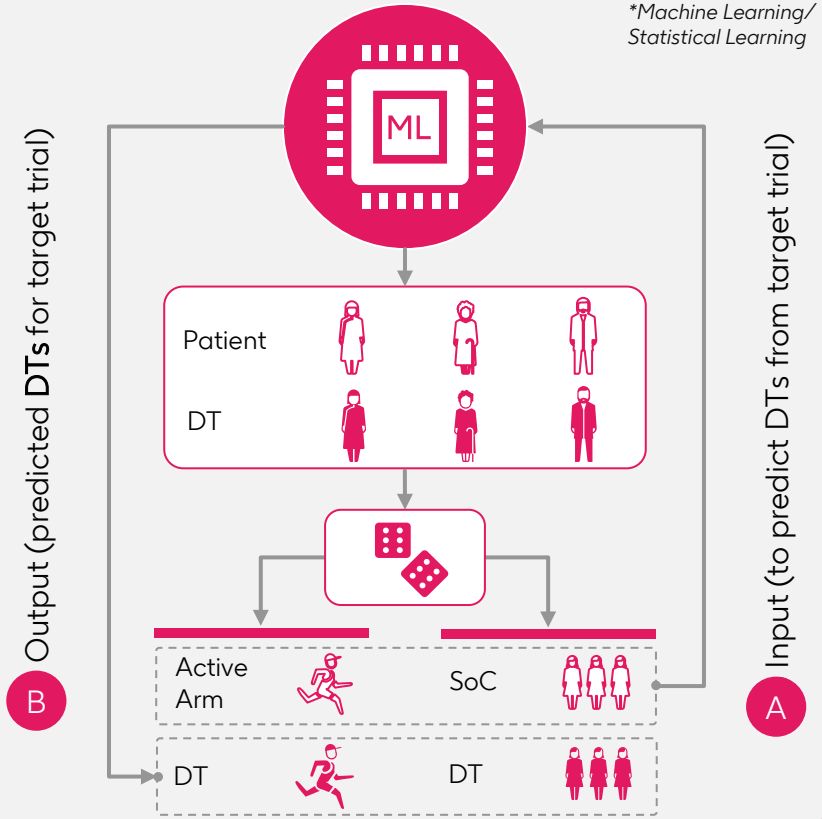

Step 3

Integrate the digital twin prediction as a 'super-covariate' into the trial's analysis model to enhance study power.

Outcome = Average treatment effect + Prognostic covariates + DT 'super-covariate'

Impact on trial design in terms of expected power gains / reduced sample sizes:

- Improvements of power of 5%+ can be expected
- Reductions of sample size (SS) of 10-30+% are reasonable

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Regulatory positions – FDA & EMA

Relevant commentary from the regulators on covariate adjustment and its value

FDA U.S. FOOD & DRUG ADMINISTRATION

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

Guidance for Industry

III. RECOMMENDATIONS FOR COVARIATE ADJUSTMENT IN CLINICAL TRIALS

*"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**."*

FDA U.S. FOOD & DRUG ADMINISTRATION

Using Artificial Intelligence & Machine Learning in the Development of Drug & Biological Products

Discussion Paper and Request for Feedback

"At an even more personalized level, AI/ML can also be used in the context of digital twins of patients, an emerging method that could potentially be used in clinical research. To create digital twins of patients, AI/ML can be utilized to build in silico representations or replicas of an individual that can dynamically reflect molecular and physiological status over time (European Medicines Agency, 2022; Laubenbacher, Sluka, & Glazier, 2021; Schuler et al., 2021). [...] the digital twin could potentially provide a comprehensive, longitudinal, and computationally generated clinical record that describes what may have happened to that specific participant if they had received a placebo."

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 September 2022
EMADOC-1700519818-907465
Committee for Medicinal Products for Human Use (CHMP)

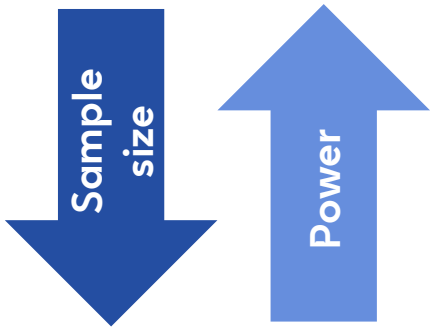
Qualification opinion for Prognostic Covariate Adjustment (PROCOVA™)

Draft agreed by Scientific Advice Working Party (SAWP)	10 February 2022
Adopted by CHMP for release for consultation	24 February 2022[1]

"CHMP qualifies PROCOVA as prognostic score adjustment and the proposed procedures, as described in a handbook for trial statisticians, could enable increases in power or precision of treatment effect estimates in controlled randomised clinical trials with continuous outcomes. ... Approaches with non-linear models for analysis and direct comparisons to such models, as well as models with treatment-by-covariate interactions are out of scope of this qualification procedure."

