Summary of regulatory guidance (FDA, EMA) on covariate adjustment and comments collated by EFSPI/PSI Regulatory SIG

PSI Webinar Covariate Adjustment: Considerations and Examples

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Overview

- Regulatory guidances
  - ICH E9 Statistical Principles for Clinical Trials from 1998
  - EMA Guideline on adjustment for baseline covariates in clinical trials from 2015
  - FDA Draft Guidance for the Industry from 2021: Adjusting for Covariates in Randomized Clinical Trials for Drugs and Biological Products
  - Conditional and marginal estimands in the context of ICH E9 (R1)
  - Summary

Regulatory Guidances
ICH E9 Statistical Principles for Clinical Trials from 1998

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ICH E9 Statistical Principles for Clinical Trials (1/2)

- ICH E9 includes high-level recommendations:
  - In some instances adjustment for covariates should be set out in the protocol
  - Pre-trial covariates should be identified and should be considered in order to
    - **improve precision** and to
    - **compensate for any lack of balance** between treatment groups
  - Appropriate to account for stratification factors in the analysis
- When doubts about value of adjustment, often advisable to nominate unadjusted analysis as primary, adjusted as supportive

ICH E9 Statistical Principles for Clinical Trials (1/2)

- Special attention to:
  - Centre effects
  - Baseline measurements of primary variable
- Not advisable to include covariates measured after randomisation
- Interactions:
  - Treatment effect may vary with subgroups or covariates
  - In most cases, subgroup or interaction analyses are exploratory
- Baseline Imbalances for not pre-defined covariates:
  - Perform additional analysis which accounts for these imbalances
  - If does not reach same conclusions, discuss the effect of the imbalances

Regulatory Guidances
EMA Guideline from 2015

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EMA guideline – Reason to adjust

Adjustment not always necessary, but

- Adjustment **improves efficiency** of analysis (smaller p-values, narrower confidence intervals) → produces stronger and more precise evidence
- **Avoids conditional bias from chance covariate imbalance**

EMA guideline – Selection of covariates and model

- Covariates to be included in primary analysis:
  - Stratification factors
  - Multicentre trials might be stratified by centre, country and/or region
  - Variables associated with primary outcome should be considered
  - Baseline values of continuous primary outcome
- How to include covariates:
  - Without prior knowledge, simple functional form (usually either linearity or categorising)
  - Covariates to be included must be pre-specified in protocol
  - Reasons for including covariate should be explicitly stated in protocol
  - Methods that retrospectively select covariates should be avoided
- Number of alternative valid analyses, pre-specified analyses will carry most credibility

EMA guideline – Number of covariates and variables not to be included

- Number of covariates:
  - Only few covariates should be included (larger studies may support more)
  - Analyses including many covariates will always be less convincing
  - Covariates should be restricted to most clinically important and/or strongly prognostic
- Covariates not to be included:
  - Variables measured after randomisation
  - Baseline imbalance observed post hoc:
    Sensitivity analyses including covariate to assess robustness
  - Treatment by covariate interactions should not be included
    If substantial interactions are expected *a priori*
    → design trial to allow separate estimates of treatment effects in specific subgroups

EMA guideline – Model checks and sensitivity analyses

- Validity of model assumptions must be checked:
  - Particularly **important for generalised linear or non-linear models**
  - Attention to possible influence of extreme outlying values
  - Subgroup analysis to assess model assumptions
- Sensitivity analyses should be pre-planned:
  - Confirm that conclusions of study are not sensitive to choice of covariates or relationship between covariates and outcome
  - Ordinary linear models:
    Adjusted estimates of the treatment effect should be compared to unadjusted estimates
  - Discrepancies should be discussed and explained

EMA guideline – Linear and nonlinear models

- Generalised linear and non-linear models:
  - Adjusted and unadjusted treatment effects may not have same interpretation - Essential that meaning of estimated effect size is explained
  - Choice of appropriate covariates critically important
  - Validity of model assumptions must be checked
    Misspecification could lead to incorrect estimates

Regulatory Guidances
FDA Draft Guidance from 2021

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FDA guidance – Reason to adjust

