Title: Improving ADHD Teen Driving

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This supplement to the manuscript entitled "**Trial of Training to Reduce Driver Inattention in Teens with ADHD"** contains the following items:

1. Original grant with original protocol and original statistical plan (**Note: The grant that was submitted and funded by NIH reflects our original protocol and original statistical plan**)
2. Final protocol
3. Final statistical analysis plan (**Note: This document summarizes the statistical analytic plan for the set of analyses presented in the manuscript submitted for publication**)
4. Summary of changes to statistical analysis
5. Summary of changes to protocol

2. SPECIFIC AIMS

Operating a motor vehicle requires a complex set of skills, the most important of which is the ability to continuously visually attend to the roadway. The vast majority of motor vehicle crashes (MVCs) involve momentary visual inattention immediately before MVC[14]. In particular, glances away from the roadway that endure for more than 1.6-2.0 secs significantly increases risk for MVCs[13, 14, 16, 17].

Experienced drivers rarely exhibit extended glances away from the roadway. However, young, inexperienced drivers frequently glance away from the roadway for longer than 2.0 secs[6, 21]. This tendency towards extended glances away from the roadway contributes to the significantly higher risk of MVCs among teen drivers. Indeed, MVCs are the leading cause of death among teens[22] and despite the fact that they represent only 7.3% of all licensed drivers, teens account for 14% of all MVC-related deaths[23].

The 8% of teens with Attention-Deficit Hyperactivity Disorder (ADHD)[24] pose an even greater driving risk[1-3, 25] - an ADHD diagnosis doubles the risk for being repeatedly (>2) involved in MVCs[3]. Driving simulator studies with adults[26] and our own research with teens[27] has shown that patients with ADHD exhibit greater variability in their speed and lane position than individuals without ADHD. We have also demonstrated that teens with ADHD have 3-times more extended glances away from the roadway compared to teens without ADHD[28] (see Preliminary Data 5.a.2). Moreover, frequency of extended glances away from the roadway mediates the relationship between ADHD diagnostic status and poor simulator driving[28] (see Preliminary Data 5.a.3).

Though other factors (e.g., impulsivity, driving while intoxicated) may contribute to ADHD-related driving deficits, our findings and the existing literature[3] suggest that diversion of visual attention from the roadway for extended durations is a key mechanism in ADHD-related driving deficits and is an appropriate intervention target. **Hence, there is a clear need for targeted interventions to address the unique driving-related deficits in teens with ADHD[29, 30]**. A driving intervention targeting extended eye glances has been developed for typical teen drivers. The PC-based FOcused Concentration and Attention Learning (FOCAL[7, 18, 19]) intervention provides teens with an operational understanding of the dangers of extended glances and trains teens to limit the length of their glances away from the roadway. In randomized clinical trials, the intervention significantly reduces the number of extended glances away from the roadway among teen drivers[18, 19] (see Preliminary Data in Section 5.a.5).

Implementing the FOCAL intervention with teens with ADHD likely requires modification, as patients with ADHD often fail to generalize learned behavior to real-world situations[31, 32]. We thus propose an enhanced FOCAL intervention (FOCAL+) that integrates repeated training of the FOCAL-learned skills in a driving simulator with immediate feedback on extended glance behavior. Our preliminary data demonstrates that a single session of the FOCAL+ intervention model substantially reduces extended glances away from the roadway among teens with ADHD (see Section 5.a.4).

The goal of the proposed research is to empirically test the efficacy of the FOCAL+ intervention at improving visual attention and driving performance in teens with ADHD. Specifically, we will conduct a randomized controlled trial using 136 teens diagnosed with ADHD. Teens will be randomized to receive the FOCAL+ intervention or a sham intervention. At baseline, and 1-, 4-, 8-, and 12-months post-randomization, we will assess extended eye glances and driving performance outcomes in order to evaluate the breadth, magnitude, and persistence of intervention effects.

The **specific aims** of this study are as follows:

Aim #1: Examine short- and long-term efficacy of FOCAL+ intervention on decreasing rates of extended glances away from the roadway among teens with ADHD;
Aim #2: Examine short- and long-term efficacy of FOCAL+ intervention on improving driving performance (e.g., weaving, MVCs) among teens with ADHD;
Aim #3: Examine how many FOCAL+ training sessions are required to normalize extended glances away from the roadway among teens with ADHD.
Aim #4: Explore potential moderators of intervention efficacy.

The public health impact of improving the driving behavior of teens with ADHD cannot be overstated. In 2010, seven teens died every day from MVCs[33]. The 2-fold increased risk of MVCs among the 8% of U.S. teens with ADHD[3] contributes to these rates and begs for a targeted intervention that can ameliorate driving-related deficits in this high-risk group. Indeed, normalization of ADHD driving through intervention would translate into a reduction of 28,200 MVCs and as many as 27,950 MVC-related injuries and 250-related deaths per year here in the U.S.