Prognostic scores in MMRM

Leverage baseline measurements and/or external data sources



Reduce sample size and/or increase power to detect average treatment effects

- Model misspecification
- Covariate selection & dimensionality
- Nonlinearity

MMRMs

- For RCTs with continuous longitudinal outcomes
- Special case of ANCOVA

$$Y_{ij} = \beta_0 + \underbrace{\beta_1 W_i}_{\text{=treatment}} \times Time_{ij} + \underbrace{\beta_2 \text{Age} + \beta_3 \text{sex} + \ldots + \beta_n \text{PC}_n}_{\text{=prognostic score, } m(x)}$$

Prognostic score m(.) computed on baseline covariates X_i for patient i

$$= \beta_0 + \beta_1 W_i \times Time_{ij} + \beta_2 m(X_i) + \epsilon_i$$

Y_{ij} continous outcome for patient i, j timepoint, i.i.d $N(\mu_W, \sigma^2)$ for treatment W=0 or 1

Treatment indicator (W_i) for patient i, W_i = 0,1

- Inherits ANCOVA properties: unbiasedness, control of type I error
- Variance reduction increases with increasing correlation between predictor m(X) and outcome Y
- Sophisticated AI models may more closely represent functional relationship between X and Y
- Out of scope: non-GLM models Y ~f(m(X)) and models with treatment-by-covariate interactions (non constant effects)

Simulation study

Overview

Generate longitudinal data

- Historical & contemporary

Construct digital twin prognostic scores (PSs)

Fit MMRMs

- Unadjusted
- Adjusted (p=10)
- + PS
- + oracle

Repeat simulations *many* times

Evaluate models

Extract:

- **Power**
- Type I error
- Coverage
- Bias
- SE
- MSE

Simulations to assess performance and robustness to assumptions

4 data-generation scenarios

1. ~~The Linear simulation scenario: the conditional average effect is $E[Y_1 - Y_0|X]$, the outcome-covariate relationship is linear in both the active and control treatment arms with a constant treatment effect.~~
2. The homogenous & non-linear simulation scenario: the outcome-covariate relationship is non-linear in both treatment arms, but the treatment effect is constant
3. The Heterogeneous simulation not constant (i.e., $E[Y_1 - Y_0|X] \neq \mu_1(X) - \mu_0(X)$).
4. The Shifted simulation scenario : the historical population used to train the prognostic model is not representative of the trial population in terms of the baseline covariates (i.e., $P_H(X' = x) \neq P(X = x)$).

