SENSORY ADAPTED DENTAL ENVIRONMENTS TO ENHANCE ORAL CARE FOR CHILDREN

(SADE-2 STUDY)

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STATEMENT OF COMPLIANCE

The study will be conducted in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice (ICH E6), the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), and the NIDCR Clinical Terms of Award. All personnel involved in the conduct of this study have completed human subjects' protection training.

SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Principal Investigator or Clinical Site Investigator:

Signed: _____ Date: _____

Name: Sharon A. Cermak, EdD, OTR/L, FAOTA

Title: Principal Investigator

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LIST OF ABBREVIATIONS

ADL	Activities of Daily Living
ADOS-2	Autism Diagnostic Observation Scale, 2nd ed.
AE	Adverse Event/Adverse Experience
ASD	Autism Spectrum Disorder
CASI-Anx	Child and Adolescent Symptom Inventory-4, Anxiety Scale
CDBRS	Children's Dental Behavior Rating Scale
CHLA	Children's Hospital of Los Angeles
CMP	Clinical Monitoring Plan
Co-I	Co-Investigator
CRIC	California Cancer Research Informatics Core
CRF	Case Report Form
CROMS	Clinical Research Operations and Management Support
CSOC	Clinical Study Oversight Committee
CFSS-DS	Childhood Fear Survey Schedule, Dental Subscale
DHHS	Department of Health and Human Services
DSSS	Dental Sensory Sensitivity Scale
eCRF	Electronic Case Report Form
EDA	Electrodermal activity
FPS-R	Faces Pain Scale - Revised
GCP	Good Clinical Practice
GI	Gingival Index
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
LAUSD	Los Angeles Unified School District
MCDASf	Modified Child Dental Anxiety Scale, faces version
MOP	Manual of Procedures
N	Number (typically refers to subjects)
NIDCR	National Institute of Dental and Craniofacial Research
NIH	National Institutes of Health

NS-SCR	Non-Specific Skin Conductance Response (reported as frequency per minute)
OCTOM	Office of Clinical Trials Operations and Management
OHI-S	Oral Hygiene Index - Simplified
OHRP	Office for Human Research Protections
OS-OT	Occupational Science and Occupational Therapy
PI	Principal Investigator
RDE	Regular Dental Environment
SADE	Sensory Adapted Dental Environment
SAE	Serious Adverse Event/Serious Adverse Experience
SCL	Skin Conductance Level
SOP	Standard Operating Procedure
SSP	Short Sensory Profile-2
UCEDD	USC University Center for Excellence in Developmental Disabilities
UP	Unanticipated Problem
US	United States
USC	University of Southern California
VABS-II	Vineland Adaptive Behavior Scales, 2nd Edition; Expressive Communication Domain
WASI-II	Wechsler Abbreviated Scale of Intelligence- second edition

PROTOCOL SUMMARY

Title: Sensory Adapted Dental Environments to Enhance Oral Care for Children (SADE-2 Study)

Précis:

This study is a randomized clinical trial investigating the efficacy of a **sensory adapted dental environment (SADE)** compared to a regular dental environment (RDE) to decrease physiological anxiety, distress behavior, perception of pain, and discomfort during a dental cleaning in children. The SADE procedure **modifies the degree and type of visual, auditory, and tactile stimulation** that children experience during dental cleanings. In this crossover design, the SADE will be compared to a RDE in a group of **children with Autism Spectrum Disorder (ASD)** with visits occurring four-six months apart**.** The outcome variables are **physiological anxiety** as measured by electrodermal activity (EDA) and **child negative responses** (distress behavior, perception of pain, sensory discomfort) exhibited by the child during dental cleaning visits. Analyses will include repeated measures ANCOVA models to examine the differences in the within-group factor (environment) in the ASD groups.

Objectives

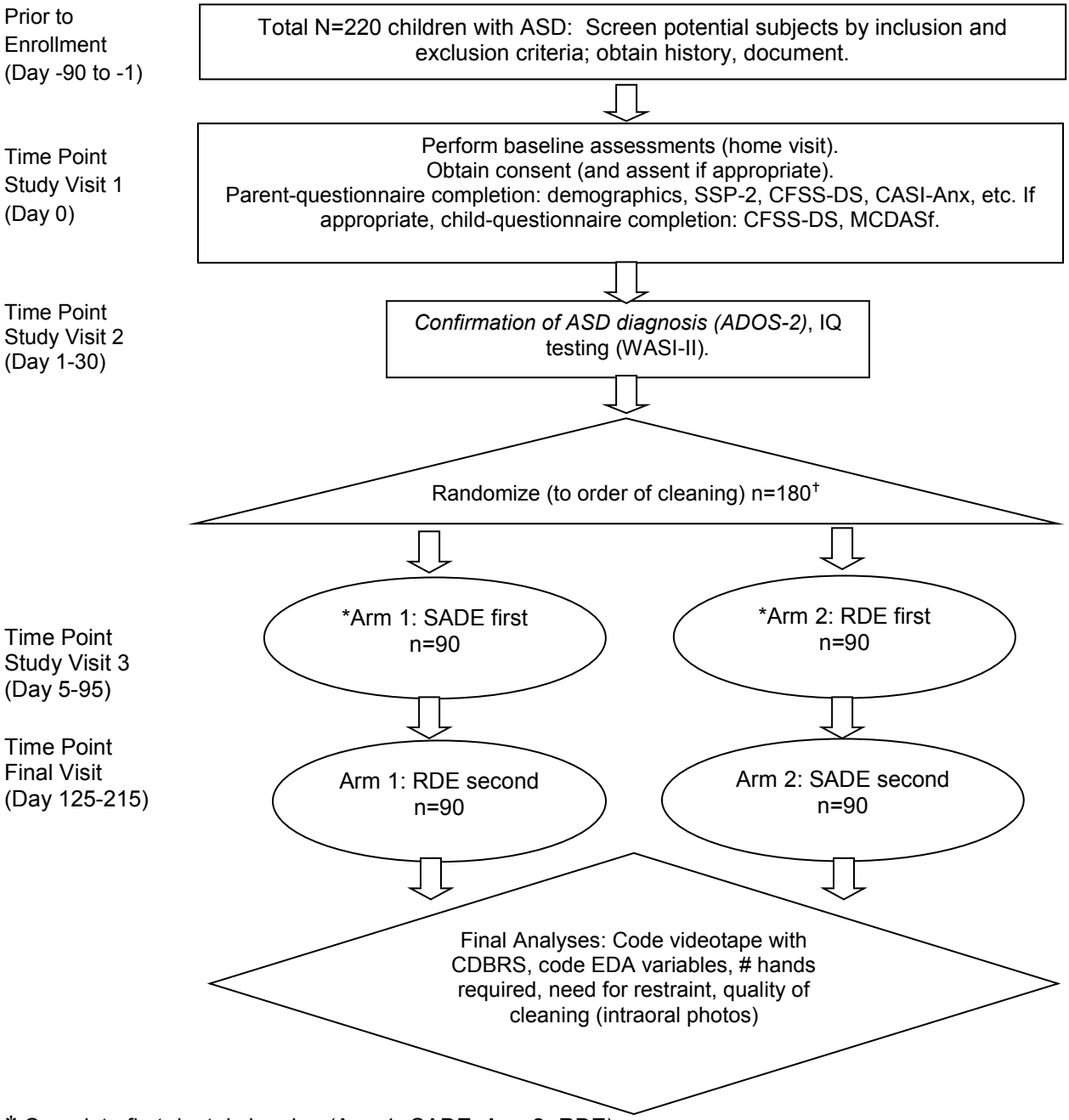
1. Primary Objective: To compare children's physiological anxiety (EDA - primary outcome) during the dental cleaning.

2. Secondary Objectives:
   (a) To compare children's negative behavioral responses (behavioral distress, perception of pain, sensory discomfort - secondary outcomes) during dental cleanings.
   (b) To test the degree to which physiological anxiety mediates the SADE intervention's effects on children's negative behavioral responses.
   (c) To test the degree to which specific child characteristics moderate the SADE intervention's effects on children's physiological and negative behavioral responses during dental cleaning.
   (d) To compare the SADE intervention to the RDE on quality of care, cost-effectiveness, and potential cost savings of dental cleaning.

Population: Participants will be 220 ethnically diverse children with ASD aged 6-12 years. All children will be Southern California residents. Participants will be recruited primarily from Children's Hospital Los Angeles (Dental Clinic, University Center for Excellence in Developmental Disabilities, Boone Fetter Clinic, AltaMed General

	Pediatrics Service) and the Los Angeles Unified School District (LAUSD), so the sample in this study will likely over-represent low income Hispanic/Latino families who are at high risk for poor oral health. Consistent with ASD prevalence statistics, we anticipate a ratio of approximately four boys for every girl in the sample.
Phase:	Clinical Phase II
Number of Sites:	One site: Children's Hospital of Los Angeles, Dental Clinic
Description of Intervention:	The SADE intervention consists of physical adaptations to the dental cleaning space meant to create a less anxiety-provoking sensory experience. Visual, auditory, and tactile stimuli will be altered in the SADE. (For more details, see Table 3, Section 6.1.)
Study Duration:	Approximately 60 months
Subject Participation Duration:	Approximately nine-fifteen months per subject
Estimated Time to Complete Enrollment:	40-44 months

SCHEMATIC OF STUDY DESIGN



* Complete first dental cleaning (Arm 1- SADE; Arm 2- RDE)
(Videotape and record EDA throughout dental cleaning, pre- and post-cleaning intraoral photos, OHI-S, GI, Plaque Index, Anxiety and Cooperation Scale, Frankl Scale, DSSS, FPS-R)
† Projection

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2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

This randomized clinical trial, entitled Sensory Adapted Dental Environments to Enhance Oral Care for Children (SADE-2 Study), is a follow up of our R34 pilot study, Sensory Adapted Dental Environments to Enhance Oral Care for Children with Autism (1R34DE022263-01). We propose to examine the efficacy of a sensory adapted dental environment to decrease physiological anxiety and negative responses (distress behavior, perception of pain, sensory discomfort) in children with autism spectrum disorders (ASD), many of whom have dental anxiety and/or sensory over-responsivity. Many of our subjects will have unmet dental needs, either from the conditions mentioned above or because our recruiting sources over-represent low income, Latino families who are reported to have greater challenges in accessing care.

Children with disabilities are almost twice as likely to suffer from unmet oral health care needs than their peers without disabilities,[1] and consequently have an increased risk and prevalence of dental disease.[2,3] Children with ASD, a condition characterized by impaired social-communication and social interaction, and restricted, repetitive patterns of behavior, interests or activities,[4] represent one such special population at high risk.[5,6] In fact, a large number of studies indicate that children with ASD exhibit a high incidence of poor oral health, as measured by caries prevalence and severity,[2,5-9] although there are a small number of contradictory studies.[10-12] The prevalence of ASD is significantly higher today than in the past, estimated in 2014 to be approximately 1 in 68 children in the US.[13] Therefore, dentists are increasingly likely to encounter children with ASD in their practices.

One factor that may contribute to oral care challenges in children with ASD is sensory over-responsivity[14] characterized by behavioral responses that are out of proportion to the type or amount of stimulation. These responses may include physical withdrawal, vocal outbursts, aggressive behaviors, tantrums, or attempts to block incoming stimulation.[15,16] Although the mechanisms underlying sensory processing disorders are not fully understood,[17-20] such problems are highly prevalent in the ASD population.[21-25] Up to 95% of children with ASD demonstrate significantly different sensory behaviors than their TD counterparts, and 61% specifically exhibit tactile over-responsivity symptoms as evidenced by difficulty tolerating grooming and hygiene tasks.[26]

Exacerbation of sensory over-responsivity in the dental office can result from exposure to bright lights, loud or high-pitched noises, reclining in the dental chair, repeated touch in and around the mouth, and the texture, taste, and smell of various oral care products. In a survey of 196 parents of children with ASD, up to 70% of parents reported that their child experienced difficulty with each of these sensory variables in the dental office, with the greatest difficulty being instruments in the mouth (70%).[27] In this study, almost 50% of parents of children with ASD strongly agreed that their child's sensory over-responsivity made visits to the dentist more challenging. Additionally, children with ASD with sensory over-responsivity, compared to children with ASD without sensory over-responsivity, exhibited a significantly greater prevalence of oral care difficulties in the home and dental office.[28] In focus groups that we conducted, parents reported reluctance to return to the dentist because of their child's negative experiences. For example, one parent stated that "The first time we took him to the dentist, when I heard him screaming for me from the front, I kind of understood how bad this was…there was like several people trying to restrain him. They had him in restraints and my wife [in the room with him] was in tears…because of that experience we were extremely hesitant to take him back."

The proposed SADE-2 intervention modifies the sensory characteristics of the dental environment. It does so by altering the degree and type of visual, auditory, and tactile stimulation that children experience during dental treatment by reducing the lighting, providing soothing sounds, and applying deep pressure input to the child during a dental cleaning. Our hypothesis is that these changes will reduce physiological anxiety, negative behavior, pain, and sensory discomfort, and enhance cooperation to enable thorough and effective oral care.