3. SIGNIFICANCE

3.a Driving requires persistent visual attention to the roadway

Driving an automobile is largely a visual task that requires persistent (i.e., ~80-90% of the time) visual attention to the roadway[34, 35]. Orienting visual attention away from the roadway has been singled out as the primary cause of most MVCs[4, 36, 37]. Yet all drivers divert their visual attention from the roadway at times to perform both driving-related (e.g., checking speedometer) as well as non-driving related tasks (e.g., adjusting radio). In order to perform secondary tasks without impairing driving performance, drivers engage in "timesharing." Timesharing refers to a set of frequent and rapid eye movements (i.e., saccades) towards the secondary task and back to the roadway that are repeated until a task is completed[38, 39]

Multiple studies have demonstrated that the critical component of timesharing is to limit the duration of each glance away from the roadway to less than 1.6 - 2 secs,[13-17, 38, 40] which translates to approximately 160 feet of distance if driving 55 mph. Glances away from the roadway of > 2 secs lead to 3.6 times more lane departures[41] and are responsible for 86% of all MVCs[42].

3.b Teen driving

While experienced drivers rarely exhibit extended glances away from the roadway, inexperienced teen drivers frequently glance away from the roadway for > 2 secs while driving[5-7]. Teen drivers are also more likely to use distracting technologies (e.g., cell phones) while driving[43, 44] and are less effective at timesharing[6]. Accordingly, a recent national study examining in-vehicle event recordings of 1,691 teen MVCs found that 6 out of 10 teen MVCs are related to visual distraction from the roadway[8]. Given the effects of driver inexperience, propensity towards more extended glances away from the roadway, a willingness to use distracting technologies while driving, and being less effective at timesharing, perhaps it is not surprising that though teens only represent 7% of all drivers, they account for 14% of all MVC-related deaths[23]. While there have been major public health efforts to address teens' driving impairments (e.g., intensive education, graduated licensing, restrictions on driving with peers), the effectiveness of these efforts has been limited as evidenced by the fact that MVCs continue to be the leading cause of death among 16-18 year-olds[22]. Importantly, the most effective of these efforts (i.e., graduated licensing[45]) does not address individual factors that increase MVC risk[46].

3.c ADHD is an especially high-risk group

Teen drivers who meet diagnostic criteria for ADHD in adolescence have considerably higher risk of adverse driving outcomes[47, 48]. In a recent large, naturalistic driving study, drivers meeting diagnostic criteria for ADHD were 2.2 times more likely to have multiple collisions as drivers without ADHD[3]. Teens with ADHD receive twice as many traffic violations, are more likely to report receiving fines and points on their license and more likely to require remedial driving classes due to their violations than teens without ADHD[1, 2, 25, 48-50]. Teens with ADHD also report significantly higher rates of MVC than their peers[48]. During driving simulation, teens with ADHD exhibit greater variability in their speed[26, 27] and lane position[27] indicating poor vehicle control (See Preliminary Data 5.a.1).

To address ADHD-related driving deficits, we must better understand the mechanism contributing to higher accident risk among individuals with ADHD[29, 51]. When asked, individuals with ADHD who have been in a MVC cite inattention as the most frequent reason for MVC involvement[52]. In fact, inattention was cited twice as frequently as any other reason (e.g., alcohol use, road conditions, speeding) for causing their MVC[52]. Accordingly, recordings of in-vehicle episodes of visual inattention were the most frequent event immediately preceding collisions among drivers with ADHD[9], and our own data indicate that teens with ADHD exhibit more extended glances away from the roadway than teens without ADHD[28] (see Preliminary Data 5.a.2). Moreover, the number of extended glances away from the roadway mediated ADHD-related deficits in maintenance of a steady lateral lane position while driving, especially during engagement in a secondary task[28] (i.e., texting; See Preliminary Data 5.a.3). Extended glances away from the roadway accounts for 32.5% of the variance in standard deviation in lateral position (SDLP) – an indicator of weaving and highly correlated with risk of a real-world traffic accident[20, 53] Moreover, accounting for extended glances in the relationship between ADHD status and driving performance makes the path between ADHD status and driving performance non-significant. Though other factors (e.g., impulsivity, drunk driving, fatigue) contribute to ADHD-related driving deficits, our findings and the existing literature[3] suggest that diversion of visual attention from the roadway for extended durations when performing secondary tasks significantly contributes to ADHD-related driving deficits and is an appropriate intervention target.

