STATISTICAL ANALYSIS PLAN

Title	Improving Dental Care and Oral Health in Children with ASD
Study Chair	Robin Steinberg-Epstein, MD Center for Autism and Neurodevelopmental Disorders University of California Irvine
Co-principal Investigators	Rachel Fenning, PhD University of California Irvine
	Eric Butter, PhD Nationwide Children's Hospital
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1 Approval Signatures

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Robin Steinberg-Epstein, MD
Study Chair
Date

Rachel Fenning 9/25/2020

Rachel Fenning, PhD
Co-principal Investigator
Date

10/16/2020

Eric Butter, PhD
Co-principal Investigator
Date

Eric A. Macklin

Digitally signed by Eric A. Macklin
DN: cn=Eric A. Macklin, o=Massachusetts General Hospital, ou=MGH Biostatistics Center, email=emacklin@mgh.harvard.edu, c=US
Date: 2020.10.16 11:24:27 -04'00'

Eric A. Macklin, PhD
Study Biostatistician
Date

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3 Abbreviations

AIR-P	Autism Intervention Research Network on Physical Health
ASD	Autism Spectrum Disorder
ATN	Autism Treatment Network
CBCL	Child Behavior Checklist
DMFT	Diseased, Missing, Filled Teeth Index
IQ	Intelligence Quotient
ITT	Intention to Treat
NCH	Nationwide Children's Hospital
SAP	Statistical Analysis Plan
UCI	University of California, Irvine
VPI	Visual Plaque Index

4 Overview

4.1 Brief Description of Study

This is a two-arm, randomized controlled trial conducted at two sites in the Autism Treatment Network (ATN) / Autism Intervention Research Network on Physical Health (AIR-P) Consortium: University of California, Irvine (UCI) and Nationwide Children's Hospital (NCH). This study will compare the efficacy of the established AIR-P Dental Toolkit to a combined regimen involving the Dental Toolkit and a parent-mediated behavioral intervention. The two co-primary outcome measures are improved compliance with twice-daily tooth brushing and improved oral health as measured by the Visual Plaque Index (VPI). The study-wide target sample size is 100 participants. Approximately 118 will be randomized, with 71 expected at UCI and 47 expected at NCH, to allow for 15% attrition. Duration of study participation is 6 months.

4.2 Scope of Analysis

This statistical analysis plan (SAP) specifies the planned primary and secondary analyses for the study. This document includes: primary analysis for each study endpoint and pre-defined secondary and exploratory analyses. Refer to the study protocol for all aspects of study design and conduct. In the case of discrepancies between this document and the study protocol, this document has priority on issues related to the analysis of study data.

5 Study Objectives and Statistical Considerations

5.1 Study Objectives

The primary and secondary aims of the study are:

Aim 1: To improve child functional and behavioral compliance with home dental hygiene.

- Hypothesis 1a (co-primary): Relative to children randomized to the control condition, children randomized to the intervention condition will exhibit greater 6-month improvement in functional compliance with home dental hygiene as measured by twice-daily tooth brushing.
- Hypothesis 1b (secondary): Relative to children randomized to the control condition, children randomized to the intervention condition will exhibit greater 6-month improvement in behavioral compliance with home dental hygiene as measured by parent-report on the Home Dental Experiences questionnaire.

Aim 2: To Improve oral health.

- Hypothesis 2 (co-primary): Relative to children randomized to the control condition, children randomized to the intervention condition will exhibit greater 6-month improvement in oral health as measured by the Visual Plaque Index (VPI) and secondary measures of DMFT/dmft score (caries risk) and the Löe & Silness index score (gingival health).

Aim 3: To reduce anxiety and improve compliance with dental visits.

- Hypothesis 3a-c (secondary): Relative to children randomized to the control condition, children randomized to the intervention condition will exhibit greater 6-month improvement in: (a) dental anxiety during dental visits as measured by the Venham Anxiety Scale, (b) behavioral compliance during dental visits as measured by the Venham Behavior Scale, and (c) completion

of dental visit procedures as measured by dentist report on the Dental Visit: Dentist Report questionnaire.

5.2 Analysis Samples

Intention-to-treat (ITT) sample – all randomized subjects classified according to their randomized treatment assignment without regard to compliance with their assigned treatment.