The proposed study attempts to replicate and extend Shapiro et al.'s previous work[49-51] with children with developmental disabilities (not including ASD) in Israel, in which a sensory adapted dental environment resulted in shorter duration of negative behaviors and greater relaxation during treatment as measured by electrodermal activity (EDA), which assesses the sympathetic "fight or flight" system. Results from our R34 pilot study examined differences in children's physiological responses in the two intervention conditions (sensory adapted environment, SADE, and a regular dental environment, RDE), finding that measures of electrodermal activity were lower (i.e. children were more relaxed) in the SADE. When examining the behavioral and survey measures, outcomes were in the hypothesized direction with primarily small effects (less uncooperative distress behavior, reduced perception of pain, and less sensory discomfort in the SADE vs. RDE). However, our R34 study was designed as a pilot study and therefore not powered to detect differences between the two dental environments. The preliminary positive benefit of the sensory adapted dental environment found in children with ASD warrants a large-scale trial to appropriately power the study and enable examination of moderating and mediating variables.

In the proposed U01, we will test the effects of the SADE in a larger group of children with ASD to examine intervention efficacy and possible mediating and moderating factors. Our sample will be ethnically diverse, with more than 50% of the sample underserved, low income Latino children.

The development of a modified dental environment may help pediatric dentists, general dentists, and dental hygienists reduce common behavioral challenges that occur in treating children receiving treatment at the dental office. Because general dentists indicate that behavior problems are the greatest barrier treating children with disabilities,[52] decreasing children's distress behaviors may increase dentists' willingness to treat children with ASD and other children who are difficult to treat, thereby contributing to a reduction in health disparities. Treatment may also become more efficient and cost effective. If the child is more cooperative, the dentist may be able to complete a more thorough cleaning and better preventive care. Safety would also increase as the need for restraint (e.g., protective stabilization provided by a papoose board) and/or pharmacological intervention (e.g., nitrous oxide, general anesthesia) decreases. Research currently indicates that restraint is utilized with children with ASD 18-33% of the time, significantly more than with TD children (1%).[27,53] In a survey study conducted by our team, 18% of children with ASD without sensory over-responsivity required restraint often or almost always for dental care, compared to 38% of children with ASD with reported sensory over-responsivity.[54] Finally, as ease of cleanings improves, parents may be more likely to bring their child to the dentist for routine oral care, which would impact public health.

2.1 Rationale

We will be testing a protocol (SADE) that has the potential to change dental clinical practice paradigms by altering the degree and type of visual, auditory, and tactile stimulation that children experience during dental treatment. Our enhanced environment will reduce the

lighting, provide soothing sounds, and apply deep pressure input to the child during a dental cleaning. Although the literature clearly documents that sensory over-responsivity is often present in children with ASD and our R34 pilot study demonstrated feasibility of clinic-based solutions, a randomized clinical trial is now needed to examine our preliminary findings with a sufficiently powered study. The SADE draws on (a) the techniques of the Snoezelen, or multisensory environmental approach,[55-59] and (b) principles of sensory integration theory and research.[60-61] In both of these approaches, the arrangement and intensity of sensory stimulation are modified.[59,62] We hypothesize that **in the SADE environment, children with ASD will have reduced physiological anxiety and negative responses (distress behavior, perception of pain, sensory discomfort), allowing for a more efficacious dental cleaning visit.**

Because the prevalence of ASD has risen dramatically in recent years,[13] it is imperative to identify innovative solutions that enable dentists to more readily perform standard clinic-based procedures for these children. In the proposed study, we will respond to this need by attempting to create an environment that prevents or reduces anxiety and negative behaviors during oral care in a real life context. Green and Flanagan[63] discuss the challenges that stem from maladaptive behaviors and emphasize that successful patient management involves creating an atmosphere that prevents these behaviors.

2.2 Potential Risks and Benefits

2.2.1 Potential Risks

This study will take the utmost precaution to ensure the welfare of the subjects. This study is a conceptual replication and extension of Shapiro et al.'s previous work with children with developmental disabilities (other than ASD) in Israel in which no immediate or long-range adverse events were reported as a result of the study intervention.[49-51] This was verified through personal conversation with Dr. Shapiro who was a consultant on the R34 grant. Additionally, in our R34 SADE pilot study (n=44 children; n=22 ASD, n=22 typically developing), there were no unanticipated problems or adverse events.

For the current study, risks from dental cleaning using SADE are similar to traditional dental visits (e.g., gingival bleeding, mild discomfort). Additional risks related to the study include the possibility of: (1) **Feeling uncomfortable answering some research-related survey questions or being videotaped**. Neither of these potential risks were a problem in the R34 SADE pilot study; however, if subjects or their parents feel uncomfortable answering some questions they may choose to not answer that question. If subjects or their parents feel uncomfortable being video-recorded, they can ask the researchers to stop the recording. (2) **Potential loss of confidentiality**. Likewise, this was not a problem in the R34 SADE pilot study. This issue will be addressed by strictly identifying video-recordings and accompanying surveys by an identification number. All videotapes and surveys will be stored at the University of Southern California in a secure file with the understanding that only those persons involved in the study will have access to this data. (3) **Skin Irritation.** We will be using the BIOPAC MP150 System from BIOPAC Systems, Inc. (Goleta, California) to collect physiological data (electrodermal activity) from human subjects. We will be using BIOPAC EL507 electrodes (silver-silver chloride electrodes with isotonic gel) placed on the tips of the second and third digits of the participant's non-dominant hand and secured with non-stick medical tape. Sensors will be attached using standard laboratory procedures; however, some participants may experience skin irritation from the conductance gel used in the sensors. This clears up quickly

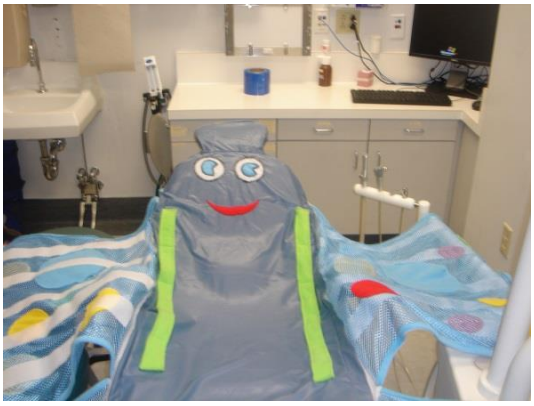
after the sensors and the gel are removed. We previously utilized this system in our R34 pilot study with no reports of injury, skin irritation, or other adverse reactions to the electrodes, gel, or tape. Additionally, BIOPAC Systems, Inc. has tested the MP150 System to applicable medical device standards, even though, strictly considered, the MP150 is not a medical device. The applicable standards for medical safety requirements are determined by IEC 60601-1 and the applicable standards for electromagnetic compatibility requirements are determined by IEC 60601-1-2 (Self-Declaration of Conformity, BIOPAC Systems, Inc., 2011; *http://www.biopac.com/Corporate.asp?Index=1*). (4) **EDA fear.** Children may also feel uncomfortable having electrodes applied to their fingers. We will minimize children's discomfort by showing the electrodes to the participants as part of a home visit prior to the dental cleaning and by providing the children with a social story that shows electrode application. (5) **Butterfly Vest.** There is a possibility that the butterfly vest could inadvertently induce anxiety in our child participants. We will address this concern as follows:

a) The purpose of the butterfly vest is to provide deep touch pressure, which has been found by many individuals to be calming and/or relaxing, as described by Temple Grandin, an adult with high functioning autism.[78] It should also be noted that the butterfly vest was not designed to achieve protective stabilization, although we recognize that it does so. As such, we will take every precaution taken with protective stabilization procedures as described in the *Clinical Guidelines for Protective Stabilization for Pediatric Dental* Patients.[79] and adhere to the *Guidelines on Behavior Guidance for the Pediatric Dental* Patient.[80]

b) The butterfly vest has been pilot tested fairly extensively in the dental clinic.[49,50,81] These studies include: (i) our own work with 22 children with ASD and 22 typically developing children,[81] and (ii) a study by Shapiro et al.[50] involving 16 children with developmental disability (not ASD) and 16 typically developing children. Among these 76 participants who utilized a butterfly vest, only two children were initially apprehensive about using the vest. The typically developing child was given the option of not wearing it, but nonetheless chose to do so. The child with ASD had recently had a negative experience with a papoose board (based on parent report), but later requested the "butterfly hug" during the dental cleaning, at which point we closed the wings. Both these reactions suggest that the risk of the butterfly vest inducing anxiety or causing traumatization of the participant is low. Additionally, in our pilot study, many parents commented informally that they really liked the vest and that their child liked the vest, and wondered out loud why other dentists didn't use something similar.

c) Weighted vests, which also utilize the principle of deep touch pressure (as does the butterfly vest), have been used extensively by occupational therapists to treat children with sensory processing disorders,[82] with a review indicating that side effects and risks are minimal.[83]

d) The parent is in the dental operatory with the child. Either the parent or the child may request discontinuation of any or all components of the intervention at any time during the dental cleaning. Additionally, in no instance will children be required to continue with the intervention (including use of the butterfly vest) if any serious reaction is noted.



Despite the fact that the available evidence supports the safety of the butterfly vest, we will enact the following precautionary strategies:

a) We will hire a special project consultant with expertise in the area of anxiety reactions in children to evaluate safety issues pertaining to the use of the vest (as well as safety issues pertaining to other intervention components).

b) As in the pilot study, any child or parent will have the option of refusing any element of the intervention. All refusals will be documented.

Figure 1. The butterfly vest with wings that wrap around (hug) the child.

c) We will enact a sequential procedure, for each research participant undergoing the SADE that consists of: (1) prior to the treatment, explaining each component of the intervention (both through a social story and verbally) and getting the child's assent (when able); (2) requiring the research team to monitor any negative reactions to the SADE adaptations; and (3) having the dental assistant or dentist remove or minimize offending stimuli that emerge during the above steps (or terminate cleaning if necessary).

d) The study will have a data safety monitoring committee (CSOC) which will review all adverse events in an effort to ensure the welfare of all research participants.

e) During the time of the COVID-19 pandemic, participants are at a small risk of contracting the virus when they leave their home and come to CHLA. CHLA has launched extensive protective measures to prevent the spread of the novel coronavirus and keep patients, families and team members safe.

2.2.2 Potential Benefits

Direct benefits for the child participant are two dental cleanings (oral exam, prophylaxis, and fluoride application) provided with no out-of-pocket costs. Additionally, scheduling both dental visits will occur with a minimal wait time (currently the dental clinic has a wait of approximately 8 or more months for scheduling a routine cleaning for a returning or new patient). Moreover, dental treatment in the SADE condition may prove more calming to children than in the regular dental environment.

The potential indirect long-term benefits of this study include contributing to knowledge of factors that reduce physiological anxiety and negative responses during dental cleanings, and help children who are anxious or fearful at the dentist. Findings from this study may contribute to safer, more efficient, and less costly treatment for both children with ASD as well as TD children with dental anxiety and/or sensory over-responsivity.

3 OBJECTIVES

3.1 Study Objectives

Primary Objective: To compare children's physiological anxiety (EDA - primary outcome) during the dental cleaning in the SADE vs. RDE.

Secondary Objectives:

a) To compare children's negative behavioral responses (behavioral distress, perception of pain, sensory discomfort - secondary outcomes) during dental cleanings in the SADE vs. RDE.

b) To test the degree to which physiological anxiety mediates the SADE intervention's effects on children's negative behavioral responses.

c) To test the degree to which specific child characteristics moderate the SADE intervention's effects on children's physiological and negative behavioral responses during dental cleaning.

d) To compare the SADE intervention to the RDE on quality of care, cost-effectiveness, and potential cost savings of dental cleaning.

3.2 Study Outcome Measures

3.2.1 Outcome Measures for the Primary Objective

Our primary outcome measure is children's physiological response measured by EDA during the dental cleaning. EDA will be measured using the BIOPAC Systems, Inc. MP150 System. This physiological response is caused by sympathetic nervous system activation, which increases during stressful or painful situations.[64] Sensors will be placed on the child's fingers and EDA recordings will be made immediately prior to and continuously throughout each cleaning. Two measures of tonic EDA will be collected: skin conductance level (SCL) and frequency of non-specific skin conductance responses (NS-SCR). See Table 1.

Table 1. Primary outcome measure of children's physiological responses for the SADE-2 Study.

Outcome measure (Completed by)	Measure & Description	Type of Measure (No. of Items)	When Administered	Specific Objective Tested	CRF Name (#)
Physiological Anxiety (Researcher-coded)	*Electrodermal Activity* (skin conductance level and frequency of non-specific responses) assesses level of sympathetic nervous system activation.	Psycho-physiological (N/A: scoring is continuous throughout recording)	Recorded at baseline and throughout both dental cleanings.	1	Scored EDA Form (23)

3.2.2 Outcome Measures for the Secondary Objectives

Our secondary outcome measures will consist of five behavioral indicators of distress (observational coding of behavioral distress from video-recordings, dentist-reported measures of child anxiety and cooperation, child self-report of pain, and child self-report of discomfort with sensory stimuli), measures of mediating factors, measures of moderating factors, and measures of cost-savings and quality of care.