3.d Need for driving interventions targeting teens with ADHD

There have been multiple calls for the development and testing of driving interventions that target teens at the highest risk for MVCs[29, 30] with increased recognition that some subgroups require additional strategies over and above strategies used for typical teens (e.g., graduated driver licensing)[29]. Given the incremental risk of an ADHD diagnosis on driving outcomes, especially among teen drivers, there is a clear and urgent need for driving interventions for teens with ADHD[54]. While ADHD medications, especially stimulants, are effective at remediating ADHD-related driving impairments[54-56], medications are only effective when they are taken and during the period of pharmacological effect. *Yet teens present with distinct temporal patterns in driving and MVCs that both peak during after-school late afternoons and evenings[8, 10-12] when stimulant medication effects are waning[57, 58].* The few non-pharmacological interventions that have been evaluated for resolving ADHD-related driving deficits target teen-parent interaction and hazard detection[54, 59]. Recent reviews of this ADHD driving intervention literature have emphasized that future development of driving interventions for teens with ADHD must be tailored to address the mechanisms contributing to ADHD driving deficits[29, 30, 54]. To date, no driving intervention studies for ADHD drivers have targeted visual attention while driving, which according to our data (see Preliminary Studies) is a key mechanism in driving deficits among teens with ADHD[28].

3.e Parallels between ADHD driving deficits and ADHD neurocognitive deficits

The apparent inability of teens with ADHD to periodically look away from the roadway for extended periods has distinct parallels to at least a couple documented ADHD-related neurocognitive deficits. First, one of the most consistent neurocognitive deficits observed in patients with ADHD at all stages of development and across many tasks (including attention tasks) is intra-individual performance variability (most often measured using SD of reaction times or RTs)[60]. While overall RTs of patients with ADHD on a cognitive task are comparable to those of typically-developing individuals, it is clear that periodically within the RT stream, patients with ADHD will exhibit intermittent instances of long RTs[61-63]. These are commonly interpreted as attention lapses[60] and have shown to correlate with rates of off-task behavior during academic tasks[64]. The neurocognitive parallel with periodic extended glances away from the roadway are these periodic long RTs or attentional lapses that are observed among patients with ADHD on attentional tasks.

A second potential ADHD-related neurocognitive deficit related to extended glances away from the roadway is an impaired sense of time. In particular, patients with ADHD have difficulty reproducing time durations[65-71], for time periods as short as 2 secs[72]. Moreover, the inability to accurately reproduce a time duration becomes more impaired in the presence of distraction[65]. The parallel between extended glances and time reproduction is that teens with ADHD may be unaware (or lose track) of the amount of time spent looking away from the roadway while driving.

3.f Attention mitigation driving interventions (the FOCAL intervention)

Donald Fisher, Ph.D., co-Investigator on this project, and his colleagues at the University of Massachusetts Amherst Human Performance Lab have developed a driving intervention for teen drivers that focuses on improving visual attention to the roadway. It is *a skills-training intervention* based on the assumption that performing secondary tasks in a safe manner while driving (i.e., without taking one's eyes off the road for extended periods) is a skill that requires training. FOcused Concentration and Attention Learning (FOCAL[7, 18, 19]) is a single-session computerized intervention that provides teen drivers with an understanding of the dangers of long glances away from the forward roadway and specifically trains teen drivers to limit their glances away from the roadway to ≤ 2 secs. See description of FOCAL intervention in Section 5.d.1.

The FOCAL training program has been tested in multiple randomized clinical trials using typical teen drivers[18, 19] (See Preliminary Results 5.a.4). At immediate post-test, teens in the FOCAL intervention engaged in fewer extended eye glances (≥2 secs) than teens who received sham intervention (i.e., learning rules of the road)[18]}. Further, during assessment on actual roadways, teens trained with FOCAL had extended glances in 49.9% of secondary task scenarios compared to 60.0% of the time for teens receiving no training[19]. In the latest evaluation of FOCAL, which involved parents in the training to help reinforce teen learnings during supervised driving, significant intervention effects on teens' glance behaviors were the strongest at 4 months post-training[18] (see Preliminary Data 5.a.4).

3.g Rationale for enhanced FOCAL intervention (FOCAL+)

While FOCAL has been effective for decreasing the duration of visual glances away from the roadway in typical teens, teens with ADHD present additional challenges that likely require adaptation of the FOCAL intervention in order to be effective. In particular, children with ADHD trained with skill-building interventions (e.g., social skills training) have consistently failed to generalize learned behaviors to actual behaviors outside of training[31]. For these reasons, Barkley[32] suggests that if skill building programs are to succeed, they must be instituted at critical points of performance in the natural ecology of the patient with ADHD. Further, patients with ADHD are able to adapt their behavior best when provided with immediate feedback on performance[73]. In

order to ensure that the skills learned during FOCAL generalize to actual roadway behavior, we have adapted the FOCAL intervention to include additional training during simulated driving with immediate feedback about glance behaviors. We anticipate that combining FOCAL training with ecologically-valid training in the driving simulator will help teens with ADHD to generalize their newly learned visual attention skills to actual driving. Indeed, a recent review of the ADHD driving literature concludes that a multimodal approach incorporating a driving simulator and including parental involvement will likely be most effective at improving driving outcomes among teens with ADHD[54].

