Study Title: A randomized, sham-controlled, crossover study to evaluate the effects of noise cancelling headphones on neurocognitive and academic outcomes in children and adolescents diagnosed with Attention Deficit Hyperactivity Disorder (ADHD)

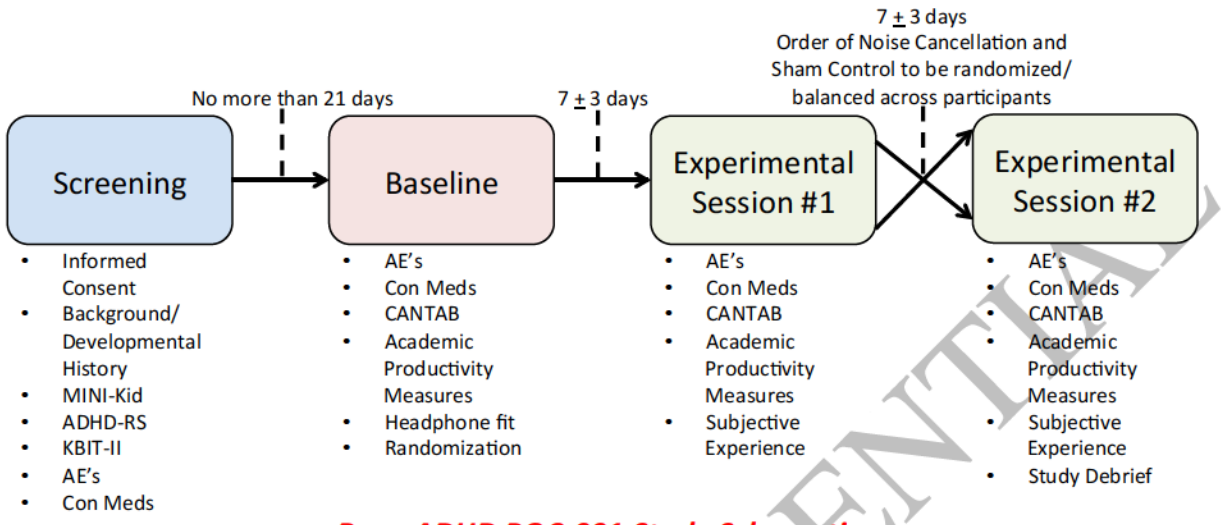
Study Sponsor: Bose Corporation

Protocol Date: 22NOV2016

NCT Identifier: NCT03216512

PROTOCOL SYNOPSIS
Bose-ADHD POC-001

Study Product	Bose QC Noise Cancelling Headphones/Earbuds
Protocol Number	Bose –ADHD POC-001
Protocol Title	A randomized, sham-controlled, crossover study to evaluate the effects of noise cancelling headphones on neurocognitive and academic outcomes in children and adolescents diagnosed with Attention Deficit Hyperactivity Disorder (ADHD)
Sponsor	Bose
Study Phase	Pilot/Proof of Concept
Study Start Date	Q1 2017
Study Centers	Number of Centers = 1 (Duke University, PI Kollins)
Hypothesis	Children with ADHD will demonstrate better performance on neurocognitive and academic outcomes in the presence of auditory distractors while using Bose noise cancelling headphones compared to performance when using a sham device.
Primary Objective Secondary Objectives	Evaluate performance on the ADHD Battery of the Cambridge Automated Neuropsychological Test Battery (CANTAB), including spatial working memory, inhibitory control, and attention while using either a noise cancelling headphone or sham headphone control in the presence of standardized auditory distractors. • Compare change from Baseline scores on the CANTAB ADHD battery with noise cancelling headphones and sham-controls. Evaluate performance on academic productivity measures (math and reading comprehension) while using either a noise cancelling headphone or a sham headphone control in the presence of standardized auditory distractors. • Compare change from Baseline scores on academic productivity measures with noise cancelling headphones and sham-controls. Evaluate subjective reports of experience using the noise cancelling headphones and sham-controls during the assessment tasks. • Compare the self-reports of noise cancelling headphones versus sham controls. Evaluate Safety • Evaluate any differences in self-reported adverse effects from using the noise cancelling headphones or sham controls.
Study Design	Overview This will be a proof-of-concept, randomized, within-subject cross-over design with the administration of noise cancelling headphones or sham headphones on two separate study days. Following screening and a baseline assessment session with no headphones, participants will be assigned to complete each experimental session. During each session, they will undergo the CANTAB and Academic tasks. The order of sessions will be randomized and balanced across participants to be either noise-cancelling headphones first followed by sham headphones; or sham headphones first followed by noise-cancelling headphones.



Bose-ADHD POC-001 Study Schematic

Inclusion/Exclusion Criteria	<u>Inclusion</u> • Age 6 to 18 at the time of parental informed consent. • Male or female. • Confirmed ADHD diagnosis at screening/baseline visit established via MINI-KID administered by a trained clinician. • Screening ADHD-RS-IV score ≥24. • Estimated IQ (measured with the KBIT-2) ≥80. • If currently medicated with a stimulant medication (amphetamine or methylphenidate formulation), off drug for a period of at least 48 hours prior to Baseline and Experimental Sessions. • Able to follow written and verbal instructions (English) as assessed by the PI and/or study coordinator. • Able to comply with all testing and requirements. <u>Exclusion</u> • Current controlled (requiring a restricted medication) or uncontrolled, comorbid psychiatric diagnosis, based on MINI-KID and subsequent clinical interviewing, with significant symptoms including but not limited to post-traumatic stress disorder, psychosis, bipolar illness, pervasive developmental disorder, severe obsessive-compulsive disorder, severe depressive or anxiety disorder, conduct disorder, or other symptomatic manifestations that in the opinion of the Investigator may confound study data/assessments (Participants with clinical history of learning disorders will be allowed to participate as long as the disorder does not impact their ability to participate based on PI judgement). • Current treatment with any non-stimulant medication for ADHD (e.g., atomoxetine, clonidine, guanfacine). • Current treatment with other psychoactive drugs. • Participant is currently considered at risk for attempting suicide by the

