Abstract: What the Estimand Framework Has Gotten Right and Wrong

In 1998, the International Conference on Harmonisation's (ICH) E9, Statistical Principles for Clinical Trials, codified basic statistical guidelines for design and analysis of confirmatory clinical trials. Notably, E9 emphasized the importance of randomization and other approaches to protect against bias. Over the ensuing years, however, many statistical analysis plans for randomized controlled trials did include randomization but structured analyses in ways that induced bias. In addition, many so-called "sensitivity analyses" were illogically linked to the primary analysis. Perhaps to correct these and other misuses of E9, in 2014 the ICH published R1, an addendum that introduced the concept of an "estimand". The ICH's rationale for R1 was to address a perceived problem: "Incorrect choice of estimand and unclear definitions for estimands lead to problems in relation to trial design, conduct and analysis and introduce potential for inconsistencies in inference and decision making." Had R1 limited its statements to advice that would lead to clarity and rigor, it would have made important contributions to the conduct and interpretation of randomized controlled trials. Unfortunately, R1 has given sometimes tacit, and sometimes explicit, permission for analyses that, by failing to respect the implications of randomization. are potentially highly biased. This talk will describe the estimand framework and R1's approach to analysis. It will point out, with examples, that some analytical strategies R1 recommends are deeply flawed. It will argue those of us involved in clinical trials should advocate for a revision of R1 that preserves the scientifically valid aspects of the estimand framework but that removes strategies that lead to biased analyses.