Finally, it is likely that teens with ADHD will need more than one training session to learn and generalize these skills. Indeed, our preliminary data suggest that though a single FOCAL+ session reduces extended glances away from the roadway in teens with ADHD, they continue to exhibit a significant number of extended glances away from the roadway (see Section 5.a.5). Thus, additional training is desirable. The exact number of sessions needed to normalize ADHD teen's visual attention while driving is an important empirical question the proposed intervention is uniquely designed to answer. In determining a schedule for repeated training, we could either mass the practice (extend the length of the training sessions) or distribute trainings over time. The literature suggests that training works best when distributed over time [74]. Moreover, it is important with skill training to over-train so that performance becomes as automatic as possible [75]. Given the logistical constraints of repeated training, we decided that training should be undertaken four times, with a week between training sessions. See 5.d.2 for a more detailed description of the FOCAL+ intervention.

3.h Impact

The impact of this intervention on teens with ADHD as well as on the general public cannot be overstated. ADHD has many associated functional impairments (e.g., poor academic achievement, social deficits, lower self-esteem, familial distress, etc.); however, no ADHD-related impairment has greater potential health consequences than those related to poor driving. Driving deficits in teens with ADHD can lead to serious injury and possibly death for teens with ADHD, passengers in their cars, and all who share the roadway with them. Hence, there is a clear patient-level and public health need to develop interventions that improve ADHD-related driving impairments. As noted in a recent editorial on teenage driving, "a challenge for this emerging field is to identify the 'sweet spots' that balance the intervention's reach to the optimal population with program cost, timing, and acceptability" (p.703)[30]. By targeting teens with ADHD, we are targeting one of the highest risk groups of drivers on the road. Given an ADHD prevalence of 8% among teens[24], the proposed intervention has relevance to approximately 1 million teens with ADHD nationwide. Were our intervention to normalize ADHD driving and be disseminated to all teens with ADHD, the potential impact on rates of MVCs and injuries and lives lost due to MVCs could be substantial (i.e., a reduction of 28,200 MVCs, 27,950 MVC-related injuries and 250-related deaths per year).

4. INNOVATION

The proposed line of research is highly innovative for multiple reasons. First, this study directly targets a mechanism – visual attention – that directly contributes to driving risk in ADHD teens. Currently, there are no driving interventions that focus on ADHD-related driving skills deficits despite the concerns of parents of teens with ADHD relative to their teens driving[76]. Families, and society, desperately need interventions that can remediate driving risks for inexperienced, high-risk (i.e., ADHD) drivers.

Second, the intervention employs ***state-of-the-art*** *driving simulator and eye-tracking technology that allow training of a complex skill in a safe environment. We feel this is the only safe method for training teens with ADHD how to drive safely in the real world. Such simulation methods are used in the aircraft industry to train pilots to safely fly aircraft.* Moreover, when testing for short- and long-term intervention efficacy, we will employ both driving simulation and road tests, also with integrated eye-tracking, to objectively assess visual attention and driving performance during performance of secondary tasks. We will also use an innovative in-car camera system (i.e. DriveCam) to gather ecologically-valid data about real-world visual behavior and driving performance pre- and post-intervention. DriveCam technology has been used to elucidate ADHD-related driving deficits including higher rates of MVCs, high g-force events, and inattentive/distracted behavior while driving among adults with ADHD compared to adults without ADHD [77].

Finally, by conducting multiple sessions of FOCAL+ training, we will be able to determine how many training sessions are necessary for teens with ADHD to learn the trained skill (i.e., reducing the number of extended glances away from the roadway to the level observed among experienced drivers). Determining the length of intervention required will impact implementation in real world settings.

5. RESEARCH STRATEGY

5.a. Preliminary Studies

5.a.1 Teen drivers with ADHD have worse driving performance in a driving simulator[27]

A total of 61 teens (ADHD = 28, Control = 33) aged 16-17 with a valid driver's license completed a simulated drive. Each participant drove for three 10-minute periods. During each period, participants were either engaged in cell phone conversation, text messaging, or no distraction. Driving performance was assessed by measuring average speed, standard deviation (SD) in speed, and SD in lateral position for each condition. Across all conditions teens with ADHD exhibited worse driving behavior as evidenced by greater variability in speed ($p<.05$) and lane position ($p<.01$) than teens without ADHD. See Figure 1 for depiction of differences in SD of lateral position across ADHD and control groups and across conditions. *Covarying parent- or self-ratings of Oppositional Defiant Disorder (ODD) did not alter the statistical significance of these effects.* This study clearly demonstrates ADHD-related driving deficits and suggests that ADHD is a serious risk to driving performance. Moreover, these preliminary data demonstrate our ability to use a driving simulator to collect data on driving performance.

