Robust integration of external control data in randomized trials

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One approach for increasing the efficiency of randomized trials is the use of "external controls" -- individuals who received the control treatment studied in the trial during routine practice or in prior experimental studies. Existing external control methods, however, can be biased if the populations underlying the trial and the external control data are not exchangeable. Here, we characterize a randomization-aware class of treatment effect estimators in the population underlying the trial that remain consistent and asymptotically normal when using external control data, even when exchangeability does not hold. We consider two members of this class of estimators: the well-known augmented inverse probability weighting trial-only estimator, which is the efficient estimator when only trial data are used; and a potentially more efficient member of the class when exchangeability holds and external control data are available, which we refer to as the optimized randomization-aware estimator. To achieve robust integration of external control data in trial analyses, we then propose a combined estimator based on the efficient trial-only estimator and the optimized randomization-aware estimator. We show that the combined estimator is consistent and no less efficient than the most efficient of the two component estimators, whether the exchangeability assumption holds or not. We examine the estimators' performance in simulations and we illustrate their use with data from two trials of paliperidone extended-release for schizophrenia.