Secondary Objective (a): Negative Behavioral Responses

Distress Behavior will be measured by video-coding of child's behavior during the cleaning and coded by the researcher using the Children's Dental Behavior Rating Scale, and dentist-report (Frankl Scale and Anxiety and Cooperation Scale). The Children's Dental Behavior Rating Scale (CDBRS) was developed and pilot-tested prior to the initiation of our previous R34 pilot study, and was found to have inter-rater reliability on children both with and without ASD, K=.97, p<.001.[81] The Frankl Scale[67] is one of the most commonly used rating scales to assess children's behavior in the dental office[84] and is universally utilized by both researchers and clinicians.[85] The scale has high inter-rater reliability and acceptable validity,[84] and has been shown to significantly correlate with other behavioral indices that are used to assess anxiety and behavior during dental treatment.[86] The Anxiety and Cooperation Scale[87] assesses children's anxiety, fear, and cooperation as rated by dentists and has established reliability and validity.[88]

Perception of Pain will be measured by child self-report utilizing the Faces Pain Scale-Revised (FPS-R),[68] which has established validity and is supported by a high positive correlation with a visual analogue scale in children aged 5 to 12 years.[68]

Discomfort with sensory stimuli will be measured by child self-report utilizing the Dental Sensory Sensitivity Scale. This tool was developed and pilot-tested alongside the CDBRS, and in our pilot study was sensitive to differences between the SADE and RDE in the ASD group (effect size = .69, p<.05).[81]

Secondary Objective (b): Mediating Factors

Outcome measures include physiological anxiety (EDA) as a mediator of negative behavior (for EDA details see above Section 3.2.1).

Secondary Objective (c): Moderating Factors

To test the effect of child characteristics as moderators of SADE, outcome measures will include age, autism severity, cognitive ability, sensory sensitivity, and anxiety.

Secondary Objective (d): Cost-Savings and Quality of Care

Outcome measures include relative cost of services provided (time to complete cleaning, number of staff required, anesthesia required), ascertained by videotaped encounters. Efficacy of dental cleaning will be assessed via coded observations of plaque index before and after dental cleanings, coded from images captured via intraoral camera.

Table 2. Secondary outcome measures of the SADE-2 Study.

Outcome measure (Completed by)	**Measure & Description**	**Type of Measure (No. of Items)**	**When Administered**	**Specific Objective Tested**	**CRF Name (#)**
Distress Behavior (Researcher-coded from video-recording)	*Children's Dental Behavior Rating Scale*, a psychometrically sound tool developed for our R34 pilot study that assesses overt distress behavior.	Observational: Coding of video-recordings (5 items, each scored the first 5 minutes of prophylaxis)	Video-recordings occur during both dental cleanings; coding occurs at a later time.	2a	Children's Dental Behavior Rating Scale (22)
Distress Behavior (Anxiety and Cooperation) (Dentist-report)	*Anxiety and Cooperation Scale,*[65] a reliable and valid tool for use during dental cleaning to assess anxiety and cooperation.[66]	Questionnaire (1)	Immediately following both dental cleanings.	2a	Behavioral Indices Form (14)
Distress Behavior (Uncooperative Behavior) (Dentist-report)	*Frankl Scale*,[67] a reliable and valid tool for use during dental cleaning to assess behavior.	Questionnaire (1)	Immediately following both dental cleanings.	2a	Behavioral Indices Form (14)
Perception of Pain (Child-Report)	*Faces Pain Scale-Revised*,[68] a valid tool comprised of six faces to assess perception and intensity of pain.	Questionnaire (1)	Immediately following both dental cleanings.	2a	Faces Pain Scale-Revised (17)

Discomfort with Sensory Stimuli (Child-Report)	*Dental Sensory Sensitivity Scale* describes the presence and magnitude of discomfort with different sensory stimuli in the dental environment.	Questionnaire (6)	Immediately following both dental cleanings.	2a	Dental Sensory Sensitivity Scale (18)
Cost-Savings (Researcher-scored)	*Duration of dental cleaning*, calculated from video-recordings and notes.	Observational (1)	Immediately following both dental cleanings.	2d	Cost-Effectiveness & Cost-Savings Form (21)
Cost-Savings (Researcher-scored)	*Number of hands required for restraint*, calculated from video-recordings and notes.	Observational (1)	Immediately following both dental cleanings.	2d	Cost-Effectiveness & Cost-Savings Form (21)
Cost-Savings (Researcher-scored, in consultation with dentist)	*Need for protective stabilization, sedation, and/or anesthesia* to complete cleaning.	Observational (1)	Immediately following both dental cleanings.	2d	Cost-Effectiveness & Cost-Savings Form (21)
Quality of Care (Dentist-scored)	*Analysis of oral health and plaque* before cleaning versus after cleaning using intra-oral photographs [90] (Rechmann et al., 2014) utilizing the *Oral Health Index-Simplified*[68] and *Plaque Index*.[70]	Observational, completion of OHI-S (12) and PIaque Index (6) based on intra-oral photographs.	Intra-oral photographs taken before and after dental cleaning; scoring to be completed at a later time.	2d	Quality of Care Recording Form (16)

Table 3. Child-descriptor variables

Child-descriptor (Completed by)	**Child-descriptor & Description**	**Type of form (No. of Items)**	**When Administered**	**Specific Objective Tested**	**CRF Name (#)**
ASD Diagnosis (Psychologist)	The Autism Diagnostic Observation Schedule-2 (ADOS-2) is used to confirm a diagnosis of ASD and provides a measure of autism severity.	Observational (varies)	Visit 2	2c	Autism Diagnostic Observation Schedule-2
IQ (Psychologist)	Wechsler Abbreviated Scale of Intelligence – Second Edition provides a measure of IQ	Observational (varies)	Visit 2	2c	Wechsler Abbreviated Scale of Intelligence – Second Edition
Short Sensory Profile-2 (Parent)	Sensory Sensitivity	Parent questionnaire (34)	Visit 1	2c	Sensory: Short Sensory Profile-2 (7)
Dental Anxiety (parent)	Children's Fear Survey Schedule- Dental Subscale measures dental anxiety.	Parent questionnaire (15)	Visit 1	2c	Children's Fear Survey Schedule-Dental Subscale (8)
General Anxiety (parent)	Child and Adolescent Symptom Inventory-4, Anxiety Scale	Parent questionnaire (21)	Visit 1	2c	Child and Adolescent Symptom Inventory-4, Anxiety Scale (6)
Expressive Communication Ability	Vineland Adaptive Behavior Scales-II, Expressive Communication Domain	Parent questionnaire (varies)	Visit 1	2c	Vineland Adaptive Behavior Scales-II, Expressive Communication Domain
Age of child (parent)	Age	Parent questionnaire (1)	Visit 1	2c	Family information (5)

4 STUDY DESIGN

This is a Phase II clinical trial utilizes a randomized cross-over design with two conditions at a single-site to test the efficacy of the SADE intervention protocol in reducing children's physiological anxiety and negative responses.

The Phase II experimental design is overviewed in the Schematic of Study Design section of the Clinical Trial Protocol Summary (pg. 11).

5 STUDY ENROLLMENT AND WITHDRAWAL

The study target sample size is 220 English- and Spanish-speaking children with ASD. We anticipate a 4:1 ratio of boys to girls in the ASD group based on current statistics[13] (CDC, 2014) and consistent with recruitment in our R34 study. Based on our results from our R34 SADE study, we anticipate that the ethnic and racial backgrounds of our sample will mirror the general population of CHLA patients. Specifically, we expect more than half of individuals to be of Hispanic/Latino origin with a preponderance of Caucasian children.

Based on our R34-funded pilot study, we plan to recruit children with ASD from CHLA Dental Clinic. Each week, study staff will review the electronic health records of the list of patients scheduled for a dental cleaning in the CHLA Dental Clinic. For those appearing to meet inclusion criteria for the study, study staff will contact the parents or guardians and invite participation in the study.

Based on our pilot study, we found that it may be difficult to recruit a sufficient number of children with a range of ASD severity. Therefore, for this study we plan to recruit children from multiple sites including CHLA (Dental Clinic, USC UCEDD, Boone Fetter Clinic, AltaMed), and the Los Angeles Unified School District. See Section 5.3 for greater detail about these sites.

5.1 Subject Inclusion Criteria

In order to be eligible for the proposed study, all individuals must meet all of the following criteria:

- Provide signed and dated informed consent (parent permission) and child assent (if appropriate) forms.
- Willing to comply with all study procedures and be available for the duration of the study.
- Male or female, aged 6 through 12 years.
- Have an accompanying parent or guardian who speaks English or Spanish.
- Live within local commuting distance of CHLA.
- Have experienced at least one prior dental cleaning.
- Diagnosed with Autism Spectrum Disorder, based on the Autism Diagnostic Observation Scale, 2nd ed (ADOS-2)[71] as administered by a psychologist from our research team.
- Need an oral cleaning (defined as no oral cleaning within the previous four months).
    - Participants are eligible to be enrolled and complete study Visits 1 and 2 if they have had an oral cleaning within the previous four months. However, participants will not be eligible to complete Study Visit 3 until a minimum of four months has passed following their previous dental cleaning.

5.2 Subject Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

- Cleft palate or other oral condition which makes dental care more difficult than usual practice.
- Prescription of anti-cholinergic drugs (which may alter EDA) (See Appendix M in MOP for a list of medications)
- Presence of orthodontia (braces).

- Significant motor impairment, such as cerebral palsy.
- Any known genetic, endocrine, or metabolic dysfunctions.
- Participation in the R34 SADE pilot study.
- Any medical condition such as significant cardiac problems that would place the individual at increased risk in the study.

5.3 Strategies for Recruitment and Retention

Recruitment at each site

CHILDREN'S HOSPITAL LOS ANGELES (CHLA). CHLA will be our main recruitment site and is a nonprofit, academic, major pediatric medical center providing healthcare to children throughout Los Angeles and surrounding counties. Within CHLA, participants will be recruited through several sources:

CHLA Division of Dentistry and Orthodontics. The Division of Dentistry and Orthodontics, aligned with the USC School of Dentistry, provides routine and specialized dental care to approximately 3,500 children and adolescents each year, including more than 300 children with ASD. Participants with ASD will be recruited from lists of currently scheduled patients; recruitment flyers will be posted in the Dental Clinic and dentists will also be asked to distribute flyers to appropriate clients who have ASD. These flyers will contain contact information for the research staff, enabling parents to contact the research team if they are interested in participating in the study.

USC Center for Excellence in Developmental Disabilities at CHLA (UCEDD). The USC UCEDD, which is part of the CHLA Division of General Pediatrics, is one of more than 65 university centers in the U.S. focused on training, service, research, and technical assistance for people with disabilities and their families. Each year, the UCEDD provides diagnostic and intervention services to over 3,000 children with disabilities, including approximately 200 children with ASD. Recruitment flyers will be posted at the UCEDD and therapists will be asked to distribute flyers to clients who have ASD.

Boone Fetter Clinic. The Boone Fetter Clinic at CHLA offers comprehensive services for children thought to have autism, neurodevelopmental, or behavioral disorders, offering clinical diagnostic and assessment services and serving as a follow-up resource referral for children with ASD. Boone Fetter provides diagnostic services to approximately 120 children with ASD each year. Recruitment flyers will be posted at the Boone Fetter Clinic and therapists will be asked to distribute flyers to clients who have ASD.

AtlaMed General Pediatrics Service. AltaMed, designed to eliminate disparities in health care access and outcomes, provides quality health and human services to 16,000 underserved Southern California children. Conservatively, 200 of these children are diagnosed with ASD. Dr. Robert Jacobs, Director of AltaMed, will assign a pediatrician as a 5% in-kind contribution to this U01 study; this pediatrician will identify potential study participants and provide them with information about the study.

Participants from previous research studies. Participants will also be recruited from a list of children with ASD who have participated in previous research studies at CHLA who have consented to be approached about additional research opportunities. These include participants

from the Tummy Troubles Study (Grant # 1R21MH089465-01, PI: Levitt). Dr. Marian Williams (Co-I) has access to this database of approximately 200 previous participants in research at CHLA, including over 100 children with ASD. Dr. Williams will provide these potential study participants with information about the study.

LOS ANGELES UNIFIED SCHOOL DISTRICT (LAUSD). In order to ensure that children with a wide range of ASD severity are recruited and enrolled in this study, LAUSD will also be a source of participant recruitment. LAUSD is the second largest public school system in the United States, enrolling over 350,000 students in our targeted age range. Conservatively, we estimate that over 2,500 are diagnosed with ASD. These local schools also serve primarily low-income Latino children (70%), similar to the demographics at CHLA. Schools within local commuting distance of CHLA have been identified, and, with principal approval, recruitment flyers will be disseminated to children with ASD. After flyer dissemination, interested parents will be responsible for contacting the research team via provided contact information (phone or email) for further details of participation.

OCCUPATIONAL THERAPY CLINICS. In order to ensure we reach target enrollment, pediatric occupational therapy clinics will also be a source of participant recruitment. *Pediatric Therapy Network* serves over 2,500 children with special needs and provides over 100,000 hours of occupational therapy, physical therapy, and speech-language therapy each year as well as offering multiple small group programs (e.g., Early Intervention, social skills, augmentative and alternative communication, etc.). *Therapy West* has three facilities in the greater Los Angeles area to provide occupational therapy, physical therapy, and/or speech and language therapy, treating primarily children with developmental disabilities including Down Syndrome, Cerebral Palsy, and Autism Spectrum Disorders.

