Charter: Priority Topic Covariate Adjustment

Objective: *Promote best practices for covariate adjustment in clinical trials. Our target audience of our activities consists of regulatory and pharmaceutical industry statisticians. Academic collaborations will also be crucial to stay up to date with the latest methodology and seize new opportunities.*

Expected Impact: *Upskilling and aligning clinical trial statisticians and regulators on the most appropriate methodology for covariate adjustment. Supporting the upcoming regulatory initiatives on covariate adjustment methodology.*

Key stakeholders and resources

Priority topic lead	Alex Ocampo
Team	Methods Leaders: Jurgen Hummel, Tobias Mielke, Kaspar Rufibach, David Wright Key WG Members: Sanne Roels (J&J), Tim Morris (NVS), Dominic Magirr (NVS)
Working groups	*We plan to collaborate with and support the EFSPI PSI SIG and ASA working group mentioned below.*

Scope, Workplan, and Deliverables

Ongoing Activities:

- ***Webinar on Covariate Adjustment planned for June 30th (in collaboration with PSI/EFSPI Causal Inference SIG)***

Introduction on the covariate adjustment topic from Dan Rubin (FDA). Dominic Magirr (Novartis) will provide an educational lecture including defining marginal vs conditional estimands in non-collapsible models. Sanne Roels (J&J) will discuss the relatively new covariate-adjusted log-rank test for time-to-event endpoints and extensions to group sequential designs. Kelly van Lanker will also outline future areas of opportunity before a panel discussion closes the event.

- ***EFSPI Regulatory Workshop session on Covariate Adjustment***

- ***ASA Biopharm Covariate Adjustment Working group***
  - *Blog-posts on considerations for covariate adjustment*
    - Daniel Backenroth (J&J), Devan Mehrotra (Merck), Leiya Han (Thermo-Fisher), Jiawei Wei (Novartis), Victoria Johnson (GSK), Alex Ocampo (Roche)
  - *Development of the Robincar2 R package for validated clinical trial analyses using covariate adjustment*

- ***Explore federated learning for prognostic scores***

Key Linkages

EFSPI/ASA SIGs:
- *PSI/EFSPI Causal Inference SIG*
- *ASA-BIOPHARM Working group on covariate adjustment*

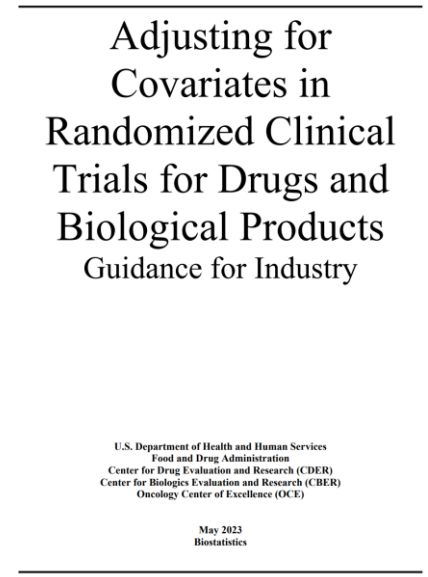
Regulatory initiatives (e.g. Concept paper):
The EMA methodology working party's draft workplan mentions that in 2026 a Q&A will be organized on baseline covariates and the use of synthetic covariates.

High-level timelines

Key Milestones	Target date
1. *Webinar on Covariate Adjustment*	1. June 30th, 2026
2. *Draft Blogposts on covariate adjustment*	2. June 11th, 2026
3. Support EFSPI Reg Stats WS on covariate adjustment topic	3. August 19th, 2026

Why the renewed focus on covariate adjustment?

- Using baseline covariate information to increase efficiency in statistical analyses is a long-standing idea dating back to Fisher in 1934
- FDA guidance in 2023 sparked newfound interest in covariate adjustment in clinical trials
  - Guidance nudges sponsors to target marginal treatment effects (estimands)
  - Sparked statistical research among both academics and industry statisticians
- Relevant work from Ting Ye from University of Washington for various outcome types:
  - Time-to-event: Covariate-adjusted log-rank test and corresponding marginal hazard ratio estimate (Biometrika, 2024)
  - Binary: "Correct" variance estimates for binary outcome when using standardization (Statistical Theory and Related Fields, 2023)
  - Continuous: ANHECOVA - include all treatment by covariate interactions as covariates (JASA, 2023)
  - RobinCar2 R package implements these methods
- Open questions remain about data-adaptive selection of covariates (blinded, algorithmic), PROCOVA, and use of ML algorithms for clinical trial analyses (e.g. TMLE)

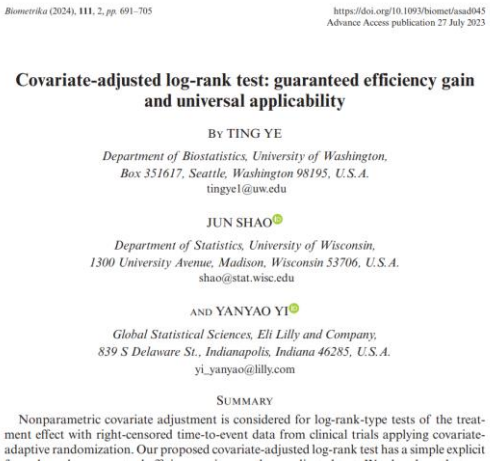


Adjusting for Covariates in Randomized Clinical Trials for Drugs and Biological Products

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



Biometrika (2024), **111**, 2, *pp.* 691–705 https://doi.org/10.1093/biomet/asad045
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Covariate-adjusted log-rank test: guaranteed efficiency gain and universal applicability

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SUMMARY

Nonparametric covariate adjustment is considered for log-rank-type tests of the treatment effect with right-censored time-to-event data from clinical trials applying covariate-adaptive randomization. Our proposed covariate-adjusted log-rank test has a simple explicit