Randomization-Based Inference Following Randomized Clinical Trials

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Abstract: Experiments rely on replication rather than sampling from a population for their scientific validity.

It was recognized by the pioneers of statistics that incorporating randomization into an experiment allows a basis for inference that cannot be obtained otherwise. Nonetheless, the advent of Neyman-Pearson inference led to inference based on random sampling becoming the standard method for analyzing randomized clinical trials. The principle reason for this anomaly was the difficulty in computing the distribution of the reference set required for inference. With the advent of computing, Monte Carlo re-randomization takes only seconds, yet the clinical trials culture of invoking a population model has not changed. The second reason is that, under the correct population model, the results of randomization-based inference and population-based inference are typically similar; but this is certainly not always the case under different randomization procedures, heterogeneity, and model misspecification.

As Kempthorne pointed out in the 1950s, the normal theory test should always be considered an approximation to the randomization test, and not vice versa. Randomization tests preserve type I error rates even under heterogeneity, they can be adapted to virtually any type of primary outcome analysis in clinical trials, to multiple treatments, covariate-adjusted analyses, and to confidence intervals. We describe how to do this and conclude that invoking a population model is no longer necessary or desirable in clinical trials practice.