Retention

To aid in retention of study participants, a series of steps will be taken. Reminder phone calls, texts, and/or e-mails for meetings and dental visits will occur (based on stated parent preference). Additionally, the first meeting, consisting of the consent process and survey completion, will take place at the family home or CHLA, whichever is more convenient for the family. Utilizing these strategies in the R34 pilot study, we were able to retain 98% of our participants. However, since not all participants will be patients in the CHLA Dental Clinic, we expect there may be a larger loss. We have allowed for a loss of 10%, targeting a sample of 165 participants with complete data from a recruited sample of 220 children with ASD.

Compensation

Families will not incur any out-of-pocket costs for participating in this study. Families' insurance will be billed for one of the two dental visits, and the other visit will be provided free of charge. If a participant does not have dental insurance, or if the insurance company denies reimbursement, both dental cleanings will be free of charge. Additionally, participants will be paid a stipend following each visit to compensate families for their time as for well as parking and transportation costs.

The amount and schedule of payments is as follows:

1. Consent and survey completion visit: $40 following completion of questionnaires

2. Administration of ADOS-2 for ASD diagnosis confirmation and IQ test (WASI-II): $40 following assessment plus $10 parking/transportation
3. First Dental Cleaning Visit: $40 plus $10 parking/transportation
4. Second Dental Cleaning Visit: $40 plus $10 parking/transportation (provided only if the study's rideshare option is not used). For our final 25 participants, new CHLA procedures that are COVID-19 related are designed to protect the safety of the parent/legal guardian and participant. Round-trip rideshare will be available for these 25 participants.
   Note: To protect the health and safety of patients and staff during the COVID-19 pandemic, CHLA implemented a new policy that requires participants to take the COVID-19 test 72 hours prior to a scheduled dental cleaning visit. This will be scheduled by CHLA at no cost to the participant. If the participant wishes, a round-trip rideshare (e.g. Lyft) will be available to the participant for this visit. In addition, the participants will be provided with a $25 stipend for their time. This additional stipend will be provided at the patient's dental cleaning visit. This process will continue as long as COVID-19 testing prior to the dental visit is required by CHLA. The study team will follow the most current CHLA procedures and guidelines and as changes are made, we will abide by the most current CHLA procedures and guidelines. See MOP Appendix P Children's Hospital Los Angeles Pre-procedural COVID-19 Testing and Appendix Q: Children's Hospital Los Angeles COVID-19 Telephone Screening Procedures for additional details about the procedures.

Participants tested prior to the pandemic were able to receive a maximum of $190. For the remaining participants affected by the CHLA policy during the COVID-19 pandemic, the participant will receive a maximum of $215.

5.4 Treatment Assignment Procedures

5.4.1 Randomization Procedures (if applicable)

Following confirmation of ASD diagnosis (administration of ADOS-2), participants will be randomly assigned to the order of treatment, receiving either the Regular Dental Environment (RDE) condition or Sensory Adapted Dental Environment (SADE) condition for their first cleaning. Because we anticipate different rates of participation between gender and age, randomization will be stratified by gender and age (6.0-9.5 years and 9.6-12.11 years) so there is a balance in order of treatment between boys and girls and younger and older children in each order of environment. Randomization will be performed by our PhD biostatistician following a blocked randomization schema for each of the gender-age stratum. We anticipate that the largest stratum will be younger boys (~56% of the sample), followed by older boys (24%), younger girls (15%), and older girls (6%), thus block sizes will vary so that the study team cannot anticipate what the first treatment for a participant will be.

5.4.2 Masking Procedures (if applicable)

For intra-oral photos and analysis of EDA recordings, coders will be blinded to condition (SADE vs. RDE). Due to the practicalities of this study and the need to modify dental environments for each patient, blinding of treatment condition for patients or dentists is not applicable.

5.5 Subject Withdrawal

Subjects may withdraw voluntarily from the study. The investigator may also terminate a subject's participation if the second scheduled dental cleaning cannot be completed within a maximum of 8 months following the first dental cleaning (see Section 7.5 for more details).

5.5.1 Reasons for Withdrawal

Subjects are free to withdraw from participation in the study at any time upon request.

An investigator may terminate a study subject's participation in the study if:

- Any clinical serious adverse event (SAE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject.
- The subject meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.
- The subject cannot tolerate electrodes placed on fingertips.

5.5.2 Handling of Subject Withdrawals or Subject Discontinuation of Study Intervention

If a study participant voluntarily withdraws from the study, the child will continue to receive dental care as usual from his/her personal dentist. If his/her dental care is at CHLA, a routine follow-up appointment will be scheduled as appropriate for his/her next dental cleaning (e.g., six months following the study-related dental cleaning). If a subject voluntarily withdraws while the study is in the enrollment window, we will replace him/her with another subject; if after recruitment and enrollment has closed, no replacement will be made.

No adverse events or unanticipated problems occurred during our R34 pilot study; however, **in the event of a serious adverse event or unanticipated problem**, as per CHLA's Committee on Clinical Investigations, the investigators and CHLA are not able to offer financial compensation or absorb the costs of treatment. If the serious adverse event or unanticipated problem is not due to the research protocol and the study is still in the enrollment phase, we will replace him/her with another subject. If it occurs after recruitment and enrollment has closed, no replacement will be made.

5.6 Premature Termination or Suspension of Study

This study may be suspended or prematurely terminated if there is sufficient reasonable cause. Written notification documenting the reason for study suspension or termination will be provided by the suspending or terminating party to the investigator, funding agency, and regulatory authorities. If the study is prematurely terminated or suspended, the principal investigator will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects.
- Insufficient adherence to protocol requirements.
- Determination of futility.

6 STUDY INTERVENTION

6.1 Study Behavioral or Social Intervention(s) Description

This study will investigate the impact of adapting the dental environment on the physiological anxiety and negative responses of children with ASD undergoing a dental cleaning. Dental cleaning in a sensory adapted environment (SADE) will be compared to usual treatment for dental cleaning in a regular dental environment (RDE).

Dental cleanings in the *control condition* (RDE) and *experimental condition* (SADE) will take place in a private room in the CHLA Dental Clinic and will each require approximately 15-45 minutes to complete, and will take place four-six months apart. Every effort will be taken to ensure that both cleanings will be performed by the same SADE-trained CHLA pediatric dentistry resident and dental assistant. The SADE environment will be set up prior to the child's entrance into the dental room by a member of the research team.

Table 3 summarizes the specific modifications that comprise the SADE intervention. Specifically, visual, auditory, and deep pressure tactile stimuli are altered in an effort to maximize relaxation. It should be noted that dentists participating in our R34 pilot study indicated that the SADE did not negatively impact their ability to perform the oral cleaning in a regular manner. This was also reported by Shapiro et al. (personal communication, February 25, 2008) who conducted a similar study with children with intellectual and developmental disabilities. This will be empirically tested in the proposed study by including a measure of quality of care. Additionally, the intervention does not require permanent renovations to the dental clinic, as the equipment is portable, requiring approximately 15 minutes to set up or to remove.

Table 3. Components of the SADE Intervention.

Visual	All direct overhead fluorescent lighting and the regular dental overhead lamp will be turned off; dark colored "black-out" removable curtains will cover the windows in the private dental room. The dentist will wear a head-mounted dental lamp directed into the patient's mouth, reducing bright lights shining into the child's eyes. Slow moving visual color effects (Snoezelen) will shine onto the ceiling in the child's visual field.
Auditory	Auditory stimuli will include rhythmic music projected via a Phillips Portable Speaker System. Music will be either Dan Gibson's Exploring Nature with Music or similar options.
Tactile / Deep Pressure	The tactile deep pressure stimulus will consist of a butterfly wrap (a modified version of the wrap developed in Israel),[49] weighted with a regular pediatric dental X-ray vest. The wrap fits around the dental chair and is made of a washable material. The "wings" of the butterfly wrap around the child from shoulder to ankles, providing a deep "hugging" pressure to produce a calming effect.

Note. See Appendices D and E for pictures of the SADE set-up and "butterfly"

6.2 Administration of Intervention

The private dental room for the SADE will be prepared by trained research team members. Following the set-up of the environment and electrode placement on the study participant's fingers, a three-minute baseline rest period will occur, followed by the dental cleaning led by the CHLA resident. In the RDE, the same research team members will video-record, place electrodes, and obtain EDA recordings, but none of the environmental adaptations will be made.

Each participant will receive a total of two dental cleanings approximately four-six months apart. In this crossover design, one cleaning will be in SADE and the other in the RDE. The duration of each dental cleaning session will be approximately 15-45 minutes.

6.3 Procedures for Training Interventionists and Monitoring Intervention Fidelity

Dental room set-up. Dr. Leah Stein Duker (Co-I) or her trained designee will be responsible for training research team members on the set-up of the private dental room for both the RDE and SADE conditions. Two trained research team members will prepare the dental treatment room for both conditions, and a checklist will be completed to ensure all equipment has been set-up correctly for each condition [Environment Set-Up Fidelity Form (CRF 24) and the Equipment Set-Up Checklist (Appendix G)].

Dental cleaning sequence of events. Dr. Stein Duker or her trained designee will be responsible for training research team members and dental residents about the sequence of events for each dental cleaning (e.g., electrode application → rest period → research-related oral hygiene assessments → traditional CHLA oral examination → intraoral photographs → prophylaxis → intraoral photographs → fluoride application → end of study procedures). At each visit a visual representation will be taped to the wall by the resident for quick reference (See Appendix C).

EDA & video equipment set-up, recording, and coding. Dr. Stein Duker or her trained designee will be responsible for training research team members on the set-up and use of both the video and EDA equipment as well as their coding. Reliability of research team members' coding of EDA recordings and video-recordings will be achieved at a K=.85 using prior recordings from the R34 pilot study. Recordings from the U01 will be coded by these reliable team members. For quality assurance 25% of EDA codings and 25% of video codings will be compared to coding by Dr. Stein Duker. If inadequate reliability is obtained, research team members will undergo retraining. This retraining will include practice coding video and/or EDA data side-by-side with a reliable coder, followed by a retest of reliability (See CRFs 22 and 23 for CDBRS and Scored EDA Forms).

Dental measures. Dr. José Polido (Co-I) will train residents on oral hygiene measures (Oral Hygiene Index - Simplified, Plaque Index, Gingival Index) and behavioral measures (Modified Anxiety and Cooperation Scale and Frankl Scale) as well as the use of the intraoral camera. Dr. Polido or the supervising attending dentist will monitor and check quality of work after the resident has completed each dental cleaning.

ASD diagnosis confirmation. Dr. Marian Williams (Co-I) will either conduct the ADOS-2 assessment herself or supervise PhD psychology residents who have been trained by formal courses offered in conjunction with Western Psychological Services in administration of the

Autism Diagnostic Observation Schedule-2 (ADOS-2). Assessments will be videotaped for co-scoring and training. Dr. Williams will co-score 10% of ADOS-2 assessments using videotapes. If a study participant has previously had the ADOS-2 administered at the CHLA UCEDD, we will accept the ASD confirmation and study results from that previous assessment.

6.4 Assessment of Subject Compliance with Study Intervention

Dentist Compliance. The Dentist Recording Form [combination of the Oral Health Indices Form (See CRF 13) and the Behavioral Indices Form (CRF 14)] will be used to record data as well as ensure fidelity to the study protocol. The Oral Health Indices Form includes the Oral Hygiene Index – Simplified (OHI-S), Gingival Index (GI), and Plaque Index. The OHI-S, GI, and Plaque Index will be completed during the oral examination portion of the dental cleaning; the PIaque Index will also be completed by blinded dentists scoring pre-examination and post-examination intra-oral photographs. The Behavioral Indices Form includes the Anxiety and Cooperation Scale and Frankl Scale and will be completed by the dentist directly following the dental cleaning. Additionally, both dental cleanings will be directly observed by research team members, and accidental straying from the protocol will be quietly but quickly corrected.

Participant Compliance. The main measure of participant compliance will be attendance at both scheduled visits. To decrease attrition, as was done successfully in our R34 pilot study, we will contact participants one day, one week, and two weeks prior to their scheduled appointments using the participants' preferred method of communication (e.g., phone call, email, text). All communication attempts will be documented manually on the Call Log Form (CRF 3) and tracked. If an appointment is missed, we will make every attempt to reschedule missed sessions.

Researcher Compliance. Prior to leaving USC OS-OT for a scheduled appointment at CHLA, the research team will complete the Equipment Fidelity Checklist to ensure all necessary equipment is packed for the study protocol. Once at CHLA, the research team will complete the Environment Set-Up Fidelity Form (CRF 24) and the Equipment Set-Up Checklist (Appendix G) to ensure appropriate set-up of both RDE and SADE conditions. Additionally, a research team member will fill out the Visit Completion Form (CRF 25) throughout the dental cleaning to ensure all time measurements have been recorded and video-recording has been completed. A second team member will complete the EDA Flag Form (CRF 26) to ensure that not only EDA has been collected, but marked in real time to designate different dental practices (e.g., beginning of oral exam, beginning of prophylaxis, etc.). Following the dentist completion of the Dentist Recording Form (Oral Health Indices Form and Behavioral Indices Form; CRFs 13 and 14), the research team will also visually inspect the forms to ensure that they have been accurately and fully completed.