PS covariate-adjustment assumptions met

Assumptions violated*

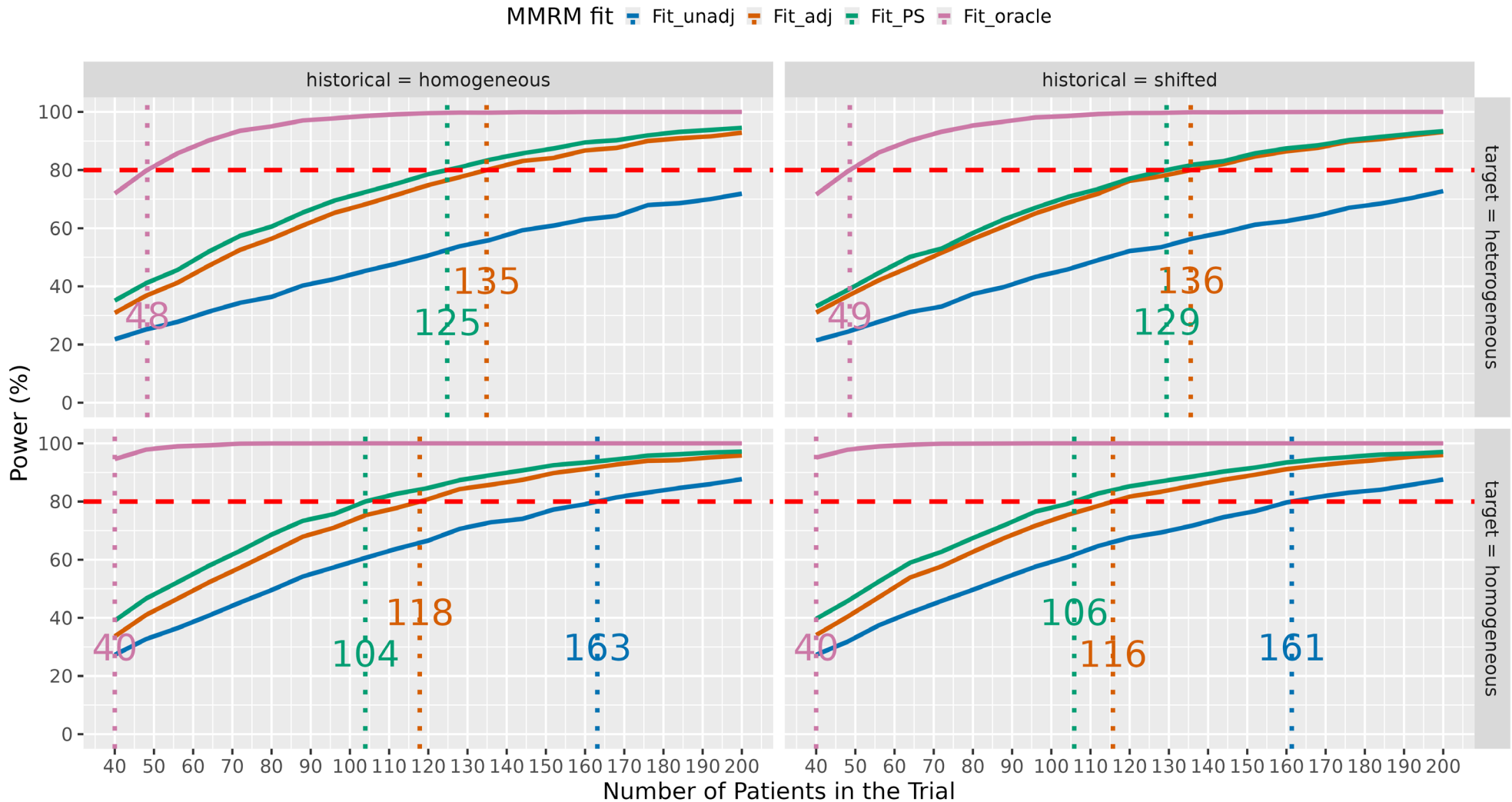
Lack of external validity

*: If the treatment effect is constant, then the optimal covariate to adjust for in ANCOVA is a prediction of the potential control outcome for a subject, based on that subject's observed baseline covariates.
https://www.ema.europa.eu/en/documents/other/briefing-book_en.pdf

Results

Comparison of Five MMRM Models: Treatment Effect = -1.2

*Fit_unadj: mmrm(Y ~ time * treatment + us(time | id);*
*Fit_adj: mmrm(Y ~ time * treatment + us(time | id) + (X1 + ... + X10) ;*
*Fit_PS: mmrm(Y ~ time * treatment + us(time | id) + estimated Prognostic Score (ePS);*
*Fit_oracle: mmrm(Y ~ time * treatment + us(time | id) + true Prognostic Score (tPS)*



10000 simulations; historical dataset is homogeneous with 5000 patients

Take homes & continued work

- We've demonstrated the benefit, in the presence of prognostic scores, the additional power gain when leveraging historical data to inform your target trial
- This has been further extended in longitudinal study setting (e.g. neurodegenerative diseases)
- **Leading to sufficiently powered trials → maximizing PoS**

Future considerations

- Including additional biomarkers, and assess the trade-off between a reduction in SS and model improvement
- Better quantify the expected precision / power gain using the relationship of the ML model & its correlation
- Extend to pMMRM analysis models for additional PoS gains.

Bibliography

- Adjusting for Covariate in Randomized Clinical Trials for Drugs & Biologics (FDA, May 2023)
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- A. Schuler *et al.*, *The International Journal of Biostatistics*. **18**, 329–356 (2022).
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