Marginal Estimands & Estimation with Covariate Adjustment for TTE Endpoints

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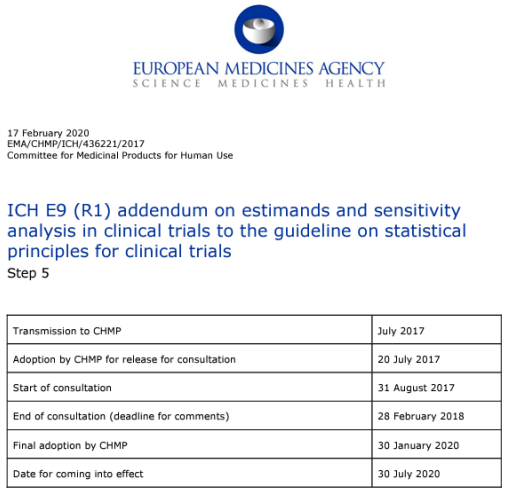
PSI 2025 CONFERENCE

Evolving HA Guidance

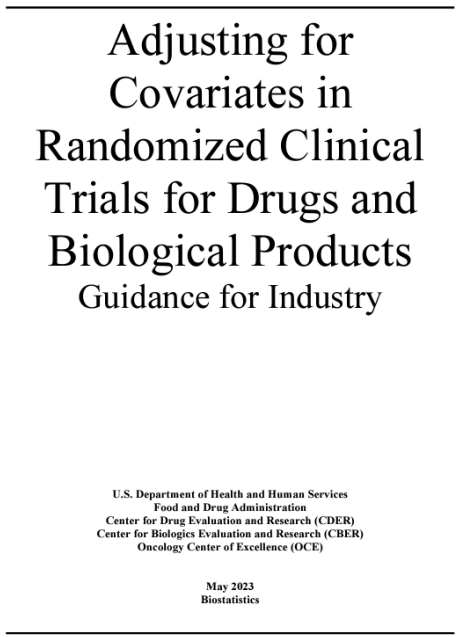


EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 February 2020
EMA/CHMP/ICH/436221/2017
Committee for Medicinal Products for Human Use

ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials
Step 5

Transmission to CHMP	July 2017
Adoption by CHMP for release for consultation	20 July 2017
Start of consultation	31 August 2017
End of consultation (deadline for comments)	28 February 2018
Final adoption by CHMP	30 January 2020
Date for coming into effect	30 July 2020



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

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

2 December 2024
EMA/324489/2024
Committee for Human Medicine Products / Methodology Working Party
Human Medicines Division

Consolidated 3-year rolling work plan for the Methodology Working Party

Chair:	Kit Roes
Vice Chair:	Kristin Karlsson

Work plan period: January 2025 – December 2027 (with a first review point after one year)