7 STUDY SCHEDULE

7.1 Screening

Screening to Determine Eligibility (Day -90 to -15)

CHLA Dental Clinic patients/previous research participants only: In order to determine *initial* eligibility, CHLA dental charts and lists of participants in previous research studies will be reviewed to identify potential participants. As successfully done for our R34 SADE pilot study, a waiver of written or signed consent will be requested from the CHLA IRB for the purposes of determining the initial eligibility of participants so we may identify appropriate children to recruit. Phone contact (see below for greater detail) will be made to families whose children meet this *initial* eligibility (See inclusion/exclusion criteria above Sections 5.1 and 5.2).

Participants from CHLA (Dental Clinic, UCEDD, Boone Fetter, AltaMed) & LAUSD

- CHLA Dental Clinic patients: We will contact the parent/guardian by telephone to tell them about the research study (CHLA Dental Clinic patients).

- Other CHLA recruitment sites (UCEDD, Boone Fetter, AltaMed), previous research subjects who have agreed to be contacted (not those who participated in R34 SADE Study), and LAUSD: The parent/guardian will contact the research team responding to recruitment brochure/flyer.

    - Following explicit statement of parent/guardian interest in participation, research staff member confirms child participant eligibility (meets inclusion criteria, has no exclusion criteria traits).

    - Following confirmation of child eligibility, if the parent is still interested in participating, an in-person visit is scheduled to conduct the written consent process and complete all questionnaires.

Note. We plan to have a rolling recruitment and enrollment in this study, such that day -30 (for example) for one child will likely be different from day -30 for another child.

7.2 Enrollment/Baseline

Enrollment Visit (Visit 1, Day 0)

- Further explain study protocol and participant responsibilities in greater detail than that discussed on the screening for eligibility phone call. Answer any parent or child questions.
- Verify inclusion/exclusion criteria.
- Obtain and document consent from parent on study consent (parental permission) form. Explain and obtain signature from parents on study HIPAA form.
- Explain and provide parents with California Bill of Rights.
- Obtain and document child assent from child subject on study assent form (if child is available and able to complete/understand form).

- Parental completion of the Parent Bilingual Questionnaire to assess the child and parent's bilingual preference (see Appendix N in MOP).
- Use the Decision Tree for Accepting Child's Data as a guideline to determine if the child is able to give assent based on the parent report (see Appendix O in MOP).
- Parental completion of study questionnaires to obtain demographic information, dental history, anxiety, and sensory over-responsivity. (Complete list of measures to be completed are listed in the Schedule of Events in Appendix A; see CRFs 5-10, 28: Child & Family Information (Demographics), CASI-Anx, SSP-2, SensOR, CFSS-DS, VABS-II Expressive Communication Domain, Dental History Form, Dental Care in Children Questionnaire)
- Child completion of study questionnaires (if able) to obtain information about child perception of dental anxiety. (Complete list of measures to be completed are listed in the Schedule of Events in Appendix A; see CRFs 11-12: CFSS-DS, MCDASf)
- Parents are shown and instructed in the use of the specialized study social story for going to the dentist and participating in the SADE study. Parents are informed that the social story will be mailed to them with instructions two weeks prior to the child participant's first (and second) dental cleaning.
- Parents and children are shown the EDA electrodes and allowed to play with them.

Note: This visit (Visit 1) will take place at the participant's home, or if the family prefers, at CHLA, prior to the Autism Diagnostic Confirmation Visit (Visit 2).

7.3 Intermediate Visits

ASD Diagnosis Confirmation and IQ Testing (Visit 2, Day 1 to 270)

- At the enrollment visit (Visit 1), parents are informed that their child will need to have the ADOS-2 and WASI-II administered at the CHLA UCEDD (parents will also be informed of this during the phone screening prior to this visit). Parent contact information will be provided to Dr. Marian Williams and her staff at the CHLA UCEDD for scheduling. A phone screening process will occur during the scheduling call to determine the appropriate ADOS module to be utilized during the ADOS-2 administration. Confirmation of ASD diagnosis through ADOS-2 administration is <u>required</u> to continue with visits for oral cleaning. If child does not meet the ASD criteria based on the ADOS-2, services or treatment at the dental clinic will continue as before but the child will not continue as a research participant nor participate in the study's subsequent visits. If a study participant has previously had the ADOS-2 administered at the CHLA UCEDD, we will accept the ASD confirmation and study results from that previous assessment.
- Child completion of study Assent (if child was not present at Visit 1 and is able to complete/understand form)
- ASD diagnostic confirmation (Autism Diagnostic Observation Schedule 2) and cognitive screen (Wechsler Abbreviated Screening of Intelligence II) administered by Dr. Williams or a psychology member of her team.

- All parents/guardians will receive written feedback (by mail) from Dr. Williams or a member of her team regarding the general results of the autism and cognitive assessments (see Appendix I in MOP)
- Following completion of Visit 2, randomization into study condition (RDE vs. SADE) for the first dental visit (Visit 3) will occur (see Section 5.4.1 for randomization details).

  ***This behavioral assessment (ADOS-II) must be completed and confirm ASD diagnosis prior to the continuation of study activities and administration of intervention.*

Intervention Condition 1 (Visit 3, Day 5 to 360)

- Obtain and document child assent from child subject on study assent form (if child was not present at Visit 1 and is able to complete/understand form).
- Child completion of study questionnaires (if child was not present at Visit 1 and is able to complete/understand form) to obtain information about child perception of dental anxiety.
- Obtain parent-report of current medications of child.
- First dental cleaning will occur, based on randomization of participant into RDE vs. SADE condition.
- Prior to first cleaning, complete Dental Room Set-Up Checklist to ensure fidelity with environment.
- Dentist will photograph child's teeth prior to cleaning.
- Concurrent with the first dental cleaning, record results of dental cleaning on Oral Health Indices Form, complete Visit Completion Form and EDA Flag Form, and collect video-recording and EDA data. (Complete list of measures to be completed are listed in the Schedule of Events in Appendix A; see CRFs 13, 25-26)
- Following administration of dental cleaning:
    - Dentist will photograph child's teeth inside the child's mouth using an intraoral camera.
    - We will obtain dentist's perception of subject's behavior throughout the dental cleaning [Behavioral Indices Form (Anxiety and Cooperation Scale and Frankl Scale); See CRF 14]; complete Usual Dental Care and Planning Form (CRF 15).
    - We will administer child questionnaires (Faces Pain Scale – Revised, Dental Sensory Sensitivity Scale, and if in the SADE environment, the Child SADE Acceptance Form; See CRFs 17-19).
    - If in the SADE environment, we will administer the Parent SADE Acceptance Form (See CRF 20).
    - If, based on the Clinical Examination, the child has any dental needs, the dentist will complete the Dental Letter to Parents (Appendix K). A copy will be given to the parent and a copy will be placed in the child's chart and his/her dental findings will be recorded in the child's e-record if the child is a CHLA dental patient.

Note-1: Scoring of intra-oral photographs will take place following the dental cleaning at CHLA by a trained dentist (CRF 16: Quality of Care Recording Form). Coding of video-recordings and EDA recordings will occur off-site (at the designated lab space of the Health Sciences Campus of the University of Southern California) at a later time. (CRFs 22-23: Children's Dental Behavior Rating Scale & Scored EDA Form)

*Note-*2: Lighting for the intra-oral photographs is provided by the camera inside the mouth and, according to the company representatives, will be comparable in both SADE and RDE conditions.

- Record and report unanticipated problems as reported by subject/parent or observed by investigator/dental staff (See CRF 27: Unanticipated Problem Form).

Intervention Condition 2 (Visit 4, Day 125-450)

- Update parent-report of current medications of child.
- Second dental cleaning will occur, based on randomization of participant into RDE vs. SADE environment.
- Dentist will photograph child's teeth prior to cleaning.
- Concurrent with the second dental cleaning, record results of dental cleaning on Oral Health Indices Form, complete Visit Completion Form and EDA Flag Form, and collect video-recording and EDA data. (Complete list of measures to be completed are listed in the Schedule of Events in Appendix A; see CRFs 13, 25-26)
- Following administration of dental cleaning:
    - Dentist will photograph child's teeth.
    - Obtain dentist's perception of subject's behavior throughout the dental cleaning [Behavioral Indices Form (Anxiety and Cooperation Scale and Frankl Scale); See CRF 14]; complete Usual Dental Care and Planning Form (CRF 15).
    - Administer child questionnaires (Faces Pain Scale – Revised, Dental Sensory Sensitivity Scale, and if in the SADE environment, the Child SADE Acceptance Form; See CRFs 17-19).
    - If in the SADE environment, we will administer the Parent SADE Acceptance Form (See CRF 20).
    - If, based on the Clinical Examination, the child has any dental needs, the dentist will complete the Dental Letter to Parents (Appendix K). A copy will be given to the parent and a copy will be placed in the child's chart and his/her dental findings will be recorded in the child's e-record if the child is a CHLA dental patient.

Note-1: Scoring of intra-oral photographs will take place at a later date following the dental cleaning at CHLA by a trained dentist (CRF 16: Quality of Care Recording Form). Coding of video-recordings and EDA recordings will occur off-site (at the designated lab space of the Health Sciences Campus of the University of Southern California) at a later time (CRFs 22-23: Children's Dental Behavior Rating Scale & Scored EDA Form).

*Note-*2: Lighting for the intra-oral photographs is provided by the camera inside the mouth and, according to the company representatives, will be comparable in both SADE and RDE conditions.

Note-3: (COVID-19 modifications) At the beginning of the COVID-19 pandemic (March 2020), all research activities were discontinued. At that time, all participants had been recruited and completed Visits 1-3. Twenty-five participants had not completed the final visit (second dental cleaning). Once permission to resume research activities is provided by USC and CHLA we will adhere to all COVID-19-related guidelines and regulations from CHLA and USC. To protect the health and safety of patients and staff during the COVID-19 pandemic, CHLA now requires participants take a COVID-19 test 72 hours prior to a scheduled dental cleaning visit. This will require an extra visit for our participants. Thus, for the remaining 25 participants who will be completing their second dental visit, the study team will inform the parent/legal guardian of the COVID-19 test (until it is no longer a requirement at CHLA) and the rideshare option for both the COVID-19 testing and the dental cleaning visit. The study team will follow the most current CHLA procedures and guidelines and as changes are made, we will abide by the most current CHLA procedures and guidelines.

- Record unanticipated problems as reported by subject/parent or observed by investigator/dental staff (See CRF 27: Unanticipated Problem Form).

7.4 Final Study Visit

Final Study Visit = Visit 4 (125-450 days)

This study's final visit will be the second dental cleaning visit at CHLA; there are no special procedures or evaluations (other than those noted in Visit 4 above) to be completed after the second dental cleaning.

Upon completion of the second dental cleaning, participants and parents will be informed that the study is complete and oral care will return to as it was prior to the study (e.g., continue recalls at CHLA every 6 months if CHLA client, or return to other dentist if not a CHLA client) with no further compensation or access to the adapted environment. Parents will again be given contact information of research team members in the case that they have any questions or want to contact the researchers (also located on the signed and dated copy of the consent form). Parents will be instructed to contact the research team if any AEs or SAEs occur following Visit 4. If appropriate, a member of the research team will follow-up via phone call to ensure that any AE/SAEs have been resolved. Individual participants will not be informed of study results.

7.5 Withdrawal Visit

There will not be a withdrawal visit and no evaluations are specifically required for the final visit as the final visit is the second dental cleaning visit (Visit 4 above).

We will make every attempt to ensure that each child gets two dental cleanings, one in each condition (SADE and RDE). Missed appointments will be rescheduled, as many times as necessary up to eight months following the child's first dental cleaning (with participants receiving priority scheduling), extra reminders made, and compensation provided to cover transportation costs and time. If a child does not complete his/her second cleaning within eight

months of his/her first, we will assume that he/she has voluntarily withdrawn and will inform parents that their child is no longer eligible to obtain the second dental cleaning, nor is part of the study anymore. Parents will also be reminded that there will be no penalty or impact on CHLA quality of care as a result of withdrawing or dropping out of the study.

7.6 Unscheduled Visit

If the child requires dental care other than routine cleaning between enrollment and completion of the study, he or she may do so at his/her regular dental provider's office (whether that is at CHLA or elsewhere). If an unrelated emergency visit before or between SADE Study dental visits occurs, we will record its occurrence and allow the participant to continue to participate in the study following review of the reason and outcome of the visit by the principal investigator and Co-I, Dr. José Polido. If an unrelated visit occurs between SADE Study visits (e.g., treatment of cavities found during Visit 3), we will also record its occurrence and allow the participant to continue to participate in the study.

8 STUDY PROCEDURES/EVALUATIONS

8.1 Study Procedures/Evaluations

Medical History

Medical history will be obtained from parent-report and will include diagnosis of ASD, list of current medications, and a list of any other medical diagnoses. This information will be obtained to ensure that the child participant does not meet any of our stated exclusion criteria (e.g., genetic, endocrine or metabolic dysfunction; significant motor impairment, cleft palate, taking an anticholinergic medication, etc.).