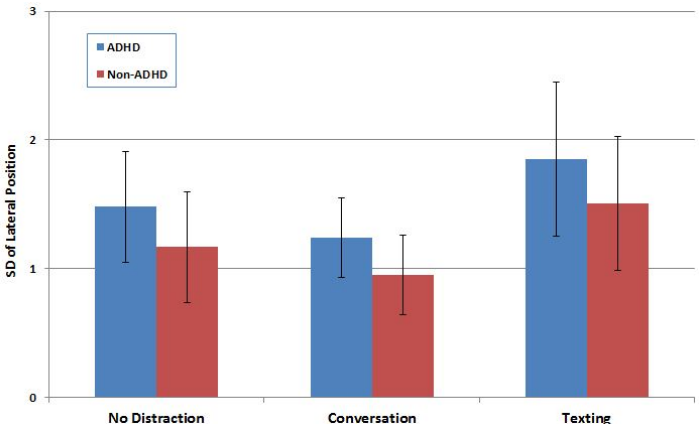

Figure 1: Group differences in lateral position across No Distraction, Conversation, and Texting conditions

5.a.2 Teen drivers with ADHD have increased numbers of extended visual glances away from the roadway during simulated driving[28]

We videotaped and behaviorally coded teens' glances while performing a secondary task (i.e., texting) during simulated driving. Teens with ADHD had significantly more glances away from the roadway lasting ≥2 secs than teens without ADHD ($p<.01$).See Figure 2. *Covarying ratings of ODD did not change this result.*

5.a.3 ADHD- and texting-related deficits mediated by extended glances[28]

We tested whether visual inattention mediated the relationship between ADHD and poor driving. We found that the number of extended glances (≥2 secs) away from the roadway mediated ADHD-related deficits in maintenance of a SDLP while driving during distraction (indirect effect beta=.10, SE=.07, $p<.05$). Notably, when accounting for extended eye glances as a mediator, the effect of ADHD on SDLP was non-significant (beta=.30, SE=.15, $p>.05$) suggesting that extended eye glances fully mediate the relationship between ADHD and driving problems. *Covarying ODD did not change this result.*

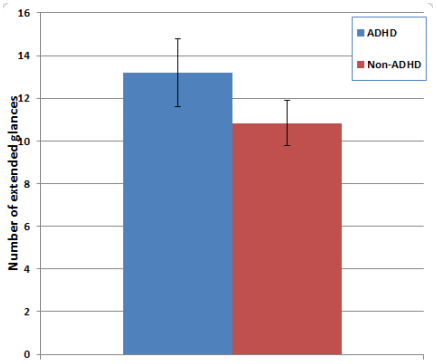

Figure 2: Mean number of extended visual glances away from the roadway for teens with and without ADHD while texting during a simulated drive.

5.a.4 Efficacy of FOCAL intervention among non-ADHD teens[18, 19]

Using a post-test only experimental design, 37 typical teen drivers (aged 16 and 17) were randomly assigned to FOCAL (n = 19) or a sham (n=18) intervention consisting of *Rules of the Road* training. FOCAL consisted of the computerized intervention described in Section 5.d.1. Driver eye glance behavior during a road test was recorded using a portable lightweight eye-tracker installed in a car. Only 19.5% of glances of teens trained using FOCAL exceeded 2 secs compared to 28.8% of glances among those in the sham group [i.e., a 30% reduction; $F(1,35)=4.57$, $p<.05$]. Teens were also tested in a driving simulator where a 50% reduction in the percentage of glances over a 2-sec threshold was observed among those who received FOCAL training compared to the sham intervention ($t_{38}=3.30$, $p<.005$).

In a separate study[18], 40 typical teens (aged 16-18) were randomly assigned to FOCAL or sham intervention. We demonstrated that the effect of training not only persists out to a 4-month follow-up assessment of visual attention during driving (FOCAL % of extended glances =19% vs. sham=29%, $t_{38} = 2.48$, $p<.05$) but are even stronger than immediate post-intervention assessment. In fact, the eye glance behavior of FOCAL-trained teens at 4-months post-intervention was not significantly different than rates of their parents (i.e., experienced drivers; percent of glances ≥2 secs for FOCAL trained teens = 19% vs. percent of glances ≥2 secs for experienced drivers = 11%).

