

Analysis Plan for IRB# 08-10-30 Resourcefulness Intervention for Parents of TD Children

ANALYSIS. We hypothesize that parents receiving the Resourcefulness Training intervention will have significant improvement in parental outcomes (psychological and physical) compared with parents in the Attention Control arm. We also hypothesize that resourcefulness will mediate the effect of the intervention on all study outcomes.

Preliminary Analyses. Exploratory data techniques will be used to examine univariate characteristics (central tendency, dispersion, and distribution) of demographics and covariates measured upon randomization in each arm. These exploratory techniques will be based on proportions (in the case of dichotomous variables) and medians and/or means (in the case of variables measured on an interval scale). Due to randomization, no formal tests of these variables will be performed because any imbalance between arms is known to be due to chance. Profile plots will also be used to describe the participant-specific (parent) and arm-specific trends for each outcome over the four time points.

Primary Analyses.

Aims 1 & 2: Analysis of the monthly rate of change in each of the parent outcomes in each arm will be estimated via linear mixed models and fit using SAS PROC MIXED. Each model will include a random intercept and slope (possibly modeled using a polynomial spline) to account for between-subject variance in each outcome over time. Conditional on these random effects, we will also explore within-subject variance in each outcome over time using different residual covariance structures and select the most appropriate structure using likelihood-based criteria. Fixed effects will include a continuous variable to represent time since randomization, an indicator variable to represent the intervention, and stratification factors used during randomization (facility, OTA technology group, sex and race/ethnicity). Assuming a linear rate of change over time, the regression coefficient of the terms representing interactions between time and the intervention indicator variable will be used to estimate the difference in the monthly rate of change in each outcome between the two arms.

To determine if resourcefulness mediates the effect of the resourcefulness intervention on parent outcomes, a model-based causal mediation model will be fit using separate generalized linear models of parent outcomes at 3 months after randomization that adjust for the intervention indicator variable, stratification factors, and the mediator at 6 weeks after randomization. This model will allow us to decompose the total effect of the resourcefulness intervention on maternal outcomes at 3 months into direct and indirect (or mediated) effects and will allow us to estimate the proportion of the total effect that is mediated. Variance estimates, and consequently 95% confidence intervals, will be estimated using a bootstrapping procedure based on 1000 bootstrap samples. To more fully explore the temporal pattern of mediated effects, we will use similar models to also estimate the mediated effect using measurements of the mediator and maternal outcome taken at other time points as well (e.g., total effect of resourcefulness intervention on parent outcomes at 6 months that are mediated by personal or social resourcefulness at 3 months).

To account for any multiple comparisons, a Bonferroni-corrected two-sided significance level will be applied to all analyses for all aims. Additionally, as with any study, we expect some level of missing data at each time point. To adjust for the missing data in all mixed-models analyses, we will use pattern-mixture models. This modeling approach will be applied to each model to ensure that missing data is adequately accounted for in each analysis. In contrast to a "completers only" approach, pattern-mixture models will provide a consistent and asymptotically efficient estimate of the effect of intervention on the monthly rate of change in parent and family outcomes when data is missing not at random.

Secondary Analyses. To obtain more precise estimates of the intervention effect on the time point interval rate of change in each parent or family outcome, additional multivariable analyses will characterize and estimate the relationship between potential covariates at baseline

and each outcome. For continuous variables that do not have a linear relationship with the outcome, appropriate transformations or categorization will be considered. For nominal and ordinal variables, the number and type of categories will be considered to obtain the optimum relationship, if any, with the outcome. Based on a two-sided significance level of 0.15, any baseline covariate found to be associated with the outcome will be included in the model described for the Primary Analyses.

Modification of the intervention effect on the monthly rate of change in each parent outcome will also be tested in each model by including an interaction between a pre-specified effect modifier measured at baseline, the intervention indicator variables, and the variable representing time since randomization. Should an interaction be detected based on a two-sided significance level of 0.05, the monthly rate of change in each outcome will be estimated in each of the arms for each level of a categorical effect modifier or at the 25th, 50th, and 75th percentiles of a modifier that is measured on an interval scale.

Sensitivity analyses will also be applied to all mediation models described for the Primary Analysis to evaluate the assumption of sequential ignorability (e.g., no unmeasured confounders of the association between the mediator and each maternal outcome). As described by Imai et al,¹¹¹ this analysis will assess how large an effect an unobserved confounder must have on both models to cause a non-significant mediated effect.