Prior to Dental Cleanings

Child-Descriptor Assessments. As detailed above (Section 7.2), immediately following the consent/assent process parent- and child-report (if child is able) surveys will be completed (See CRFs 5-12, 28: Child & Family Information, CASI-Anx, SSP-2, CFSS-DS (parent), VABS-II Expressive Communication Domain, Dental History Form, Dental Care in Children Questionnaire, CFSS-DS (child), MCDASf), and SensOR. These forms will provide information about the child's sensory processing difficulties, dental anxiety, and previous dental experiences. Children with ASD will come to CHLA for an additional visit to confirm ASD diagnosis via administration of the ADOS-2 test. At this visit, the psychologist will also administer the WASI-II in order to assess child IQ.

During the Dental Cleanings

Oral Care-Related Assessments. Consistent with routine practice at CHLA Dental Clinic, an oral examination (including assessment of caries, developmental defects, and general oral growth and development) will be conducted prior to each of the child's dental cleanings. The dentist will also conduct the Oral Hygiene Index-Simplified, Plaque Index, Gingival Index (OHI-S, PI, GI; located in Oral Health Indices Form, CRF 13). The first exam will take place at approximately the appropriate recall time (e.g., approximately 6 months following the last dental cleaning) for the child participant; the second will occur approximately four-six months following the first study-related dental visit. Both dental visits will include an oral examination, prophylaxis, and fluoride application.

As part of this study, a dentist blinded to the experimental conditions will also complete the Plaque Index from intra-oral photographs taken at the beginning of the cleaning and the end of the dental treatment in order to obtain further information about the oral health of the study participants. Comparison of pre- vs. post-cleaning Plaque Index scores will be included as a quality of care measure. This scoring will take place at a later time (See CRF 16: Quality of Care Recording Form).

Behavioral and Physiological Measures of Distress. Both dental cleanings will be video-recorded in their entirety, with a focus on the child's face and on the number of hands being used to restrain the child. This information will be video-coded by the research team at a later time using the Children's Dental Behavior Rating Scale (CDBRS) to gather information about overt distress behaviors exhibited during the dental cleanings. Additionally, EDA will be recorded from the child's index and middle fingers of his/her non-dominant hand. Electrodes will be placed and secured using medical tape, with recordings sent directly to a computer in the private dental room via the BIOPAC system. Like the video-recordings, these EDA recordings will be analyzed at a later time (See CRFs 22-23: CDBRS & Scored EDA Forms).

Immediately Following the Cleanings (at CHLA)

Dentist. Following the completion of each of the two dental visits, the dentist will take additional intra-oral photographs for later scoring of quality of care. He/she will also complete the Anxiety and Cooperation Scale and Frankl Scale to report on distress behavior displayed during each cleaning (See CRF 14: Behavioral Indices Form).

Child. Following the completion of each of the two dental visits, the child (if able, and with assistance), will report on perception of pain using the Faces Pain Scale – Revised (FPS-R) and rank the degree of bother of the sensory stimuli encountered during the dental visit using the Dental Sensory Sensitivity Scale (DSSS). Additionally, following the dental visit in the SADE, children will be asked five additional questions as part of the Child SADE Acceptance Form to elicit information about whether or not they liked/enjoyed the specific adaptations made to the environment (See CRFs 17-19).

Parent. Following the dental visit in the SADE, parents will be asked to complete the Parent SADE Acceptance Form to elicit information about how they felt themselves about the SADE adaptations and whether or not they perceived that these adaptations helped make their child's experience better (See CRF 20).

Scoring Occurring at a Later Time (at CHLA or USC)

Dentist-Scoring. At CHLA, a dentist blinded to condition (RDE/SADE) will score the intra-oral photographs using the PIaque Index. (See CRF 16: Quality of Care Recording Form). The rater will be a dental resident who has achieved both inter-rater and intra-rater reliability.

Researcher-Scoring. At USC, a researcher will code video-recordings of the child behavior during the cleaning using the training program developed by Dr. Elyse Peterson and the study team during the R34 (it is not possible to blind to environment on video-recordings as the environment is obvious based on amount of ambient light in the room); this coder will achieve inter-rater reliability with Dr. Stein Duker (Co-I) and will change once per year. A researcher blinded to environment (RDE/SADE) will score the EDA recordings using the BIOPAC program Acq*Knowledge;* this coder will achieve inter-rater reliability with Dr. Stein Duker (Co-I) and will be responsible for EDA analyses for the entirety of the study (See CRFs 22-23: CDBRS & Scored EDA Forms).

9 ASSESSMENT OF SAFETY

9.1 Specification of Safety Parameters

Safety monitoring for this study will focus on unanticipated problems involving risks to participants, including unanticipated problems that meet the definition of a serious adverse event.

Some of the children who participate in this study may experience adverse events that are not related to study procedures, but are related to the participants' diagnosis of Autism Spectrum Disorders, and the treatment for these conditions. Such events will not be captured and reported for the study, as they will not meet the definition of an unanticipated problem.

9.1.1 Unanticipated Problems

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to subjects or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

9.1.2 Adverse Events

An adverse event is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research. Adverse events related to participants' ASD diagnosis and related treatment will not be reported in this study, as these are not considered Unanticipated Problems. Adverse events, unless serious, will not be reported.

9.1.3 Serious Adverse Events

A serious adverse event (SAE) is one that meets one or more of the following criteria:

- Results in death
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred)

- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant disability or incapacity
- Results in a congenital anomaly or birth defect
- An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Adverse Events related to participants' diagnosis of ASD will not be reported, as these are not considered Unanticipated Problems.

9.2 Time Period and Frequency for Event Assessment and Follow-Up

Unanticipated problems will be recorded in the data collection system throughout the study.

A trained research team member will record all reportable events with start dates occurring any time after informed consent is obtained until 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of UPs, and of SAEs not related to participants' diagnosis of ASD or related treatment, since the last visit. Events will be followed for outcome information until resolution or stabilization (See CRFs 27-29: Unanticipated Problem Form, Serious Adverse Event Form).

9.3 Characteristics of an Adverse Event

9.3.1 Relationship to Study Intervention

To assess relationship of an event to study intervention, the following guidelines are used:

1. Related (Possible, Probable, Definite)
    a. The event is known to occur with the study intervention.
    b. There is a temporal relationship between the intervention and event onset.
    c. The event abates when the intervention is discontinued.
    d. The event reappears upon a re-challenge with the intervention.
2. Not Related (Unlikely, Not Related)
    a. There is no temporal relationship between the intervention and event onset.
    b. An alternate etiology has been established.

9.3.2 Expectedness of SAEs

The NIDCR Medical Monitor and the Study PI will be responsible for determining whether an SAE is expected or unexpected. An adverse event will be considered unexpected if the nature,

severity, or frequency of the event is not consistent with the risk information previously described for the intervention.

9.3.3 Severity of Event

The following scale will be used to grade adverse events:

1. Mild: no intervention required; no impact on activities of daily living (ADL)
2. Moderate: minimal, local, or non-invasive intervention indicated; moderate impact on ADL
3. Severe: significant symptoms requiring invasive intervention; subject seeks medical attention, needs major assistance with ADL

9.4 Reporting Procedures

9.4.1 Unanticipated Problem Reporting to IRB and NIDCR

Incidents or events that meet the OHRP criteria for unanticipated problems require the creation and completion of an unanticipated problem report form. As per OHRP recommendation, the following information will be included when reporting an adverse event, or any other incident, experience, or outcome as an unanticipated problem to the IRB:

- appropriate identifying information for the research protocol, such as the title, investigator's name, and the IRB project number;
- a detailed description of the adverse event, incident, experience, or outcome;
- an explanation of the basis for determining that the adverse event, incident, experience, or outcome represents an unanticipated problem;
- a description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the unanticipated problem.

To satisfy the requirement for prompt reporting, unanticipated problems will be reported using the following timeline:

- Unanticipated problems that are serious adverse events will be reported to the IRB and to NIDCR within 1 week of the investigator becoming aware of the event.
- Any other unanticipated problem will be reported to the IRB and to NIDCR within 2 weeks of the investigator becoming aware of the problem.
- All unanticipated problems should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within one month of the IRB's receipt of the report of the problem from the investigator.

All unanticipated problems will be reported to NIDCR's centralized reporting system via Rho Product Safety:

- Product Safety Fax Line (US): 1-888-746-3293
- Product Safety Fax Line (International): 919-287-3998
- Product Safety Email: rho_productsafety@rhoworld.com

General questions about SAE reporting can be directed to the Rho Product Safety Help Line (available 8:00AM – 5:00PM Eastern Time):

- US: 1-888-746-7231
- International: 919-595-6486

9.4.2 Serious Adverse Event Reporting to NIDCR

Any AE meeting the specified Serious Adverse Event criteria will be submitted on an SAE form to NIDCR's centralized safety system via Rho Product Safety. This report may be sent by fax or email. Once submitted, Rho Product Safety will send a confirmation email to the investigator within 1 business day. The investigator should contact Rho Product Safety if this confirmation is not received. This process applies to both initial and follow-up SAE reports.

SAE Reporting Contact Information:

- Product Safety Fax Line (US): 1-888-746-3293
- Product Safety Fax Line (International): 919-287-3998
- Product Safety Email: rho_productsafety@rhoworld.com

General questions about SAE reporting can be directed to the Rho Product Safety Help Line (available 8:00AM – 5:00PM Eastern Time):

- US: 1-888-746-7231
- International: 919-595-6486

The study clinician will complete a Serious Adverse Event Form and submit via fax or email within the following timelines:

- All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the Serious Adverse Event Form and submitted to Product Safety within 24 hours of site awareness.
- Serious adverse events other than death and immediately life-threatening events, regardless of relationship, will be reported by fax within 72 hours of site awareness.

All SAEs will be followed until resolution or stabilization.

9.4.3 Reporting of SAEs and AEs to FDA

Not applicable.

9.4.4 Events of Special Interest (if applicable)

Not applicable.

9.4.5 Reporting of Pregnancy

In the highly unlikely event that a 6-12 year-old is found to be pregnant during the course of the study, it will be noted in the database and the subject will be discontinued from the study.

9.5 Halting Rules

Safety findings that would temporarily suspend enrollment and/or study interventions until a safety review is convened include SAEs. A safety review will be conducted if there are a large number of SAE's overall, a large number of occurrences of a particular type of SAE, severe AEs/reactions, or increased frequency of events.

Subsequent review of serious, unexpected problems by the Medical Monitor, CSOC, IRB, the sponsor(s), or the relevant local regulatory authorities may also result in suspension of additional enrollment as well as further trial interventions.

10 STUDY OVERSIGHT

In addition to the PI's responsibility for oversight, study oversight will be under the direction of a Clinical Study Oversight Committee (CSOC) composed of members with expertise to oversee the study including expertise in autism spectrum disorders, occupational therapy, pediatric dentistry, and statistical analysis of clinical trials data. The CSOC will meet to review the clinical protocol before study recruitment begins, and then approximately annually to assess unanticipated problems, study conduct, and progress. If major concerns arise, more frequent meetings may be held. The CSOC will operate under the rules of an NIDCR-approved charter that will be approved at the organizational meeting of the CSOC. At this time, most data elements that the CSOC needs to assess will be clearly defined. The CSOC will provide recommendations to the NIDCR. In addition to the CSOC, an internal system for monitoring adverse events will be set up in conjunction with the study's database system. As per NIDCR guidelines, members of the CSOC will be appointed by NIDCR.

11 CLINICAL SITE MONITORING

Clinical site monitoring is conducted to ensure that the rights of human subjects are protected, that the study is implemented in accordance with the protocol and/or other operating procedures, and that the quality and integrity of study data and data collection methods are maintained. Monitoring for this study will be performed by NIDCR's Clinical Research Operations and Management Support (CROMS) contractor. The monitor will evaluate study processes and documentation based on NIDCR standards and the International Conference on Harmonisation (ICH), E6: Good Clinical Practice guidelines (GCP).

Details of clinical site monitoring will be documented in a Clinical Monitoring Plan (CMP) developed by the CROMS contractor, in collaboration with the NIDCR Office of Clinical Trials and Operations Management (OCTOM) and the NIDCR Program Official. The CMP will specify the frequency of monitoring, monitoring procedures, the level of clinical site monitoring activities (e.g., the percentage of subject data to be reviewed), and the distribution of monitoring reports. Some monitoring activities may be performed remotely, while others will take place at the study site(s). Staff from the CROMS contractor will conduct monitoring activities and provide reports of the findings and associated action items in accordance with the details described in the CMP. Documentation of monitoring activities and findings will be provided to the site study team, the study PIs, OCTOM, and the NIDCR. The NIDCR reserves the right to conduct independent audits as necessary.

12 STATISTICAL CONSIDERATIONS

12.1 Study Hypotheses

Primary Objective: To compare children's physiological anxiety (EDA - primary outcome) during the dental cleaning in SADE vs. RDE.

Hypothesis 1: Children will exhibit less physiological anxiety (SCL and NS-SCR frequency) during routine dental care in the SADE condition compared to the RDE.