(B) Activities to be started in 2025

Multidisciplinary

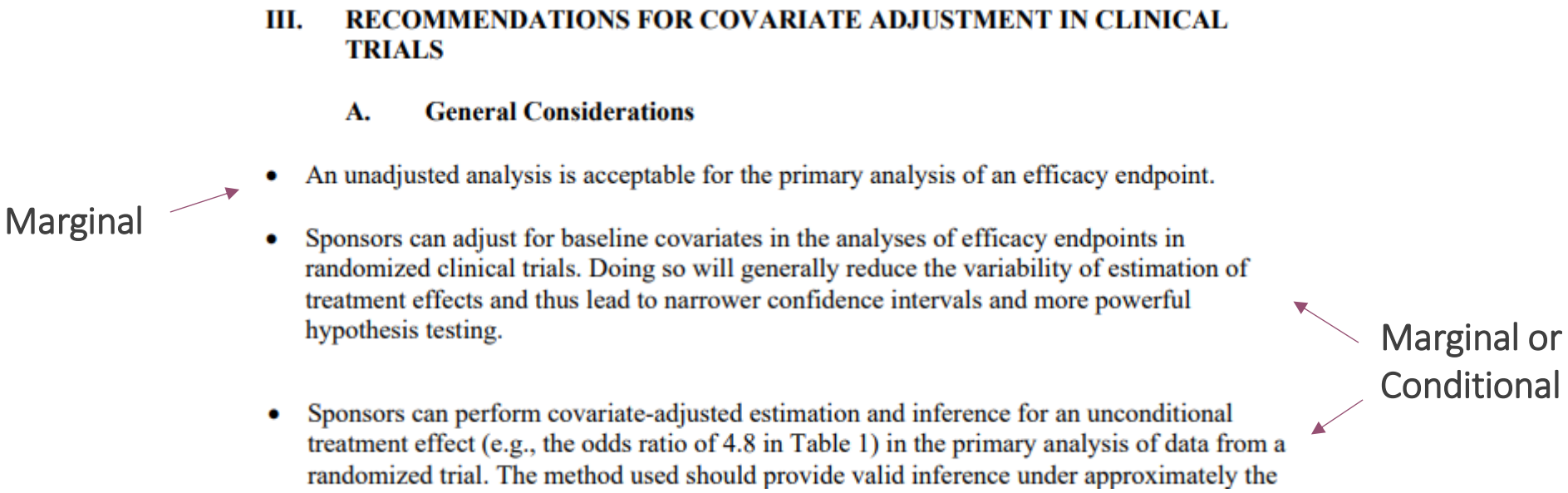
- Biostatistics and RWE: Q&A to be read in conjunction with the baseline covariates guideline to take into account the use of synthetic covariates

ICH-E9(R1) Guidance: https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e9-r1-addendum-estimands-and-sensitivity-analysis-clinical-trials-guideline-statistical-principles-clinical-trials-step-5_en.pdf
FDA Cov Adj Guidance: https://www.fda.gov/media/148910/download
EMA Methodology Workplan: https://www.ema.europa.eu/en/documents/other/consolidated-3-year-rolling-work-plan-methodology-working-party-2025-2027_en.pdf

FDA Covariate Adjustment Highlights and Gaps

Estimands

- No clear recommendation for either unconditional (marginal) or conditional estimands



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 can perform covariate-adjusted estimation and inference for an unconditional treatment effect (e.g., the odds ratio of 4.8 in Table 1) in the primary analysis of data from a randomized trial. The method used should provide valid inference under approximately the

- Some advice on how to explore model misspecification for both unconditional and conditional estimands
  - Still lack of clarity on whether a conditional estimand can be used and how we can demonstrate robustness to model misspecification

FDA Covariate Adjustment Highlights and Gaps

Further Considerations

- Key point for binary and TTE endpoints: Non-collapsibility

Table 1: Non-collapsibility of the Odds Ratio in a Hypothetical Target Population

	Percentage of target population	Success rate		Odds ratio
		New drug	Placebo	
Biomarker-positive	50%	80.0%	33.3%	8.0
Biomarker-negative	50%	25.0%	4.0%	8.0
Combined	100%	52.5%	18.7%	4.8

- But, what about other issues – not highlighted for *adjusted* unconditional (marginal) effects for TTE endpoints i.e. marginal hazard ratios
  - Selection bias
  - Non-proportional hazards

- Rhian will introduce some of these more technical points from a causal inference perspective

Time-to-Event Endpoint Trials

Estimation

- Traditionally, stratified Cox Model using stratification factors was and still often specified as a primary analysis method

Post-ICH E9(R1)

What estimand does this target? Is that what we are truly interested in?

What about estimation methods for marginal estimands (after covariate adjustment)?

- Sanne and Dominic will cover some alternative estimation methods and estimands
- Tim will highlight some practical challenges

Session Overview

1

Rhian Daniel (University of Cardiff)

Marginal Hazard Ratios and Covariate Adjustment – A Causal Inference Perspective

2

Sanne Roels (Johnson & Johnson) & Dominic Magirr (Novartis)

Estimation in the context of Covariate Adjustment, Model-free Summary Measures, and Alternatives to the Marginal (Average) Hazard Ratio

3

Tim Morris (MRC Clinical Trials Unit at UCL)

Ensuring Covariate Adjustment Methods Are Fit For Use

4

Panel Discussion

Chair: Sarwar Mozumder

Armin Koch, David Wright, Rhian Daniel, Sanne Roels, Dominic Magirr and Tim Morris