Advocating for Supports to Improve Service Transitions (ASSIST)

NCT04173663

Statistical Analysis Plan

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STATISTICAL DESIGN AND POWER

Effects of the Intervention: Aims 1 and 2: Generalized linear models will be used to estimate the effect of treatment group assignment on each of the outcome variables considered. All models will include an indicator variable for treatment group and a treatment by time interaction while controlling for site and sex to improve the precision of the treatment effect estimate. We choose to model site as a fixed effect (2 d.f.) rather than a random effect because there are too few sites to have a stable estimate of a random effects variance.

For **Aim 1**, continuous outcomes (empowerment, advocacy skills, advocacy activities) will be modeled using linear regression and ordinal outcomes (knowledge) will be modeled using proportional odds ordinal logistic regression. The proportional odds model generalizes the non-parametric Wilcoxon rank sum test to a regression setting and is applicable to a wide variety of outcome types. However, we will consider parametric models for count data including Poisson and Negative Binomial regression if appropriate. In these cases, sensitivity analyses will be conducted to evaluate if our conclusions are robust to the choice of regression model.

The general analysis plan for **Aim 2** will be identical to Aim 1, except indicators of youth outcomes will be considered. Continuous outcomes (e.g., social participation) will be modeled using linear regression, binary outcome (e.g., employment/PSE) will be modeled using logistic regression, and ordinal outcomes (e.g., number of services) will be modeled using proportional odds ordinal logistic regression (or another model, as specified in Aim 1). Time since beginning the VAP-T workshop will be the time scale of interest for all subjects, and we will flexibly model changes over time using restricted cubic splines. Significant changes over time will be assessed using likelihood ratios tests. For continuous outcomes, we will fit separate linear mixed effects models that include a random intercept to account for correlation arising from taking repeated measurements on the same subject over time. In sensitivity analyses we will use the Akaike Information Criterion to compare different models of the longitudinal correlation (e.g. random intercept, autoregressive, unstructured). For binary and ordinal longitudinal outcomes, we will use generalized estimating equations (GEE) and the robust Huber-White sandwich estimator clustering on participant identifier to account for longitudinal correlation. Analyses for Exploratory Aims 2a (using data collected from youth with ASD) and 2b (examining maintenance of treatment effects) will follow this same approach.

Aim 3: While evaluating the main effects of interventions is critical to improving outcomes, it is also important to examine mediators of randomized-controlled trials – even those that are unsuccessful – in order to determine how interventions may work[84,85]. Examining mediators will provide evidence for the mechanisms of change, offering direction for program implementation and future research[86]. To assess direct and indirect effects of potential mediator variables, we will follow the steps outlined by MacKinnon and colleagues[79,80] to establish mediation. Regression models will be specified to preserve temporal ordering by considering covariates collected at the prior wave and outcomes collected at the current wave. Model-based causal mediation analysis will be proceeded in two steps: (1) specifying the mediator model for the conditional distribution of the mediator given treatment and pre-treatment covariates and (2) specifying the outcome model for the conditional distribution of the outcome given treatment, the mediator, and covariates. Models will be estimated using the mediation package in R which allows for linear, logistic, ordinal, and generalized linear statistical models for both the mediator and outcome models[81]. Bootstrapping will be used to estimate a non-parametric 95% confidence interval for the indirect effect. The indirect effect will be statistically significant if the confidence interval does not contain 0. We will conduct sensitivity analyses to evaluate the sequential ignorability assumption, which is also available in the mediation package in R. Furthermore, we will consider sensitivity analyses using structural equations models, and multivariable models adjusting for potential confounders will be used to confirm any findings.

Exploratory Aim 4: The starting point for multivariable modeling is an additive effects model. A purely additive model, even one with allowance for flexible nonlinear relationships, will not fit adequately if interactive or synergistic effects exist. Empirical search for interactions is unreliable because there are too many possible interactions (product terms) and frequently interactions found by intensive search techniques are spurious. Instead, interactions will be pre-specified based on subject matter knowledge and all results reported, regardless of statistical significance. Separate models will be fit for each moderator by including an interaction between the potential moderator and the treatment by time interaction. A similar model fitting strategy as outlined for Aim 1 and Aim 2 will be followed.

