

# Covariate adjustment in randomised clinical trials

## EMA MWP Interested Parties Meeting

**Henrik Ravn, Senior Statistical Director, Novo Nordisk A/S**  
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# Background

- **What** is covariate adjustment in RCTs?
  - Use of information measured on a subject before the time of randomization for estimating and testing population-level treatment effects between randomised groups
- **Why** do covariate adjustment in RTCs?
  - Improve statistical power for testing and precision of treatment effect estimates
  - Covariate-adaptive randomisation

# Why now?

- Modern **causal inference** methods for marginal treatment effects (aka ATEs) seem ripe:
  - Parametric regression models and g-methods
  - Data-adaptive methods with doubly-robust estimators coupled with machine learning
- ‘Natural’ extension to estimands incorporating ICEs (see also meeting topic on *Causal Inference in Clinical Trials*)

# Challenges

- Covariate adjustment may change the definition of the treatment effect that is being estimated:
  - Should only affect **HOW** to estimate, but not **WHAT** to estimate
- **Pre-specification:** What to submit when adjusting for covariates?
  - *Prospectively specify the covariates and the mathematical form of the covariate adjusted estimator in the protocol or statistical analysis plan\**
  - What if data-adaptive methods?

# Choices & Consequences

- What method to use for continuous, binary, ordinal, count, time-to-event, and recurrent events?
- Impact on bias and type I error rate
- Missing values for covariates and endpoints
- Competing risks
- Sensitivity analyses
- Samples size
- Superiority and noninferiority trials
- Group sequential design (interim)

\* [FDA – Guidance Snapshot: Adjusting for Covariates in Randomized Clinical Trials for Drugs and Biological Products](#)

# Next steps

## Collaboration warranted:

- Agree on best practices (pilots)
- Pre-specification
- Software
- Update and develop guidelines
- Reporting and communication

## Public-Private-Partnerships