Secondary Objective 2: To compare children's negative behavioral responses (behavioral distress, perception of pain, sensory discomfort - secondary outcomes) during dental cleanings in SADE vs. RDE.

Hypothesis 2: Children will exhibit fewer negative behavioral responses during routine dental care in the SADE condition compared to the RDE.

Secondary Objective 3: To test the degree to which physiological anxiety mediates the SADE intervention's effects on children's negative behavioral responses.

Hypothesis 3: Physiological anxiety mediates the effect of the intervention in decreasing child negative behavioral responses.

Secondary Objective 4: To test the degree to which specific child characteristics moderate the SADE intervention's effects on children's physiological and negative behavioral responses during dental cleaning.

Hypothesis 4: The magnitude of physiological and negative behavioral response change in the SADE, relative to the RDE, will be greater in children with ASD with increased sensory over-responsivity, high dental anxiety, greater ASD severity, lower IQ, and/or younger age.

Secondary Objective 5: To compare the SADE intervention to the RDE on quality of care, cost-effectiveness, and potential cost savings of dental cleaning.

Hypothesis 5a: The SADE intervention, compared to the RDE, is cost-effective and results in decreased overall costs.

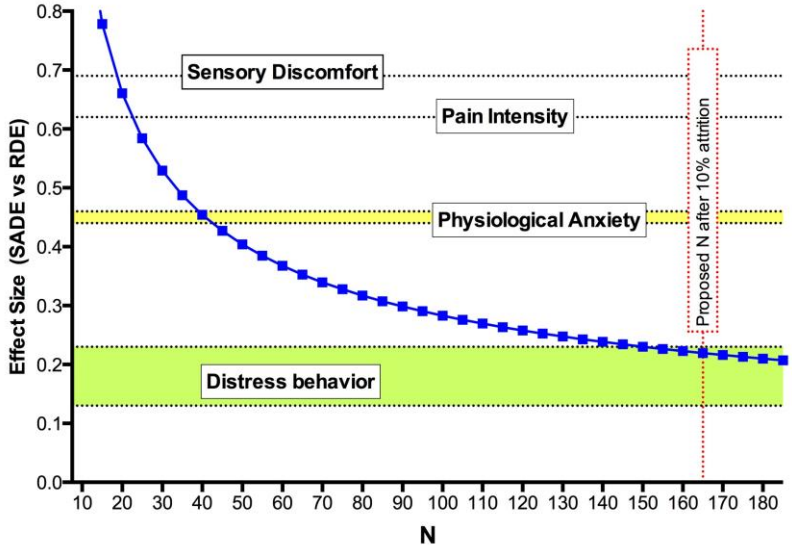
Hypothesis 5b: The SADE intervention, compared to the RDE, results in improved quality of care as evidenced by thoroughness of dental cleaning.

12.2 Sample Size Considerations

The R34 pilot study provided estimates of effect size used for sample size calculations, which ranged greatly across measures for children with ASD. Figure 1 shows the N required to detect a difference between dental environments based on the results from the pilot study. As these effect sizes were typically smaller than those found by Shapiro et al.,[50-51] they represent a more conservative estimate of sample size, and have the benefit of being specific to the population and measures proposed here. Sample size estimates were computed to detect the effect of the repeated measurement environment for outcomes specified in the primary objective, with EDA being the primary outcome (Hyp 1) and distress behavior, perception of pain, and sensory discomfort secondary, with 1–□=0.80 and □□□=0.025 (Hyp 2). In the R34 pilot study, the effect sizes for EDA difference between environments ranged from Cohen's d = 0.44-0.46 (see Figure

1). The effect size of the environment difference for sensory discomfort and pain intensity were large (d's = 0.69 and 0.62, respectively), while distress behavior measure effects were small (d's ranging from 0.11 to 0.23), likely due to the restricted range of answers in those measures. Attrition in the pilot data was extremely low (2%), however the more conservative attrition estimate of 10% was used for these calculations. Thus we will recruit 220 children with ASD, anticipating having repeated measures on 165. This N will allow for the detection of a within group change attributable to environment of Cohen's d = 0.22. Figure 1 shows the estimated sample size, including the effect sizes from the R34; as indicated, our target sample size, after attrition, should have sufficient power to detect differences in our primary outcome.

Figure 1. Sample size estimates based on ASD participants of R34 Pilot and Feasibility Study



12.3 Planned Interim Analyses (if applicable)

Not applicable.

12.3.1 Safety Review

Not applicable. This is a low risk study and safety will be monitored by research team members, the PI, IRB and the CSOC. For the current study, risks from dental cleaning using SADE are similar to traditional dental visits (e.g., gingival bleeding, mild discomfort). For a full list of potential risks, see Section 2.2.1.

12.3.2 Efficacy Review

There are no interim analyses planned for this trial. Efficacy of the primary factor of environment will be determined as defined in the final analysis plan.

12.4 Final Analysis Plan

Descriptive statistics will be performed for all variables of interest to describe the participant population at baseline, including attrition rate and missing data, to compare those randomized to SADE first vs. those randomized to RDE first. We anticipate a low attrition rate (~10%) and will impute missing data for intent-to-treat analyses using Markov Chain Monte Carlo (MCMC)

imputation with multiple values imputer for each missing value averaged for an estimation for analyses. Bivariate associations between outcomes (physiological anxiety and children's negative behavioral responses), environment (SADE or RDE), and covariates (age, gender, order of visit, autism severity, IQ, and sensory sensitivity) will be described. The primary objective of determining difference between dental environments will be tested using intent-to-treat models examining the within-subject factor of dental environment (SADE vs RDE) using repeated measures ANCOVA for each outcome. *A priori* covariates include age (continuous), randomized order of visit, gender, and temperature. Other participant characteristics that are unbalanced between order of visits will be included as covariates *ad hoc*.

The secondary objective of examining the mediating effect of physiologic response on behavioral outcomes will be tested by first examining the bivariate relationships between EDA and behavioral outcomes, and then adding EDA estimates (SCL and NS-SCR) to models of dental environment difference on behavioral outcomes, and examining the change in the within group coefficients. A change in coefficient >15% will be considered evidence of mediation. While we have several outcomes, we specify only one mediator, thus we will apply a rational approach to examination of multiple outcomes, and will assess the fidelity of our study by estimating effect sizes (Cohen's d) of the dental environment before and after the mediation factors are assessed to confirm that statistical results were supported by clinical relevance of findings. If physiological anxiety does mediate the environment's effect on negative behavioral responses, we anticipate that the anticipated effect of environment will be eliminated once we add in EDA to the models specified in Hypothesis 2. Analyses will be performed using SPSS (v.22); *a priori* two-sided □ = 0.05.

Primary Objective: Hypothesis 1
The primary objective is to test the effect of the environment (SADE vs RDE) on physiological anxiety. Hypothesis 1 specifies an effect of environment on the outcome, thus the main effect of interest will be B_1, the dental environment.

*Hyp 1: EDA = B_0 + B_1*Environment + Covariates*

Secondary Objective 2: Hypothesis 2
The secondary objective explores further outcomes and mechanisms of the group differences. Hypothesis 2 is analogous to those in the primary aim and have the same coefficients of interest. However, there are multiple, secondary outcomes including behavioral distress, perception of pain, and sensory discomfort). As noted above, we will apply a rational approach to examination of multiple outcomes and will assess effect sizes of the coefficients, in addition to the statistical significance.

*Hyp 2: Negative behavior = B_0 + B_1*Environment + Covariates*

Secondary Objective 3: Hypothesis 3
Hypothesis 3 seeks to test the degree to which physiological anxiety mediates the effect of the SADE intervention's impact on negative behavior. To test this hypothesis, we will add to the model for Hypothesis 2 above and look at the change in the coefficient and effect size of B_1 as well as the effect of EDA (B_2) on negative behavior.

*Hyp 3: Negative behavior = B_0 + B_1*Environment + **B_2*EDA** + Covariates*

Secondary Objective 4: Hypotheses 4a & 4b
Hypothesis 4 seeks to determine whether there is a moderating effect of EDA and negative behavior variables on the impact of the environment. It is anticipated that there is greater benefit of the SADE intervention for ASD children with greater ASD severity, decreased IQ, increased sensory over-responsivity, higher dental anxiety, and/or younger age. These models are exploratory and will be assessed initial with each moderator alone. Then a stepwise regression model will be built to see if there are moderators that are more important than others. The previously described associations will assist us in determining if there is a risk of collinearity amongst the variables.

*Hyp 4: EDA or Negative behavior = B_0 + B_1*Environment + B2*Moderators +* ***B3*(Environment*Moderators****) + Covariates*

Secondary Objective 5: Hypotheses 5a & 5b
Hypotheses 5a and 5b are similar, examining the environment difference on the costs and quality of care. The general model is presented below. Quality of care will be determined by scoring of pre- vs. post- intra-oral photographs on the OHI-S and PIaque Index measures. Health care costs are defined as personnel time burden, including direct costs of the intervention (e.g., training, materials, overhead, and direct patient care). The cost-effectiveness of the SADE intervention will be represented in the form of an incremental cost-effectiveness ratio of the cost (C) relative to the quality of care (E): $(C_{SADE} – C_{RDE})/(E_{SADE} – E_{RDE})$.

*Hyp 5: Cost or Quality = B_0 + B_1*Environment*

These models are paired and will involve paired t-tests or non-parametric corollary for continuous outcomes if the outcome is normal or non-normally distributed, respectively. For dichotomous outcomes (e.g., need for sedation), McNemar's test will be used to examined differences in need for the paired observations.

Cost Effectiveness Analysis. In assessment of medical interventions, cost-effectiveness evaluations become increasingly relevant.[72] Using this evaluation approach and the comparative intervention RDE as the reference standard, the cost-effectiveness of the SADE intervention will be represented in the form of an incremental cost-effectiveness ratio as: $(C_1 - C_0)/(E_1 - E_0)$, where the subscript 1 refers to the SADE intervention arm and the subscript 0 refers to the RDE comparative arm. C_1 represents the average net cost of implementing the intervention; C_0 represents the average net cost of the RDE comparative arm; E_1 represents the quality of care associated with the SADE intervention; and E_0 represents the quality of care associated with RDE. We will consider alternative effectiveness outcomes.

We will use alternative measures of effectiveness in conducting our economic evaluation of the intervention. We will also combine several of the effectiveness scales into a measure of dental performance using structural equations models with unobservable dental health status as a latent variable in a multiple indicators, multiple causes framework.[73] In this approach, all structural measures of dental treatment including patient functional status and patient outcome measures will be used as health status indicators, whereas clinical, environmental, and background characteristics will serve as causal factors in explaining dental health status changes. We will compute confidence intervals for the cost-effectiveness ratios using bootstrapping and develop cost-effectiveness acceptance curves.[74]

13 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

The study staff will maintain appropriate medical and research records for this study, in compliance with ICH E6, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects. Study staff will permit authorized representatives of NIDCR and regulatory agencies to examine (and when required by applicable law, to copy) research records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress and data validity.

14 QUALITY CONTROL AND QUALITY ASSURANCE

This study has a comprehensive manual of procedures (MOP), including standard operating procedures (SOP) for each study-related task.

The research team will meet every other week to review structure and processes, identify any errors, and determine ways to prevent future errors. Dr. Leah Stein Duker (Co-I), who is responsible for implementation of staff training and quality assurance, will meet with the PI and Project Specialist on alternate weeks, and as needed in the interim times. When errors occur, we will consider the following: Are there adequate written procedures? Were the procedures followed? Was training done? Was it adequate? Is work being monitored? Are individual roles and responsibilities clear and defined? Clarifications and additions will be made as needed.

All hard-copy documents will be visually checked by a member of the research team after completion and again prior to filing to ensure 100% completion of forms. All forms (parent-, child-, dentist-, and researcher-report forms) will be entered into our database and visually data checked to ensure quality and accuracy of data reporting; if there are more than 4-6 errors per 1,000 entries, we will re-train data entry staff and check the subsequent 1,000 entries. If again there are more than 4-6 errors per 1,000 entries we will switch to double data entry in the Café Database. Additionally, 25% of all video-recordings and EDA recordings will be double-coded to ensure proper inter-rater reliability and adherence to scoring protocols.

Dr. Leah Stein Duker (Co-I) will be responsible for addressing quality assurance issues by asking detailed questions of research members collecting data and visually inspecting one of every 10 child's forms. Quality assurance/quality control tasks regarding data entry will include visual data checking by one independent research assistant. Following a noted discrepancy, the Project Coordinator, Research Assistant (OTD Resident), PhD Student, Project Specialist, or Dr. Stein Duker will check the source document to resolve disagreement, determine how the error was made (e.g., mis-entry, illegible handwriting, etc), and the correct data will be input into the Café database. Dr. Stein Duker will then review data entry processes with the data entry research team member who entered the data incorrectly, ensuring that no questions or confusion exists in regard to his/her job responsibilities.

