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QMP Quantitative Methodology Program

Cluster-level dynamic treatment regimens and sequential, multiple assignment, randomized trials: Estimation and sample size considerations

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MICHIGAN STATISTICS

Overview

Cluster-level dynamic treatment regimens (DTRs) can be used to guide sequential treatment decision-making at the cluster level in order to improve outcomes at the individual-level. In a cluster-level DTR, the treatment is potentially adapted and re-adapted over time based on changes in the cluster that could be impacted by prior intervention. Cluster-randomized sequential multiple assignment randomized trials (SMARTs) can be used to answer multiple open questions preventing scientists from developing high-quality cluster-level DTRs. In a cluster-randomized SMART, sequential randomizations occur at the cluster level and outcomes are at the individual level. We make two contributions to the design and analysis of cluster-randomized SMARTs: First, a weighted least squares regression approach is proposed for comparing the mean of a patient-level outcome between the cluster-level DTRs embedded in a SMART. The regression approach facilitates the use of baseline covariates which is often critical in the analysis of cluster-level trials. Second, sample size formulae are derived for use when the primary aim is a between-DTR comparison of the mean of a continuous patient-level outcome.

Motivating Example

These methods are motivated by the Adaptive Implementation of Effective Programs Trial (ADEPT). The overall aim of ADEPT is to develop a cluster-level DTR to improve the adoption of a patient-level evidence based practices (EBPs) for mood disorders in community-based mental health clinics across Colorado and Michigan.

An Example of a Cluster-Level DTR

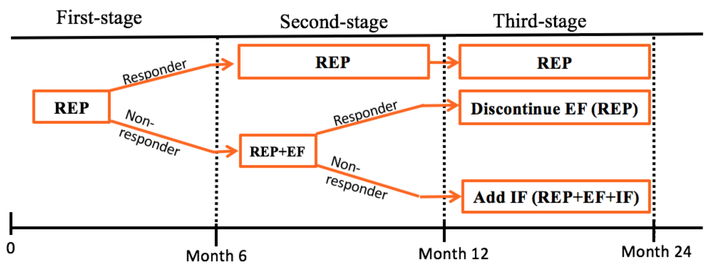

Figure 1: Example Cluster-Level DTR within ADEPT

Sequential, Multiple Assignment Randomized Trials with Cluster-level Randomization

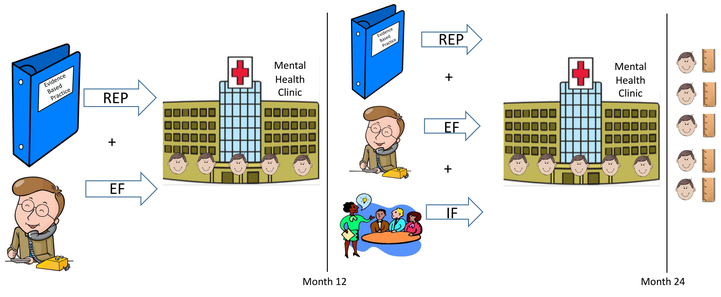

Figure 2: Intervening at the cluster-level with outcomes at the patient level

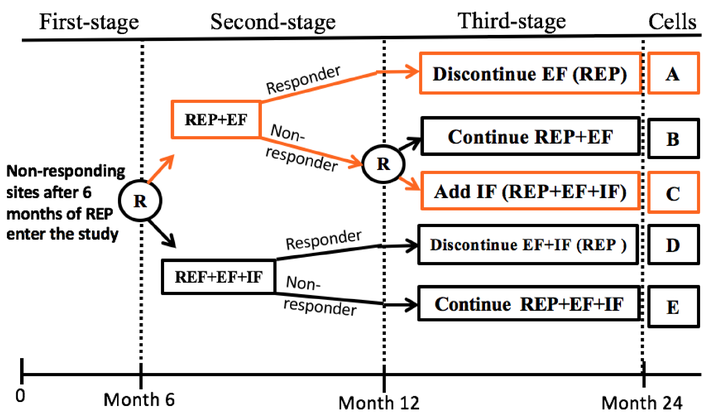

Figure 3: Schematic of ADEPT

DTR Label (a_1, a_2)	Second-stage Treatment	Status at end of second-stage	Third-stage Treatment	Cell in Figure	Known IPW
$(1,1)$	REP+EF	Resp	REP	A	2
		Non Resp	REP+EF	B	4
$(1,-1)$	REP+EF	Resp	REP	A	2
		Non Resp	REP+EF+IF	C	4
$(-1,.)$	REP+EF+IF	Resp	REP	D	2
		Non Resp	REP+EF+IF	E	2

