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DISCUSSION

Discussion on "Improving precision and power in randomized trials for COVID-19 treatments using covariate adjustment, for binary, ordinal, and time-to-event outcomes" by David Benkeser, Ivan Diaz, Alex Luedtke, Jodi Segal, Daniel Scharfstein, and Michael Rosenblum

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The paper entitled "Precision and Power in Randomized Trials for COVID-19 Treatments Using Covariate Adjustment, for Binary, Ordinal, and Time-to-Event Outcomes" is a welcome addition to the literature on covariate adjustment in clinical trials conducted for medical research. The authors' work has the potential to make a substantial impact on drug development through increased use of an extremely underutilized tool for improving precision in clinical trials, thereby reducing the number of studies that fail due to insufficient power. And the timeliness of this research could not be better, with the number of clinical trials currently being planned or already in the field to combat COVID-19. Both the urgency with which safe and effective treatments are needed in a pandemic and the competition that inherently follows multiple trials launched at the same time, for the same purpose (i.e., finding those safe and effective treatments), result in an unusually high need for accurately sized trials optimized to reach their goals.

The advantages of covariate adjustment in the much simpler linear model context have been known for a while, and the method is popular with clinical trialists for its ability to improve the precision of treatment effect estimates with minimal assumptions. I have written before (LaVange 2014, 2019) of my quandary, after arriving at FDA in 2011, about the lack of a covariate adjustment guidance document, only to find that one had been drafted in the early 2000s but never published. The guidance was apparently shelved because, although noncontroversial for linear models, regulators were concerned that covariate adjustment would be misused in nonlinear models without appropriate guidance for that more complicated setting. As Biostatistics Office Director in the Center for Drug Evaluation and Research, I was able to prioritize an update of this guidance, which was completed soon after I left and issued in 2019 (FDA, 2019).

An examination of the delay in FDA's issuance of a covariate adjustment guidance helps to explain the importance of the Benkeser *et al*. paper to the drug development enterprise. The International Council on Harmonisation (ICH) published the guideline, *E9 Statistical Principles for Clinical Trials* (ICH, 1999), calling for the adjustment of covariates, measured before randomization, that were correlated with the primary trial outcomes. Purposes of this adjustment were twofold, to improve precision and adjust for imbalances between treatment groups. The European Medicines Agency (EMA) followed with a Points to Consider document in 2003 and a guidance document in 2015, both providing similar advice on covariate adjustment for trials regulated in the European Union (EU) region. The FDA guidance followed much later—20 years after ICH E9—and the primary reason was the inability to endorse a simple analytical tool like analysis of covariance when the analysis model was nonlinear. As the FDA guidance makes clear, prespecification of any covariate adjustments is required to ensure that the chance of making an erroneous conclusion about drug effects is not increased due to experimenting with different model adjustments after the trial concludes. The guidance also makes clear that even if the analysis model is inaccurate, the advantages of

covariate adjustment in the linear model setting still apply, and the resulting treatment effect estimates are valid to support inference about the drug. Such a statement could not be made in the nonlinear setting, or at least not with respect to an approach that was widely accepted in the early 2000s, and that was, in large part, the source of the delay in issuing the guidance.

Noteworthy is the fact that the FDA guidance remains silent on the use of covariate adjustments to correct for imbalances between treatment groups for purposes of producing unbiased estimates of the drug's effects. Any differences between treatment groups are a random occurrence, provided only prerandomization covariates are used for adjustment. Although adjusting for such imbalances has the potential to substantially improve the precision of estimates and the power of hypothesis tests about those estimates, the unadjusted estimates are still valid for the true drug effects. The advantage lies in the improvement of precision (Permutt, 2009). This point is often missed, but importantly, a misunderstanding about the purpose of covariate adjustment has over time led to its use primarily in small clinical trials, where investigators worry that treatment group imbalances can bias the study results. With large clinical trials, covariate adjustments are more often viewed as a nice-to-have but not essential component of the trial design, thinking random imbalances tend to decrease as sample sizes increase. Senn (1989), however, noted for the bivariate normal case, "covariate imbalance is as much of a concern in larges studies as in small ones" due to the fact that, although absolute differences in baseline covariates (absolute imbalance) may decrease as sample sizes increase, standardized differences do not, and standardized differences are the ones impacting precision. Senn goes on to advocate for analysis of covariance with prespecified covariates as best practice for studies of all sizes, regardless of any random imbalances that may be observed in the study.

Around the same time, Gary Koch and colleagues were exploring randomization-based methods of covariate adjustment in both linear and nonlinear model settings, resulting in a series of publications for a variety of endpoints (see, e.g., Tangen and Koch, 1999; Saville and Koch, 2013). These randomization- based methods have a particular advantage in large, confirmatory clinical trials conducted for regulatory approval, where the primary objective relates to hypothesis testing, as minimal assumptions are required for their use. The emphasis by Benkeser *et al*. on the utility of covariate adjustment in large trials follows this earlier work by Senn and Koch with a consistent message. By expanding the analytical tools available for ordinal outcomes and, in addition, providing performance results of covariate adjusted estimators for binary and time-to-event outcomes, the use of covariate adjustments in large clinical trials, where endpoints are more often of those categories, should see a dramatic increase. In my opinion, this is the major contribution of the paper and one that makes me very excited to see it in publication!

The authors give the results of extensive simulations for a variety of estimands of interest when primary clinical outcomes correspond to the occurrence of, or time to, an event or an ordinal scale. The control arm distributions were based on real-world data from two highly relevant sources, and sizable power gains or relative efficiencies are reported for all estimands examined. Looking across the National Institutes of Health Accelerating Covid-19 Therapeutic Interventions and Vaccines (ACTIV) master protocols launched during this past year, an array of outcomes is specified, including disease severity assessed by seven-point or eight-point ordinal scales, symptom counts, time on ventilation or in the intensive care unit, time to recovery, and mortality. With the authors' proposed methods, covariate adjustments could be prespecified in planning the analyses of all primary and key secondary endpoints in these trials, thereby increasing the power of tests and improving the precision of estimates to characterize every important dimension of the pandemic's toll.

Enough cannot be said about the advantage of producing valid estimates of drug effects even in the presence of model misspecification. Prespecification of a clinical trials' statistical analysis plan provides the foundation for FDA's assurance that sponsors are not presenting the most promising set from a range of exploratory results in their regulatory submissions. If model misspecification cannot be determined until after treatment codes are known and preliminary analyses are conducted, then such prespecification is not possible. The authors provide a framework to drug developers for optimizing their planned analyses without requiring post hoc model fitting. With publication of this paper, there really should be no remaining barriers to the use of covariate adjustment when analyzing the endpoints relevant to the health and well-being of patients. In the time of a pandemic, realizing the advantages of covariate adjustment to reduce sample sizes and get answers about promising therapies sooner is invaluable. The authors' contributions in this regard are to be commended.

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