# ADJUSTING FOR NON-COMPLIANCE IN META-ANALYSIS OF CLINICAL TRIALS USING POOLED INDIVIDUAL DATA

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When combining individual data in a meta-analysis of several clinical trials to estimate a causal effect of treatment, differential non-compliance and differential follow-up distributions across studies present difficulties. To adjust simultaneously for bias from both differential compliance and the potentially increased health of compliers, we employed a modification of the approach described by Cuzick et al. (Cuzick, Edwards et al. 1997), referred to as CES. Their instrumental-variable approach allows estimating the effect of treatment (relative to the control group) among compliers, defined for this presentation as those subjects compliant at least once to treatment. They apply an adjustment to the control-group event rate to provide a valid contrast with the observed rate among compliers. In our modification of the CES approach, we apply their adjustment to the cumulative event rates through the follow-up period of interest (e.g., 12 years) as estimated by the Kaplan-Meier method, rather than to event rates estimated as binomial proportions, avoiding the problems of differential follow-up and compliance. We illustrate this method on a meta-analysis of three trials of fecal occult blood test screening for colorectal cancer to derive an estimate of the mortality effect overall and by age and sex subgroups and evaluate how the adjusted effect differs from intention-to-treat.