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A Causal Inference Approach to Estimating the External Validity of Clinical Trials

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Introduction: Despite the perception of randomized controlled trials (RCTs) as the highest grade of clinical evidence, inferences from RCTs are threatened by limitations to both their internal and external validity. External validity is difficult to study empirically given confounding due to time, location, and population under study. The PRECIS-2 tool offers methodology to qualitatively grade the external validity of clinical trials, but robust approaches for quantitative estimation of external validity are lacking. Here, we propose the use of a causal framework to compare the outcomes of mortality and hospitalization between an RCT and observational study that concurrently enrolled HIV-Exposed Uninfected newborns in Botswana.

Methods: The Mpepu Study was a clinical trial, stopped for futility, that enrolled HEU newborns in Botswana to determine whether co-trimoxazole provided survival benefit. The Maikaelelo study was an observational study that enrolled HEU newborns in Botswana with telephone follow-up and no in-person visits. Hazard ratios were estimated to determine the effect of the clinical trial setting on morbidity and mortality and to determine whether the effect varies over time. The inverse probability weighted estimator was used to determine the potential outcome means had everyone been enrolled in the observational setting and the average treatment effect to estimate the causal effect of enrollment into the RCT.

Results: In total, 4,010 infants were included; 1,306 were enrolled into Maikaelelo and 2,704 were enrolled into Mpepu. No significant differences in mortality were observed between the two settings (HR: 1.28, 95% CI: 0.76, 2.13), but RCT participants had a lower risk of hospitalization (HR: 0.72, 95% CI: 0.58, 0.89) that decreased with age. The causal risk difference in hospitalizations attributable to the trial setting was -0.03 (95% CI: -0.05, -0.01), a reduction in morbidity of approximately 30%. Sensitivity analyses conducted with more flexible exclusion criteria indicated that the RCT setting caused a reduction in morbidity of approximately 40%.

Conclusions: Children in an RCT with rigorous application of national standard of care guidelines experienced a significantly lower risk of hospitalization than children participating in an observational study that did not alter clinical care. The reduction in morbidity is time-varying, consisting of both physician-directed hospitalization in the early RCT setting and protective effects seen after six months of life. Future research is needed to further investigate outcome disparities where real-world care does not

mirror care in the RCT setting. Finally, we demonstrate that causal inference methods may be appropriate for comparing trial and non-trial settings in meta-epidemiologic studies, if and only if study design and conduct are carefully and judiciously considered.

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