Table 1: The three DTRs embedded in ADEPT

Methodology

Marginal Mean Model

We consider the following marginal mean model for the mean of an individual level outcome Y under DTR (a_1, a_2) given baseline covariates X, i.e. $E_{a_1,a_2}(Y|X)$:

$$\mu(a_1, a_2, X; \beta, \eta) = \beta_0 + \beta_1 a_1 + \beta_2 a_2 I_{a_1=1} + \eta^T X.$$

Estimation

Given the observed data arising from a SMART, we present an estimator for the marginal mean models. We obtain estimates for β, η by solving the following estimating equation.

$$0 = \sum_{i=1}^{N} W_i \sum_{(a_1,a_2)} I\{\text{cluster i is consistent with DTR } (a_1, a_2)\} \cdot D(\mathbf{X}_i, a_1, a_2)^T V(a_1, a_2, m_i)^{-1}(\mathbf{Y}_i - \boldsymbol{\mu}(\mathbf{X}_i, a_1, a_2; \beta, \eta))$$

Sample Size Formula

We develop sample size formula for detecting a difference between effects of DTRs beginning with different first stage treatments, i.e. $(1, a_2)$ and $(-1, b_2)$.

Without Covariates:

$$N = \frac{4(z_\beta + z_{\alpha/2})^2}{\delta^2} \cdot \frac{(1+(m-1)\rho)}{m} \cdot (1 + \frac{1-p_1}{2})$$

2 arm RCT | Scaled Variance Inflation Factor | SMART Specific Constants

With a Cluster-Level Covariate:

$$N = \frac{4(z_\beta + z_{\alpha/2})^2}{\delta^2} \cdot \frac{(1+(m-1)\rho^*)}{m} \cdot (1 + \frac{1-p_1}{2})(1 - \text{Cor}^2(X,Y))$$

Deflated ICC | Variance Deflation Factor

where z_β and $z_{\alpha/2}$ are standard normal quantiles, p_1 is the probability of response given your initial treatment was $A_1 = 1$, ρ is the ICC, m is the cluster size, δ^2 is the standardized effect size, and $\text{Cor}(Y, X)$ is the scalar correlation between the individual outcome and the cluster-level covariate.

Sample Size Formulae Are Robust to Working Assumptions

Below we evaluate our sample size formula both when working assumptions are satisfied and violated. Our pre-specified power value is 90% and we use simulation to determine the 'true' power of our calculated sample size, under various settings.

ICC ρ	Effect Size δ	Cluster Size m	Sample Size N	Working Assumptions are correct	Violating Non-Responder Variance Assumption	Violating Homoskedastic Assumption
.01	.2	5	306	.894	.891	.886
		20	88	.917	.890	.876*
	.5	5	49	.909	.898	.880*
		10	26	.906	.878*	.893
.1	.2	5	412	.910	.901	.870*
		20	213	.922*	.902	.891
	.5	5	66	.909	.888	.898
		20	34	.915	.913	.889

Table 2: Simulation results, pre-specified power 90%, 1000 Monte Carlo iterations
**The proportion is significantly different from .9 at the 5% level.*

Future Work

- Using the estimator with different link functions in order to analyze, for example, binary, count, or zero-inflated outcomes.
- Using variance components models based on likelihood estimators, i.e., random-effects models which are now-standard in the analysis of randomized trials.
- Experimental studies aimed at developing DTRs where sequences of decisions are made at *both* the cluster and individual level.

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