The ITT sample will be used for analysis of all analyses.

5.3 Outcome Measures

- (Aim 1. Hypothesis 1a) Frequency of successful (twice-daily) tooth brushing completed at home during the past week.
- (Aim 1. Hypothesis 1b) Parent report of occurrence and severity of behavior problems during home dental hygiene during the past week. We will use the mean of the 8 behavior issues rated 0-9.
- (Aim 2. Hypothesis 2) Dentist reported child oral health according to the VPI (primary) and secondary measures of DMFT/dmft score (caries risk) and the Löe & Silness index score (gingival health).
- (Aim 3. Hypothesis 3a) Child anxiety rated from the videotaped dental visit by blinded observers using the Venham Anxiety Scale.
- (Aim 3. Hypothesis 3b) Child behavioral compliance rated from the videotaped dental visit by blinded observers using the Venham Behavior Scale (primary). Dentist reported child challenging behavior will be examined as a secondary endpoint.
- (Aim 3. Hypothesis 3c) Dentist report of completed exam procedures (primary). Dentist rated adequacy of the dental visit (secondary). We will use the mean of the 16 procedures rated 0-9 for problem severity.

5.4 Baseline Characterization

Children and parent will be described overall and by treatment group for the following characteristics: age, race, ethnicity, IQ (child only), Vineland (child only), intellectual disability (child only), ASD symptom severity (child only), CBCL total behavior problems t-score (child only), age at first dental visit (child only), education (parent only), living situation (parent only), and income (parent only).

5.5 Safety Outcomes

5.6 Disposition

The number of participants consented, failed screening, determined eligible, randomized, initiated treatment, completed scheduled follow-up, and prematurely terminated study participation will be summarized overall and by treatment group. Reasons for screen failure and for withdrawal from study will be presented.

6 Statistical Considerations

6.1 Statistical Analysis

Standard summary statistics for all study measures will be prepared. All analyses will us the intent-to-treat sample. With two co-primary outcomes, each will be consider statistically significant for two-tailed

$p < 0.025$ to ensure an overall type I error rate of 5%. Nominal p-values without adjustment for multiple comparisons will be reported for secondary outcomes.

6.1.1 Longitudinal Change Models

A generalized random effects model will be used to assess change over time in outcomes for aims 1 to 3. Frequency of successful brushing (hypothesis 1a) will utilize a binomial distribution with a logit link for the model, while all other outcomes will use a gaussian distribution and an identity link. Each model will have a shared group mean at baseline and separate treatment-group specific means at each of the 3- and 6-month follow up times. Each model will include a random intercept by site to account for covariance among participants at the same site and a random intercept by participant to account for covariance among repeated measures of the same participant. Fixed baseline covariates will include child age and child age x visit interaction. Secondary analyses may include additional covariates. The primary significance test will compare the treatment groups for change from baseline to 6 months. Supporting analyses of this endpoint will look at group differences at 3 months and the overall time trend.

Results will be presented as means and confidence intervals at each visit and treatment group and odds ratios with 95% confidence intervals comparing treatment groups. Model results will also be used to create graphical group comparisons of change over time for each outcome.

6.2 Missing Data

Random effects models provide unbiased estimates in the presence of missing data when the expected value of missing data are predictable from the observed data as modeled (i.e. data are conditionally missing at random).

6.3 Power Calculations

Assuming a balanced 15% attrition rate, at least 30% correlation between baseline and follow-up estimates, and two-tailed testing at alpha = 0.025 to accommodate two co-primary outcomes (tooth-brushing and VPI), a sample size of 100 allows us to detect an effect size of 0.6 with 80% power

6.4 Statistical Software

All analyses will be done in the latest version of SAS and R available at the Massachusetts General Hospital Biostatistics Center. The version currently available at time of SAP preparation is version 9.4 for SAS and version 4.0 for R.

6.5 Reporting and Scoring Conventions

Percents will be reported in whole numbers (no decimal places), rounded as needed. The percents for valid responses will be based on non-missing responses (e.g., if the variable has responses for Yes and No, the total of the two percents will be 100 even if some data are missing). For continuous variables, results will generally be reported to a precision that provides three significant figures at the mean.