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Covariate adjustment: Traditional principles and challenges by new approaches

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Disclaimer

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Outline

- EMA GL on adjustment for baseline covariates
- New approaches to develop synthetic (prognostic) covariates for adjustment with special focus on PROCOVA
- Challenges by new approaches

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Guideline on adjustment for baseline covariates in clinical trials

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General GL requirements for primary analysis

- Covariates included in the primary analysis must be pre-specified
- No post-baseline covariates
- No treatment by covariate interactions

GL Recommendations

- Justification for including each of the covariates should be provided
- Main reason to include a covariate is evidence of strong or moderate association between the covariate and primary outcome measure
  - Adjustment for such covariates generally improves the efficiency of the analysis
- Stratification variables should usually be included as covariates or stratification variables in the primary analysis regardless of their prognostic value
- No more than a few covariates should be included in the primary analysis
  - It is safer to pre-specify a simple model
  - More likely to be numerically stable
  - Assumptions underpinning the statistical model are easier to validate
  - Generalisability of the results may be improved

GL recommendations (ctd)

- Without prior knowledge, a simple functional form should be assumed for the relationship between a continuous covariate and the outcome variable
- Validity of model assumptions must be checked when assessing the results
  - Particularly important for generalised linear or non-linear models where mis-specification could lead to incorrect estimates of the treatment effect

GL ‚messages‘

- Simply producing smaller P-values not sufficient to produce convincing evidence of a clinically useful effect
- Important considerations beyond p-value:
  - Size of the treatment effect
  - Consistency across levels of covariates

New proposals

- Era of big data and artificial intelligence
  - How can these tools be used to improve efficiency of clinical studies?
- Borrowing
- Enrichment of study population based on predicted response
  - Exclusion/down-weighting of expected placebo responders

→ Concerns with t1e control and external validity

- Develop new prognostic covariates (‘synthetic covariates’)
  - Adjust for these in primary analysis

→ Promise to improve efficiency while preserving properties of ‘classical‘ analyses

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Qualification opinion for Prognostic Covariate Adjustment (PROCOVA™)

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PROCOVA

- Develop prognostic score for the outcome under control based on a historical data set independent from the study data
- Account for prognostic score when estimating the sample size of new trial
- Apply prognostic score as covariate in an ANCOVA model for a new trial
- Procedure can utilize a prognostic score generated by any prognostic model
  - Mechanistic models
  - Linear and non-linear statistical models
  - Models with interactions between covariates
  - Machine-learning-based methods
- Prognostic model development out of scope of the qualification procedure

CHMP qualification opinion

- PROCOVA could enable increases in power or precision of treatment effect estimates in controlled randomised clinical trials with continuous outcomes
- Method can be regarded a special case of ANCOVA sharing the properties of type 1 error control and asymptotically unbiased estimates of the treatment effect
- Advantage over using no adjustment or ANCOVA with single covariate adjustment should be justified to support application of the PROCOVA method

Remarks

- Comment on PROCOVA: Idea to develop prognostic score and adjust for it is not new
- Similar proposals were made/are currently discussed
  - Not all propose sample size reduction
  - Broader scope than PROCOVA: not restricted to linear models
- CHMP: Not intended to single out PROCOVA as ‘the’ method

Traditional principles challenged

- Stratify and/or adjust for clinically important covariates

  vs

  Adjust for prognostic score (on top) with no direct clinical interpretation

- Include no more than a few covariates

  vs

  Include a prognostic score covering the information from many covariates

- Simple functional form for relationship between covariates and outcome

  vs

  Prognostic score based on complex prognostic model

Pros and cons

- Pros
  - Gain in efficiency
  - Only one covariate added
    - No concerns regarding degrees of freedom, numerical stability
- Cons
  - Adding synthetic covariate on top of adjusting may introduce collinearities
  - Prognostic score resulting from a complex, poorly understood model/black box?
    - Reproducible?
    - Interpretable?
  - Interpretability of subgroup analysis endangered?
    - PROCOVA handbook advises against using same model for subgroup by treatment interaction

- Do we sacrifice clinical interpretability for small p-values?

Linear models and synthetic covariates

- Targeted treatment effect (=estimand) is independent from covariates
- ANCOVA does not require that prognostic model is correct
- Interpretability
  - Do we need to understand the covariate?
  - Subgroups?

  → Potential benefits, not much harm?

Generalized linear and non-linear models and synthetic covariates

- Frequently used GLMs or non-linear models provide conditional treatment effects
  - Logistic regression, Cox regression
- Conditional treatment effect = (average of) treatment effect for patients with same covariates
- Targeted treatment effect depends on covariates
- Interpretation requires to understand on what is conditioned

→ Usually not fulfilled for synthetic covariate
→ Appears currently not recommendable

- Other GLMs or non-linear models providing unconditional effects?
  - Aiming to use a synthetic covariate is not a sufficient reason to use a specific estimand

Transparency

- Proposals were made to keep prognostic model to derive prognostic score confidential
  - Only score is provided to study sponsors
- Model needs to be understood by all stakeholders and transparent to public
- Who has access to training data sets?
  - Data protection
  - Consent
  - Data owners

Thank you very much for your attention!

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Short Topic EFSPI 2022
How would you think about this situation?

- Sponsor created a prognostic score
- It is a blackbox machine learning model
- Only internally validated with a hold-out test set
- Not adopted in clinical practice or used by other trials
- Score used as covariate in analysis of single pivotal randomized controlled trial
- With covariate: clinically relevant treatment difference & p = 0.01
- Without covariate: difference borderline clinically relevant & p = 0.08
- Sponsor argues that the drug should be approved, because
- This appropriately estimates the treatment effect an individual patient could expect
- Using such a covariate is solely a sponsor risk (for commonly used regression models mis-specified covariate relationships at worst reduce power, but do not inflate type I error)