All training will be conducted by Dr. Stein Duker. Staff will complete mock administrations of all forms, including consent and assent. Video-recording training will occur on-site at CHLA regarding camera placement and goals of recordings. Video-recording coding training (how to code the CDBRS) will occur at USC. The training video will be viewed, questions will be asked of Dr. Stein Duker, and a minimum of 10 videos will be viewed and scored, ensuring inter-rater reliability with Dr. Stein Duker, with a minimum of 85% agreement. Training in the use of electrodermal equipment will include practice set-up and recording of volunteer students and other research team members. Training to understand psychophysiological concepts and administer and score EDA recordings will include five hour-long lectures and one hour-long laboratory activity by Dr. Dawson (Co-investigator and EDA expert) followed by practice scoring, supervised by Dr. Stein Duker. At least 10 recordings coded independently by the team member with a minimum of 85% agreement with Dr. Stein Duker will be required, ensuring inter-rater reliability on this measure. Dr. Stein Duker will also train all data entry staff on the use of the SADE database in the Café system, originally created for the R34 and modified for the U01.

15 ETHICS/PROTECTION OF HUMAN SUBJECTS

15.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, as drafted by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6; 62 Federal Regulations 25691 (1997).

15.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the IRB for review and approval. Approval of the protocol, consent form, and assent form will be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented in the study.

Note. This study will obtain dual approval, as done in the R34 Pilot Study, from Children's Hospital Los Angeles IRB (the Committee on Clinical Investigations) as well as the University of Southern California's IRB (Health Sciences Review Board).

15.3 Informed Consent Process

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation. Extensive discussion of risks and possible benefits of study participation will be provided to subjects and their families, if applicable. A consent form describing in detail the study procedures and risks will be given to the subject. Consent forms will be IRB-approved, and the subject will be required to read and review the document or have the document read to him or her. The investigator or designee will explain the research study to the subject and answer any questions that may arise. In order to assure that the subject understands, the investigator will ask the subject to verbally summarize what they are going to do. The subject will sign the informed consent document prior to any study-related assessments or procedures. Subjects will be given the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. They may withdraw consent at any time throughout the course of the study. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their clinical care will not be adversely affected if they decline to participate in this study.

Study assent forms will be used for children with ASD when appropriate. The study will be verbally described to the child and the child subject will be provided with a simplified form (assent) providing the details of the study intervention, study procedures, and potential risks. In order to assure that the child understands, the investigator will ask the child to verbally summarize what they are going to do. The child will then sign and date the assent. For those subjects who are unable to give assent based on their cognitive abilities, the subject will be informed about the trial to the extent compatible with the subject's understanding.

The original signed and dated consent/assent forms will be retained by the study staff. However, a second original of each form will be given to subjects for their records, and a copy of each form will be placed in the child's CHLA dental chart.

Additionally, as this study will recruit both English- and Spanish-speaking families, professionally translated consent and assent documents will be available to parents and child. Additionally, appropriate study team members who are fluent in Spanish, will conduct the consent and assent procedures.

The consent process will be documented in the clinical and research record. The NIDCR Informed Consent and Assent Documentation Checklist will be reviewed to be sure all aspects are included in the Consent (see Appendix L in MOP). The two documents, "Documenting the Consent Process" and "Suggestions for Consenting/Assenting Research Subjects/Participants" will be used as training tools and serve as a reminder of the tasks associated with adequate consent practices and documentation.

15.4 Exclusion of Women, Minorities, and Children (Special Populations)

Our study excludes children younger than 6.0 years and older than 12.11 years, as well as participants (parents) who do not fluently speak English or Spanish.

Age. Research indicates that younger age is associated with the presence of uncooperative behaviors in the dental operatory in children with ASD.[75-77] Additionally, this project provides a conceptual replication and extension of Shapiro et al.'s previous work[50-51] with children with developmental disabilities (other than ASD) in Israel; in this study a similar age-range was used.

Language. Participants will be recruited primarily from CHLA and LAUSD, which provides services to an ethnically diverse population, with approximately 60-70% Hispanic/Latino. Therefore, we anticipate that the majority of our sample will be either English- or Spanish-speaking. Additionally, some of the tools we will be using have only been validated in English and Spanish.

15.5 Subject Confidentiality

Subject confidentiality is strictly held in trust by the investigators, study staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to any study information relating to subjects.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. Only the Principal Investigator, Dr. Leah Stein Duker (Co-I and responsible for training and quality assurance), the Project Specialist, and members of the research staff collecting or participating in data entry will have access to study records (e.g., forms, video-recordings, EDA recordings, etc.). No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Principal Investigator.

The study monitor, representatives of the NIDCR, and IRB representatives may inspect all study documents and records required to be maintained by the investigator, including but not limited to, all CRFs, video-recordings, intra-oral photographs, and EDA recordings for the study subjects. The study site (office containing CRF, etc. storage, not CHLA where intervention is performed) will permit access to such records.

15.6 Future Use of Stored Specimens and Other Identifiable Data

The consent form will include, as one of its stipulations, the agreement to have the child's oral cleaning and ADOS assessment videotaped. Assurances related to secure storage of data will be provided. As video-recordings will be utilized for coding training purposes, the recording itself will not be de-identified (children may be called by their first name by the dental professional or parent during the oral cleaning or by the psychologist during the ADOS and child's face will be seen in videos), but video files will only be named via identification number. EDA recordings and intra-oral photographs will likewise be named via identification number.

All video data, electrodermal data, photographs, completed documents, questionnaires, and CRFs will be personally transported to USC in a privately owned vehicle by a research team member immediately following collection at CHLA. Electronic data (video-recordings, EDA recordings, and intra-oral photographs) will be transferred onto a secure server in the Division of Occupational Science and Occupational Therapy where it will be password protected so that only members of the research team may access it. The primary server is backed up twice a day in California as well as replicated to a remote site in Arizona once a night. Primary back-ups are retained for 31 days, at which point a monthly tape back-up is made. Additional back-up copies will be kept on an external hard drive that will be stored in a locked cabinet in the Principal Investigator's office.

The hard-copy documents (completed ADOS assessments, questionnaires, and CRFs) will be kept in a locked file cabinet in Lucía Floríndez's (Bilingual Project Coordinator) office. The key to the identification code will be stored in a locked file in Dr. Sharon Cermak's personal office. Hard-copy documents, video- and EDA recordings, and intra-oral photographs will be stored for six years following the completion of the study.

Additionally, as part of the consent form, parent(s) and children (if able) will have the option to have the child participant's dental cleaning video utilized in publications and/or professional conferences. When the results of the research are published or discussed at conferences no information will be included that would reveal any participant's identity; however, the child's face may be viewed with permission from the parent.

Genetic testing will not be performed.

Per CHLA's new policy that is related to COVID-19, new procedures were implemented to protect the safety of the participant and parent/legal guardian. A nasopharyngeal swab is collected during the COVID-19 testing at the COVID-19 Testing Clinic at CHLA and will be labeled, bagged, and sent to their lab. The management of the sample is at CHLA and not USC. The study team will follow the CHLA guidelines and requirements until notified that CHLA has discontinued the process.

16 DATA HANDLING AND RECORD KEEPING

The investigators are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. The investigators will maintain adequate case histories of study subjects, including accurate case report forms (CRFs), and source documentation.

Data will be retained for a minimum of six years following closure of the study; identifiers will be destroyed at the end of the study. Data will only be shared with members of our research team. Video and electrodermal data will be stored on a secure server in the Division of Occupational Science and Occupational Therapy where it will be password protected so that only members of the research team may access it. The primary server is backed up twice a day in California as well as replicated to the remote site once a night (in Arizona); primary back-ups are retained for 31 days, at which point a monthly tape back-up is taken. After the completion of the study, back-up copies will be kept on an external hard drive that will be stored in a locked cabinet in the Principal Investigator's office. After the completion of the study, original documents, including questionnaires and data collection sheets, will also be kept in a locked cabinet in Dr. Stein Duker's (Co-I) or Dr. Cermak's (PI) office. Original hard copies of our consent, assent, and HIPAA documents will be kept in a locked, secure cabinet in the Principal Investigator's office.

16.1 Data Management Responsibilities

Data collection and accurate documentation are the responsibility of the study staff under the supervision of the investigator. All source documents and CRFs must be reviewed by the study team and data entry staff, who will ensure that they are accurate and complete. Unanticipated problems and adverse events must be reviewed by the Principal Investigator.

All data will be entered into a database (Café) created for our R34 Pilot study and updated for our U01 study. This database was developed and programmed by the University of Southern California Cancer Research Informatics Core (CRIC). All data will be entered by trained members of our research team, and data will be exported by our statistician, Dr. Cheryl Vigen (Co-I); the role of CRIC as our data coordinating center will be adding new forms and updating existing forms, troubleshooting if any questions and/or problems arise using the Café database throughout our study and summary reports delivered every other month.

16.2 Data Capture Methods

All data collected, with the exception of video-recordings, EDA recordings, and intraoral photographs will be paper documents. Video-recordings, EDA recordings, and intraoral photographs will be electronic in nature. Paper documents will be entered into our secure and password-protected database (Café) by trained research assistants; data entries will be visually checked by a second trained research assistant, ensuring accuracy and quality control of data entry. The original copies of these paper forms will be securely stored in a locked cabinet in CHP 222-W. All consent and assent forms will also be stored in a locked cabinet in the PI's office (CHP 222-V).

Video- and EDA recordings and intra-oral photographs will be transferred to a secure computer server that is backed-up nightly and is accessible to only those with the correct security clearance and password; original files (e.g., the camera recording stored on the camera) will

then be deleted. After these recordings are scored and recorded onto the appropriate CRF, the scored data will also be entered into our Café Database system.

Data entry of paper forms will occur within 8 weeks following the visit; visual data checking will occur by two months. Entry of data that requires coding and/or double coding prior to database entry (e.g., CDBRS score from video-recordings, SCL/NS-SCR data from EDA data; oral hygiene measures from intra-oral photographs) will occur within six months of the visit. Data will be continuously entered into our database throughout the study, but will undergo batched processing following the locking of the database when study activities are completed.

Data will be centralized. All data will be collected either at the subject's home (child-descriptor assessments) or at CHLA (ASD diagnosis confirmation, IQ assessment, dental cleaning assessments). However, all system components (research staff, clerical staff, software applications, servers, locked cabinets, etc.) will be located at SADE-dedicated space in the USC Division of OS-OT located on the Health Sciences Campus.

16.3 Types of Data

Data collected will include descriptive data of the participants and outcome measure data. Descriptive data characterizing the participants will include questionnaire responses from parents and children. Outcome measure data will include questionnaire responses from children and dental professionals, oral health indices, physiological recordings from children, and video-recordings of children undergoing dental cleanings (See CRFs 5-23 for a list of all child-descriptor and outcome measures; see Appendix A for Schedule of Events).

As our intervention modifies the dental environment and does not change the traditional dental cleaning protocol, we will question parents and dental professionals regarding adverse events and serious adverse events as our safety data collection. This will occur prior to and following each dental visit, and information will be stored in the same secure Café database as our other data.

16.4 Schedule and Content of Reports

Reports to monitor enrollment will occur monthly and will include a de-identified list of children as well as their gender, race, ethnicity, and age. This will be generated and maintained by Ms. Annie Hong, Project Specialist.

Reports for study progress will occur two times per year and will contain preliminary descriptive analyses of all child-descriptor variables; these will be conducted by our statistician, Dr. Vigen (Co-I).

The database will be locked by the Café database CRIC administrator prior to data export by our statistician for final data analysis.

16.5 Study Records Retention

Study records will be maintained for at least six years from the date that the grant federal financial report (FFR) is submitted to the NIH.

16.6 Protocol Deviations

A protocol deviation is any noncompliance with the clinical study protocol, Good Clinical Practice, or Manual of Procedures requirements. The noncompliance may be on the part of the

subject, the investigator, or study staff. As a result of deviations, corrective actions are to be developed by the study staff and implemented promptly.

These practices are consistent with investigator and sponsor obligations in ICH E6:

- Compliance with Protocol, Sections 4.5.1, 4.5.2, 4.5.3, and 4.5.4
- Quality Assurance and Quality Control, Section 5.1.1
- Noncompliance, Sections 5.20.1 and 5.20.2

All deviations from the protocol will be addressed in study subject source documents and promptly reported to NIDCR and the local IRB, according to their requirements.

17 PUBLICATION POLICY

This study will comply with the *NIH Public Access Policy*, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

Study results will be made available as soon as possible. Final peer-reviewed journal manuscripts that arise from NIH funds will be submitted to the digital archive *PubMed Central* immediately upon acceptance for publication. The MyNCBI's My Bibliography feature will be used to monitor Public Access Compliance.

The Principal Investigator will inform the NIDCR Project Officer of manuscripts and presentations prior to publication. All publications and presentations will be shared with NIDCR.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy requires that all clinical trials be registered in a public trials registry such as *ClinicalTrials.gov*, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. For interventional clinical trials performed under NIDCR grants and cooperative agreements, it is the grantee's responsibility to register the trial in an acceptable registry, so the research results may be considered for publication in ICMJE member journals. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have questions about the need to register on the site of registration, or consult the editorial office of the journal in which they wish to publish.

U.S. Public Law 110-85 (Food and Drug Administration Amendments Act of 2007 or FDAAA), Title VIII, Section 801 mandates that a "responsible party" (i.e., the sponsor or designated principal investigator) register and report results of certain "applicable clinical trials."

This study will follow USC guidelines in regard to developing publication procedures to resolve authorship issues.

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