5.a.5 Preliminary evidence of FOCAL+ efficacy in teens with ADHD

Twelve teens with ADHD (ages 16-17) participated in a preliminary randomized controlled trial examining the relative effectiveness of the FOCAL intervention compared to the enhanced FOCAL+ intervention (see Section 3.d.2). The FOCAL+ intervention consisted of FOCAL training followed by a training session in the

driving simulator. The enhanced FOCAL+ simulator training included a 10-minute driving simulation training during which an eye tracker monitored eye movements and provided the teen with immediate feedback (i.e., an auditory alarm) when visual glances away from the roadway exceeded 2 secs. To control for exposure to the driving simulator, teens randomly assigned to the non-enhanced FOCAL also had a 10-minute driving simulator session with eye tracking, however no feedback was provided regarding eye glances. All teens completed two 5-minute drives in the driving simulator before training (pre) and again immediately after training (post). The pre- and post-simulated drives consisted of driving along suburban roads with 4 “toll booth” events during which an on-screen alert notified the driver of a toll amount and teens were required to find and pay the correct amount by selecting identically-shaped coins from a container and paying the experimenter. Figure 3 illustrates the moderate decrease (pre-post effect size Cohen’s d =.64) in the number of extended (>2 sec) glances away from the roadway among teens randomly assigned to the FOCAL intervention and the substantial decrease (pre-post effect size Cohen’s d = 1.19) in the number of extended glances away from the roadway among teens randomly assigned to the FOCAL+ intervention. These data demonstrate 1) the excessive number of extended glances away from the roadway (i.e., approximately 2.5 extended glances away from the roadway per minute) among teens with ADHD at baseline; 2) the relative efficacy of the two interventions at exacting change on the eye glance behavior of adolescents with ADHD; and *3) that teens with ADHD are still exhibiting extended glances away from the roadway after a single FOCAL+ training session.*

5.a.6 Experience with sample retention

The PI (Epstein) was the site coordinator (and later co-Investigator) for the Multimodal Treatment Study of Children with ADHD (MTA)[78] at the Duke site. The retention rate for MTA participants at the Duke site at the 14-month assessment point was 97.9%. In addition, here at the Center for ADHD, the research team has conducted several NIH-funded ADHD treatment studies that have required retention of the study sample for 12 months. For example, in our most recent CCHMC-based ADHD treatment study (R34MH095911), the retention rate at 12 months was 94%.

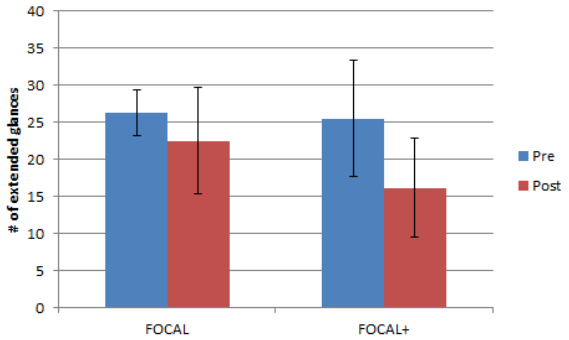

Figure 3: Mean number of extended visual glances away from the roadway across the two intervention groups before and after training.

5.b Overview of proposed research

Licensed teen drivers (aged 16-19) with ADHD (n=136) will be phenotyped and then randomly assigned to either (1) the computerized FOCAL driving intervention including visual attention training in a driving simulator (FOCAL+) over the course of 4 weeks, or (2) sham intervention using rules of the road taught over the course of 4 weekly sessions. At 1-, 4-, 8- and 12-months post-randomization, teens’ driving skills will be assessed using a driving simulator and a road test. In addition, the car most often driven by the teen will be outfitted with a DriveCam video event monitoring system to collect information about actual driving performance in real road conditions over the course of one year post-training. Finally, we will collect driving records covering the entire period of the study to assess the impact of the interventions on real-world driving outcomes such as MVCs and citations. *Analyses will focus on comparing driver visual attention and driving performance outcomes in the intervention vs. the sham intervention groups in an effort to determine whether the FOCAL+ training is superior to sham intervention for teens with ADHD. Consistent with findings from a longitudinal examination of FOCAL in neurotypical teens[18]. we expect nonlinearity in the response to this intervention with strongest effects occurring at follow-up . In order to test the short- and long-term effects of FOCAL+ compared to sham intervention we plan 4 follow-up assessments including an immediate post-intervention assessment (1-month) and 3 long-term follow-up assessments (4-, 8- and 12-months). Finally, exploratory analyses will examine whether any baseline driver characteristics (e.g., gender, psychiatric comorbidity) moderate treatment outcomes.*

5.c. Participants

136 teens (aged 16-19) with ADHD will be recruited to participate in the study. An ADHD diagnosis will be based on the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS[79]) interview with parent and adolescent.

