A Causal Inference Approach to Estimating the External Validity of Randomized Controlled Trials

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Introduction

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.

Questions

Does enrollment into the RCT setting cause a reduction in morbidity or mortality for HIV-Exposed Uninfected (HEU) infants?

Do the benefits conferred by RCTs vary over the time enrolled into the trial setting?

Methods

RCT Setting: The Mpepu Study was a clinical trial, stopped for futility, that enrolled HEU newborns in Botswana to determine whether co-trimoxazole provided survival benefit (NCT01229761).

Observational Setting: The Maikaelelo study was an observational study that enrolled HEU newborns in Botswana with telephone follow-up and no in-person visits (32AI007433-21).

Association Measure: Adjusted Cox-proportional hazard models were fitted and the proportional hazards assumption was assessed through restricted cubic spline transformation of the HR.

Causal Measure: The inverse probability-weighted estimator was used to determine the causal effect of RCT enrollment on morbidity and mortality.

Table 1. Adjusted Cox Proportional Hazards Model

	Non-Time Varying: Time to Death HR (95% CI)	Non-Time Varying: Time to First Hospitalization HR (95% CI)	Time-Varying: Time to First Hospitalization HR (95% CI)
Participating in RCT Non-Time-Varying	1.28 (0.76, 2.13)	**0.72** (0.58,0.89)**	N/A
Participating in RCT Time Varying	N/A	N/A	**0.42*** (0.31, 0.58)**

Figure 1. Spline Transformation of RCT HR

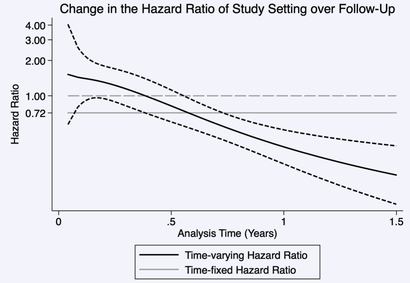

Table 2. Causal Effect Estimation of RCT

A) Primary Analysis	Coefficient	P > |z|	95% CI
Risk of Mortality in Observational Setting[1]	0.02	<0.001	(0.01, 0.02)
Difference in Mortality caused by RCT[2]	0.00	0.263	(-0.00, 0.01)
Risk of Morbidity in Observational Setting[1]	0.12	<0.001	(0.10, 0.13)
Difference in Morbidity caused by RCT[2]	-0.03	0.001	(-0.06, -0.01)

B) Sensitivity Analysis	Coefficient	P > |z|	95% CI
Risk of Mortality in Observational Setting[1]	0.02	< 0.001	(0.01, 0.02)
Difference in Mortality caused by RCT[2]	0.00	0.947	(-0.01, 0.01)
Risk of Morbidity in Observational Setting[1]	0.12	< 0.001	(0.10, 0.13)
Difference in Morbidity caused by RCT[2]	-0.05	< 0.001	(-0.07, -0.02)

Table 2. Treatment effect analysis of morbidity and mortality. [1] Indicates potential-outcome mean (POM) had all children been enrolled into Maikaelelo (observational).[2] Indicates average treatment effect (ATE) attributable to enrollment into Mpepu (RCT).

Results

Enrollment in the RCT setting did not cause a reduction in the risk of mortality (RD: -0.01, 0.01).

Enrollment in the RCT setting reduced the risk of hospitalization between 30-40% (RD: -0.06, -0.01).

The risk of hospitalization decreases over time with continued enrollment into the RCT setting (TV AHR: 0.31, 0.58).

Conclusions

The standard of care in an RCT reduced morbidity for HIV-Exposed Uninfected infants in Botswana compared to routine clinical care.

The effect of RCT participation on morbidity is time-varying, with physician-directed hospitalization contributing to an artificially elevated "excess risk" prior to six months of life (critical period) and elevated standard of care benefits contributing to a lower risk after six months of life.

Here, we provide some of the first robust empirical evidence of external validity that motivates the conduct of pragmatic trials. We demonstrate that the external validity of RCTs is limited by differences in standards of care between trial and non-trial settings and that enrollment into the RCT setting can affect health outcomes.

Interpretation

Randomized controlled trials provide important evidence for the efficacy of interventions. However, their conduct does not reflect real-world care but whether or not this difference affects health outcomes has never been estimated. Here, we show that the conduct of an RCT reduces the risk of hospitalization by up to 40%.