Improving Safety Analyses for Clinical Trials with Noncompliance

David Lewin
Dylan Small

Abstract

It is well established that a randomized controlled trial (RCT) is the gold standard design for medical studies. However, understanding the safety of a treatment based on a clinical trial can be difficult due to the length of the trial, unmeasured side effects, multiplicity, and rare events. We focus on another general challenge that compliance is rarely 100%. In this setting the intent-to-treat, as-treated, and per-protocol estimates will be biased and can severely inflate the error rate for hypothesis tests. When the risk of having a side effect is underestimated this can lead to dangerous decisions, and when it is overestimated potentially beneficial treatments may not be approved. In the presence of noncompliance instrumental variable estimates can provide a more accurate estimate of the biological effect of the treatment on side effect risk (i.e., the outcome if a subject takes the treatment versus the outcome if that same subject did not take the treatment). The estimate of this effect may be more useful to doctors and patients, as well as to generalize the occurrence of side effects that will occur post-marketing. The goal of this presentation is to communicate analytical and simulation results that propose when and how IV estimating methods can be used to extract more accurate safety information from a RCT.

Keywords: Instrumental variables, safety, causal inference, compliance.