Though we are interested in examining the potential role of race/ethnicity as a modifier, it may be difficult to disentangle the effects of race/ethnicity from study site (as the geographic area of each site has a different racial/ethnic make-up). We will examine cross tabulation tables of the association between race/ethnicity and

site to determine how strongly they are associated. If possible, we will examine race/ethnicity as a moderator.

We will present any race/ethnicity results cautiously and clearly indicate the associations with site that could confound the observed associations.

As part of Aim 4, we will also use qualitative data analysis to code information gained from the open-ended questions regarding ways to adapt the intervention for youth with ASD. All interviews will be recorded and transcribed verbatim. With Atlas-TI, emergent coding [87] and constant comparative analysis will be used to identify themes in the transcripts[88].

Missing Data. An advantage to our proposed random effects longitudinal models is that they will readily incorporate both missing waves of data and mistimed measurements. In general, we will assume that data are missing-at-random (MAR) for the growth models and missing completely at random (MCAR) for binary and ordinal outcome models estimated using GEE and mediation analysis. Attrition analysis will be used to evaluate these assumptions. Analysis methods will also consider subjects who fail to complete the study ("dropouts"). Indirect information about the dropouts will be obtained by using binary logistic models to predict the probability of dropping out on the basis of all baseline predictor variables. When a variable is a significant predictor of dropout, the distribution of that variable differs for completers and subjects who drop out.

Power/Sample Size: We plan to recruit 180 subjects and after dropout expect to retain 162 subjects through initial post-test (Aim 1) and 152 subjects (76 per treatment group) through the 12-month follow-up (Aims 2 - 4). For power calculations, we consider baseline to post-test changes using the smaller sample size of 152. For continuous outcomes, the size of effect that we will have 80% power to detect will be impacted by the correlation between the pre and post measurement of the outcome. At worst (r=0), we will have 80% power to detect a 0.46 sd difference in continuous outcomes. If the correlation is 0.2 or 0.4, we will be able to detect a 0.29 or 0.17 sd difference, respectively. We believe these estimates are conservative because, from our pilot work, correlations between baseline and post-test scores of intervention targets were 0.56 (empowerment), 0.39 (advocacy skills), and 0.57 (knowledge). For binary outcomes, in pilot data, the probability of being employed or in PSE was about 0.5, so under this assumption we will have 80% power to detect a relative risk of 1.44. Regarding Aim 4, we will have 80% power to detect a 0.42 sd modification of the treatment effect assuming a r=0.2. All calculations assume a two-sided significance level of 0.05.

The power to detect mediation effects were made using the MedPow package in R[82,83]. For the power calculation, we considered moderate associations between (1) VAP-T and the mediator ($r_{X,M}$=0.3), (2) Mediator and outcome, controlling for VAP-T ($r_{M,Y|X}$=0.25), (3) VAP-T and the outcome controlling for the mediator (($r_{X,Y|M}$=0.1) using a fixed sample size of 152 (α=0.05). Under these assumptions, we have 83% power to detect the indirect effect of VAP-T on the outcome through the mediator.

Additional Analyses. In addition to these key analyses, we will conduct descriptive analyses to inform future research and development of the VAP-T. For example, we will carefully examine the attendance data to determine whether there is a number of sessions that seems necessary to benefit from the VAP-T, whether any particular sessions seem to be more important, and if accessing a greater proportion of sessions outside of the group format (i.e., at home, online) limits effectiveness. Analyses will include (but not be limited to) examining frequencies, medians, and means on intervention target scores for those who attended (vs. missed) each session and examining the distribution of outcome variables by the number of sessions in which content was accessed in the group format and by any format (in-person and online combined). We will also perform variable clustering and redundancy analysis by examining the correlation among the potential attendance predictors. We will work closely with our biostatistician to identify appropriate inferential statistics if these initial analyses appear informative to the further development of the VAP-T program.

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