- Unadjusted analysis is acceptable, but adjustment
  - Will generally **reduce variability**
  - Lead to narrower confidence intervals and **more powerful hypothesis testing**

- Guidance provides more detailed recommendations for use of
  - Linear models for covariate adjustment
  - **Covariate adjustment using nonlinear models**

FDA guidance – Selection of covariates and model

- Covariates to be included in primary analysis:
  - Covariates most strongly associated with outcome
  - Stratification factors
  - Baseline measurements of an outcome
  - Adjustment acceptable even if covariates are strongly associated with each other
- How to include covariates:
  - Covariates and mathematical form of adjustment should be prospectively specified before any unblinding of comparative data
- More weight will be given to the prespecified primary analysis than to post-hoc analyses using different models or covariates

FDA guidance – Number of covariates and variables not to be included

- Number of covariates:
  - Number of covariates small relative to sample size
  - If number of covariates large relative to sample size sponsors should provide justification
- Covariates not to be included:
  - Variables measured after randomization – Guidance focuses on baseline covariates
  - Interactions:
    - Treatment by covariate interactions may be included
    - However, primary analysis still based on model without interaction

FDA guidance – Linear models

Linear models:

- Covariate adjustment is an acceptable method
- Generally provides reliable estimation and inference for average treatment effect
- Covariate adjustment through linear model also estimates conditional treatment effect

FDA guidance – Nonlinear models (1/2)

Nonlinear models

- Covariate adjustment with nonlinear models is often used
  - binary outcome,
  - ordinal outcome,
  - count outcome, or
  - time-to-event outcome.
- Adjustment using nonlinear models is a potentially acceptable method
  - Conditional and unconditional treatment effects can differ
  - This is non-collapsibility, distinct from confounding -> More details in other talk

FDA guidance – Nonlinear models (2/2)

- Covariate-adjusted nonlinear regression estimate conditional effect
  - Can provide more personalized information than unconditional treatment effect
  - Model will generally not be exactly correct
  - Results can be difficult to interpret if model is misspecified and treatment effects substantially differ across subgroups
  - Sponsors should discuss specific proposals of nonlinear regression to estimate conditional treatment effects
- Covariate adjusted estimation for unconditional treatment effect can also be performed
  –> More details in other talks (g-computation or standardization)

FDA guidance – Nonlinear models example

- Example from guidance

	Percentage of target population	Success rate		Odds ratio
		New drug	Placebo	
Males	50%	80.0%	33.3%	8.0
Females	50%	25.0%	4.0%	8.0
Combined	100%	52.5%	18.7%	4.8

- Which treatment effect (Odds ratio of 8.0 or 4.8) is preferred?

Conditional vs. unconditional – Comment by EFSPI

- Question not discussed: When is unconditional estimates preferred compared to conditional estimates and vice versa?
  - For most situations conditional treatment effect appears to be preferred as it "can provide more personalized information than unconditional treatment effect"
  - ICH E9 (R1) states:

"Central questions for drug development and licensing are to establish the existence, and to estimate the magnitude, of treatment effects: how the outcome of treatment compares to what would have happened to the same subjects under alternative treatment (i.e., had they not received the treatment, or had they received a different treatment)."

- In the example: Is the odds ratio of 4.8 important?
  - All individual patients have an odds ratio of 8.0
  - Odds ratio of 4.8 is only true for population with 50% females and 50% males

FDA guidance – Few additional comments by EFSPI

- Factors with many levels such as centre are not discussed – random effects?
- Guidance how to include baseline if endpoint is a function of change from baseline (e.g. percentage change from baseline)
- “This guidance does not address … use of covariate adjustment for analyzing longitudinal repeated measures data”
  Clarification requested why guidance is not applicable
- Could association be assessed based on blinded data of the same trial?
- General recommendation to not use standard model-based variance estimators seems to be not justified

Summary

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Summary and comparison of FDA and EMA guidances

- Guidelines are generally consistent
- FDA guidance with more details on e.g.
  - Nonlinear models and conditional vs. unconditional treatment effects
  - More technical details
- EMA guidance with more details on e.g.
  - Variables to be included and reason for inclusion
  - Sensitvity analyses and check of validity of model assumptions
- Discussion of estimand missing:
  When to use marginal vs. conditional treatment effects?