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

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) Scott N. Goldie at 301-796-2055 or (CBER) Office of Communication, Outreach, and Development at 800-835-4709 or 240-402-8010.

**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)**

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Contains Nonbinding Recommendations

Draft — Not for Implementation

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2 **and Biologics with Continuous Outcomes**
3 **Guidance for Industry¹**

4 This draft guidance, when finalized, will represent the current thinking of the Food and Drug
5 Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not
6 binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the
7 applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible
8 for this guidance as listed on the title page.

9 **I. INTRODUCTION**

10 This draft guidance, when finalized, will represent the current thinking of the Food and Drug
11 Administration on adjusting for covariates in randomized clinical trials in drug² development
12 programs. This guidance provides recommendations for adjusting for covariates in randomized
13 clinical trials with continuous endpoints that are appropriate for analysis with normal-theory
14 methods, such as the two-sample t-test. Nonparametric methods, categorical outcomes, and
15 survival methods, among others, are outside the scope of this document, although some of the
16 same principles might apply to those methods as well.

17 In general, FDA's guidance documents do not establish legally enforceable responsibilities.
18 Instead, guidances describe the Agency's current thinking on a topic and should be viewed only
19 as recommendations, unless specific regulatory or statutory requirements are cited. The use of
20 the word *should* in Agency guidances means that something is suggested or recommended, but
21 not required.

22 **II. BACKGROUND**

23 The target population for a new drug usually includes patients with diverse prognostic factors³,
24 and the population studied in clinical trials should reflect this diversity. However, potential
25 baseline differences between treatment groups in prognostic factors increase the variability of
26 estimates of treatment effects and reduce the power of significance tests. Incorporating
27 prognostic factors in the primary statistical analysis of clinical trial data can result in a more
28 efficient use of data to demonstrate and quantify the effects of treatment.

¹ This guidance has been prepared by the Office of Biostatistics in the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research at the Food and Drug Administration.

² The term *drug* used in this guidance refers to both human drugs and biological products.

³ As used in this guidance, the term prognostic factor refers to a variable, typically measured before randomization, that is likely to be correlated with the outcome of primary interest.

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29 The ICH guidance for industry *E9 Statistical Principles for Clinical Trials*⁴ addresses these
30 issues briefly. The ICH E9 guidance encourages the identification of “covariates and factors
31 expected to have an important influence on the primary variable(s).” The ICH E9 guidance
32 strongly advises prespecification of “the principal features of the eventual statistical analysis,”
33 including “how to account for [covariates] in the analysis to improve precision and to
34 compensate for any lack of balance between treatment groups.” The ICH E9 guidance also
35 cautions against adjusting for “covariates measured after randomization because they could be
36 affected by the treatments.”

37 This guidance provides more detailed recommendations for the use of covariates in the primary
38 analysis in randomized clinical trials. In the case of continuous covariates, the method of
39 adjusting for covariates is usually referred to as *analysis of covariance* (ANCOVA). The
40 guidance, however, also applies to categorical covariates or a mixture of categorical and
41 continuous covariates. For simplicity, this guidance also uses the term ANCOVA even when
42 there are categorical covariates, although *analysis of variance* or *linear model* would be more
43 common usage in that case.

III. RECOMMENDATIONS

- 45 • Sponsors can use ANCOVA to adjust for differences between treatment groups in relevant
46 baseline variables to improve the power of significance tests and the precision of estimates of
47 treatment effect.
- 48 • Sponsors should not use ANCOVA to adjust for variables that might be affected by
49 treatment.

50 The closer the model approximates the true relationship between the outcome and the
51 covariates, the greater the improvement in the power of significance tests and the precision of
52 estimates compared to not using ANCOVA. However, even when the ANCOVA model does
53 not closely approximate the true relationship between the outcome and the covariates, the
54 probability of type I error is still maintained at the nominal level, and therefore
55 misspecification of the relationship between the outcome and the covariates will not
56 invalidate the results. For example, if there is truly a quadratic relationship between the
57 outcome and a covariate, a quadratic model would provide the best fit and thus the greatest
58 possible improvement in power; but if the quadratic relationship had not been foreseen and a
59 straight-line model had been prespecified, the straight-line model would still be acceptable.

⁴ We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page at <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

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- 60 • The sponsor should prospectively specify the covariates and the mathematical form of the
61 model in the protocol or statistical analysis plan. When these specifications are
62 unambiguous, FDA will not generally be concerned about the sensitivity of results to the
63 choice of covariates because differences between adjusted estimators and unadjusted
64 estimators of the same parameter, or between adjusted estimators using different models, are
65 random.

- 66 • Interaction of the treatment with covariates is important, but the presence of an interaction
67 does not invalidate ANCOVA as a method of estimating and testing for an overall treatment
68 effect, even if the interaction is not accounted for in the model. The prespecified primary
69 model can include interaction terms if appropriate. However, interaction means that the
70 treatment effect is different for different subjects, and this fact could be relevant to
71 prescribers, patients, and other stakeholders. Therefore, even though a primary analysis
72 showing an overall treatment effect remains valid, differential effects in subgroups can also
73 be important.

- 74 • Many clinical trials use a change from baseline as the primary outcome measure. Even when
75 the outcome is measured as a change from baseline, the baseline value can still be used
76 advantageously as a covariate.