Most of our ADHD research participants will be current or past patients at the Center for ADHD at Cincinnati Children’s Hospital Medical Center (CCHMC). Approximately 900 patients with ADHD are seen at our Center each year. We have over 2000 patients in our patient registry who have agreed to be contacted to participate in future research studies. 812 former patients within our patient registry will be in the 16-19 year

old age range during the course of this study. We foresee that we will be able to successfully recruit the majority of our sample using our Center's registry.

5.c.1 Inclusion criteria

1) Aged 16-19. **Rationale**: This age range represents the period of greatest driving risk[80].
2) Teens in ADHD group will meet DSM ADHD criteria for ADHD-Predominantly Inattentive Presentation or ADHD-Combined Presentation based on the K-SADS interview. **Rationale**: Inattentiveness - elevated in both of these ADHD subgroups - confers driving risk in teen drivers[81].
3) Possess a valid driver's license and regularly spend at least 3 hours per week engaged in unsupervised driving. **Rationale**: Must be legal for participant to drive independently since driving risk among teen drivers is greatest in absence of adult supervision[80]. Further, there is a need to collect ample DriveCam outcome data during unsupervised driving conditions to test for intervention effects. Other driving studies have used similar inclusion criteria for number of hours of independent driving[82].
4) IQ ≥80 as measured by the Wechsler Abbreviated Intelligence Scale-II (WASI-II)[83]. **Rationale**: Teens with cognitive challenges may not be able to understand intervention instructions.
5) Parent willing to participate. **Rationale**: Teens will be asked to refrain from taking medication on days of driving assessment (i.e., driving simulation). Since driving to our facility for testing without taking medication may put the teen at risk, a parent will need to agree to drive the teen to these visits. Parents will also be participating in the intervention (see Section 5.d.1).

5.c.2 Exclusion criteria:

1) On ADHD medication that cannot be washed out on assessment days. **Rationale**: Since we desire to test teens off medication on the assessment days, only medications with a half-life <12 hours can be allowed.
2) Drug or alcohol dependence. **Rationale**: Teens meeting criteria for drug or alcohol dependence according to K-SADS interview likely require more intensive and other interventions.
3) On psychotropic or neuroleptic medications. **Rationale**: These psychotropic medications often impact patient attention. Also, these medications cannot be titrated down quickly.
4) Require eye glasses (contacts acceptable) for driving (corrective vision restriction on driver's license). **Rationale:** The eye tracking equipment that will be used during driving simulation and the road test to measure eye glances cannot be used if the participant is wearing glasses.

5.d Description of FOCAL+ and Sham Intervention Groups

5.d.1 FOCAL+ Intervention

Initially, and then once a week for the next 4 weeks after the initial training, teens with ADHD randomized to the FOCAL+ intervention will participate in FOCAL+ training sessions (total of 5 sessions). FOCAL training begins with the Attention Maintenance Assessment Program (AMAP). AMAP is a computerized program designed to assess visual attention. During AMAP, the computer screen is split horizontally in order to simulate distracted driving. Participants can either view a windshield-view video of driving in the top portion of the screen (primary task) or view a map on the bottom portion of the screen (secondary task). Participants toggle between views by pressing the spacebar on the keyboard. Only the top or bottom view is visible at any one time with the non-selected portion of the screen blacked out. Although blacked out when viewing the map, the video of the drive continues to progress in real time while the map is being viewed. During AMAP, the participant is given three street names. By toggling between the views of the top and bottom halves of the display, they are asked to identify street signs in the driving video (top portion) while concurrently determining whether the street names exist on the map (bottom portion).

After AMAP, feedback and training begin in four separate phases. (1) Participants learn to appreciate how long they looked away from the driving scenario during AMAP by viewing their own AMAP performance. During this viewing the top portion of the screen (simulated video drive) is blacked out for as long as the participant viewed the map during the AMAP testing. For example, if the teen diverted his attention to the map for 3.8 secs during the initial driving task, the screen is blacked out for the same 3.8 secs during video playback. (2) In a subsequent feedback period, the AMAP video is played back again with a blacked out screen during times the teen was looking away. In addition, a timer is added to the screen to show the teen how long they looked away during each instance. (3) Next, teens are again asked to watch a 3-minute driving video while performing the map search (just as in AMAP). However, during these trials, teens are instructed to initially limit their glances towards the map to ≤3 secs. They learn to limit their glance durations to the threshold duration in two steps. In the first set of trials, the map is displayed for exactly the threshold duration. In the next set of trials, teens control the duration of the map display during 3-minute drives. They receive an auditory warning when their glance away from the roadway to the map extends beyond 3 secs. The participant repeats the task until no glances exceed 3 secs for the duration of the 3-minute drive up to a maximum or 3 extra 3-minute drives. (4) In