	Investigator, or is currently demonstrating active suicidal ideation or self-injurious behavior, as measured by MINI-KID Suicidality Module C. • Documented hearing loss. • Recent history or suspicion (within the past 6 months) of substance abuse or dependence. Any other medical condition that, in the opinion of the Investigator, may confound study data/assessments.
Study Protocol	<u>Recruitment & Randomization</u> 30 children ages 6 to 18 will be recruited to participate. Following a baseline assessment, participants will be randomized to receive 2 different sequences of experimental sessions (Noise cancellation headphones, then sham headphones; or sham headphones, then noise cancellation headphones). All participants will have a clinical diagnosis of ADHD and be willing to washout of any approved medication for 48 hours prior to the baseline and each experimental session. <u>Screening (Visit 1) Procedures</u> • Parental informed consent and participant assent will be obtained and demographic/contact. • MINI-KID to confirm ADHD and assess presence of any other exclusionary psychopathology; and any suicidal ideation or behavior. • Clinician-completed ADHD-RS to assess frequency/severity of ADHD symptoms. • KBIT-2 to assess estimated IQ/intellectual functioning. • Medical and developmental history, including current and past treatment. • Participants who meet all inclusion and no exclusion criteria following screening will be scheduled for a baseline visit within 21 days of screening. <u>Baseline (Visit 2)</u> • Participants and their parents/caregivers will be assessed for any adverse events or changes in medical status since the last visit. • Participants will complete the CANTAB ADHD battery with no headphones with standardized auditory distractors present. The CANTAB ADHD battery consists of the following subtests: Spatial Working Memory (SWM), Rapid Visual Information Processing (RVIP), and Stop Signal Task (SST). • Participants will complete the Academic Productivity tasks for both math and reading comprehension with no headphones with standardized auditory distractors present. • Participants will be fitted for the proper earbud size for headphones and practice inserting the earbuds. • Participants will be randomized to one of the two experimental sequences and scheduled for Visit 3, to occur 7±3 days following the baseline visit.

	Experimental Sessions (Visits 3-4) • Participants and their parents/caregivers will be assessed for any adverse events or changes in medical status since the last visit. • Participants will complete the CANTAB ADHD battery with either noise cancelling headphones or sham headphones control (depending on randomized sequence) with standardized auditory distractors present. The CANTAB ADHD battery consists of the following subtests: Spatial Working Memory (SWM), Rapid Visual Information Processing (RVIP), and Stop Signal Task (SST). • Participants will complete the Academic Productivity tasks for both math and reading comprehension with either noise cancelling headphones or sham headphone control (depending on randomized sequence) with standardized auditory distractors present. • Depending on which randomization sequence to which participants are assigned, either the noise cancellation or sham control earbuds will be used.
Analysis/Power Considerations	This study is designed as a proof-of-concept determination of the effects of noise cancelling headphones *vs.* sham headphone control on neurocognitive and academic outcomes. Power The current study is powered to detect a "moderate" yet clinically relevant effect size estimate of 0.50. Sample size calculations assumed a 2-tailed statistical test of size $\alpha = 0.05$, power $1\text{-}\beta = 0.90$, approximate normality of the test statistic, no period effect, equal carryover effects between the two sequences, a correlation between groups of 0.60, and equal variances between groups. Under these assumptions, a sample size of 28 will allow us to detect a "moderate" standardized effect size of 0.50 between the noise cancelling headphone condition and the sham headphone condition on the primary scalar outcome of interest. Data Analysis Data will be analyzed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA). Data will be tested for normality using the Kolmogorov-Smirnov 'Goodness of Fit Test.' For normally distributed data, *t*-tests will be used to compare outcomes between noise cancelling headphones and sham headphone controls; for data that are not normally distributed, Wilcoxon's test will be used. We will also investigate for the effects of sequence on the outcomes. This will be accomplished using analysis of variance (RMANOVA) with a within factor of 'noise cancelling headphones on first study visit' *vs.* 'noise cancelling headphones on second study visit.' Because of the use of multiple tests on the same set of data, alpha adjustment will be conducted in accordance with the Bonferroni-Holm procedure. We will also calculate Cohen's d values for all outcomes as an estimate for relevant effect size estimates for future studies. Missing data will be managed using standard multiple imputation procedures.

Study Table of Assessments

	Screening	Baseline	Experimental Session 1	Experimental Session 2
Visit	**1**	**2**	**3**	**4**
Day	**0**	**1-21**	**28±3**	**35±3**
Informed consent and child assent	X			
Demographic & contact information	X			
Medical & Developmental History, including current medication status	X			
MINI-Kid	X			
ADHD-RS	X			
KBIT-II	X			
Adverse Events	X	X	X	X
Concomitant Medications	X	X	X	X
Headphone Fit & Adjustment		X		
Randomization		X		
Subjective Experience			X	X
CANTAB		X	X	X
Academic Productivity Measures		X	X	X
Study Debrief				X