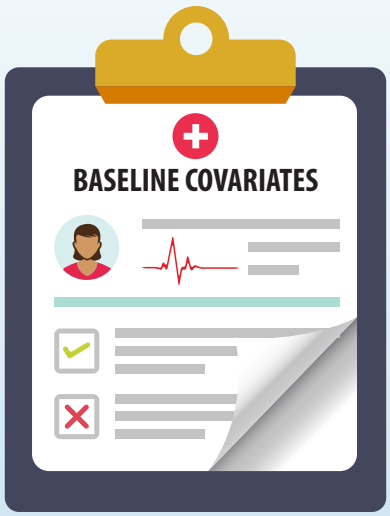
U.S. FOOD & DRUG ADMINISTRATION

Adjusting for Covariates in Randomized Clinical Trials for Drugs and Biologics with Continuous Outcomes

Revised Draft Guidance

What is recommended in this guidance?

A revised draft guidance has been issued providing recommendations on adjusting for covariates in randomized clinical trials to improve statistical power and the precision of treatment effect estimates.



What is covariate adjustment?

Covariate adjustment refers to the use of information measured on a subject before the time of randomization (e.g., demographic factors, disease characteristics) for estimating and testing treatment effects between randomized groups.

Sponsors should adjust for baseline covariates that are strongly associated with an outcome in a clinical trial population.

Why is covariate adjustment helpful?

It is desirable to study a population in clinical trials that reflects the variability of the target population, but doing so may make it harder to detect a treatment effect. Covariate adjustment allows for incorporation of prespecified prognostic factors in the statistical analysis and can result in narrower confidence intervals and a greater statistical power to detect treatment effects.

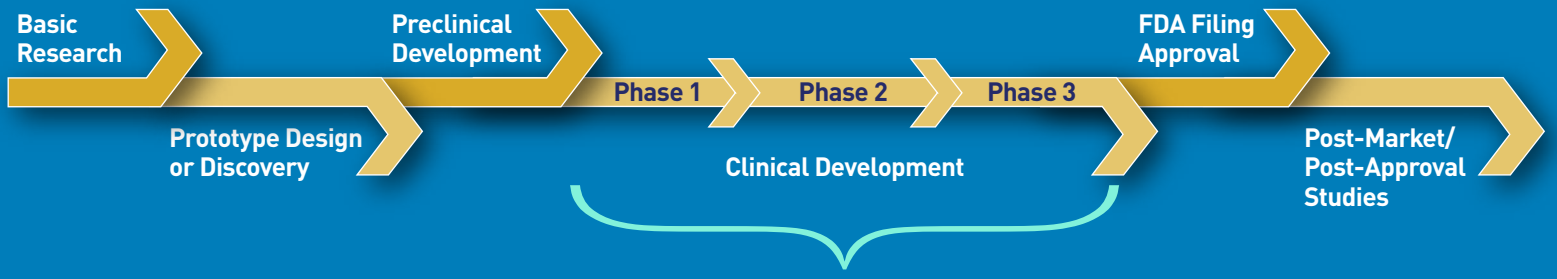
Please note: This is a revised draft guidance. FDA has not made a decision as to whether the recommendations in this document will be adopted in the final version.

Guidance Snapshots are a communication tool and are not a substitute for the guidance document. To learn more about adjusting for covariates, read the revised draft guidance.

What to submit when adjusting for covariates?

Sponsors should prospectively specify the covariates and the mathematical form of the covariate adjusted estimator in the protocol or statistical analysis plan. The prespecified primary analysis will be emphasized in review rather than post-hoc analyses using different models or covariates. If the number of covariates is large relative to the sample size or covariates are adaptively selected, sponsors should discuss the method of adjustment with the FDA during review of the protocol or statistical analysis plan.

Drug Development Timeline – When to Apply the Guidance Recommendations?



During Clinical Development: FDA strongly recommends that sponsors considering use covariate adjustment in a primary analysis to prespecify the details of the proposed analysis in the study protocol or statistical analysis plan. In general, sponsors should use existing pathways for interacting with the FDA during the course of the clinical development program, including Type A, Type B, Type B end-of-phase, and Type C meetings, as well as the IND amendment review process.

Continue the Conversation

Share your thoughts on the revised draft guidance:

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Guidance Recap Podcast – Hear Highlights Straight From FDA Staff

Speaker: Dr. Dan Rubin, Statistician in the Center for Drug Evaluation and Research's Office of Biostatistics

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Guidance Snapshots are a communication tool and are not a substitute for the guidance document.
To learn more about adjusting for covariates, read the revised draft guidance.
To see additional Guidance Snapshots, check out the pilot program.