the last phase, the same two steps are repeated in this fourth phase as were repeated in Phase 3 but with a 2-sec threshold. Due to concerns that teens with ADHD might have decreased ability to generalize the visual glance skills they learn during FOCAL training to actual driving conditions[31, 32], we have enhanced the FOCAL intervention to specifically train generalization to a driving environment. Immediately following each FOCAL training session, teens will enter the driving simulator equipped with eye tracking technology. They will complete two 5-minute drives. During the drives, approximately once per minute, the driver will be alerted with an auditory tone that they need to search for the letter "A" within a 32x32 array of letters on the screen located within a computer monitor situated within a virtual dashboard. They will need to indicate whether the A was present or absent with a button press. They will be given 20 secs to complete the search. During the FOCAL+ drive, the eye tracker will monitor eye glances and teens will be provided with real time immediate auditory feedback when a visual glance away from the roadway exceeds 2 secs. Specifically, an auditory alarm will sound when the glance duration exceeds 2 secs and will continue to sound until visual gaze returns to the roadway. All teens will complete two 5-minute drives under these conditions. However, if a teen is still demonstrating any glances away from the roadway that are ≥2 secs, they will complete additional 5-minute drives under the same conditions until they succeed in having no ≥2 secs glances during the 5-minute drive up to a maximum of 3 extra 5-minute drives. Each training session lasts approximately 1.5 hours.

During the initial training session, as teens are completing the FOCAL+ training, parents will complete the FOCAL training in a separate room so that they can learn the skills being taught to the teen and can thereafter provide feedback to the teen regarding extended visual glances during supervised driving.

5.d.3 Sham intervention: *Similar to teens randomized to the FOCAL+ intervention, teens with ADHD randomized to the sham intervention will engage in sham training initially and then once a week for the next 4 weeks after the initial training (total of 5 sessions).* The first hour of each training session will consist of computer-based training about the rules of the road. Teens will learn about traffic codes, laws, and rules of the road. In order to control for the extra time that teens assigned to FOCAL+ will spend in the driving simulator during FOCAL+ training, teens in the sham intervention will also drive in the driving simulator after each training session for a comparable length of time (i.e., two 5-minute sessions). This time in the driving simulator will be contextualized as a time for them to practice the rules of the road they learned during training. Importantly, teens in the sham intervention group will NOT receive any feedback regarding their eye gaze during simulated driving. Parents will also participate in the PC-based rules of the road training separately from the teen. This is the same sham intervention used in the preliminary study assessing long-term efficacy of the FOCAL intervention (see Section 5.a.4).

5.e Measures

Study measures (See Table 1 on following page) include those needed for (1) establishing inclusion criteria (IN); (2) assessing intervention outcomes (O); (3) measuring potential moderators of treatment outcome (M); (4) potential covariates (C); and (5) evaluating satisfaction and perceived effectiveness of the intervention (S). Note that some measures may serve more than one purpose. Since stimulant medications can impact driving performance, we will request that participants refrain from taking stimulant medications on the day of the assessment.

5.e.1 Description of measures

Vanderbilt ADHD Parent and Teacher Rating Scales[84]: *This DSM-based checklist allows parents and teachers to each rate the teen on each of the 18 ADHD core symptoms. Parents and teachers also rate the teen on a variety of domains of functional impairment.*

Conners-3 Self-Report[85]: *This self-report checklist allows adolescents to rate themselves on ADHD core symptoms as well as their perceptions of their own learning problems, aggression, family relations, etc.*

Estimates of Driving Ability Questionnaire[86]: Individuals with ADHD overestimate their abilities in a variety of contexts (e.g., social, academic[87]), a phenomenon known as positive illusory bias. Teens will be taught the concept of percentiles and then be asked to provide a percentile ranking of their driving ability. After completing the driving simulator assessment at baseline, participants will also be asked to percentile rank their driving performance in the simulator. Discrepancy scores will be created by comparing individual's perceived percentile ranking to actual driving performance percentile rankings based on the performance of neurotypical controls available through the University of Massachusetts Amherst Human Performance Laboratory. Discrepancy scores indicate positive illusory bias of driving ability in teens and will be used to assess whether positive illusory bias moderates intervention outcomes.

Go/No-Go task: The Go/No-go task consists of 300 stimuli which appear on the computer screen, one at a time, each for approximately 500 milliseconds. The inter-stimulus interval will be 3 secs. The task will last for 12 minutes. Participants are instructed to press the response pad for every stimulus except for the target

stimulus (e.g., the letter "X"). The event rate, or percentage of trials when non-target stimuli (e.g., other letters) appear, will be 90%. Reaction time will be measured from the point at which a target stimulus appears on the screen until the response pad is depressed. The primary outcome measure on this task will be the ex-Gaussian indicator of RT skew, tau. Tau is a robust estimator of intra-individual variability (IIV)[63, 88, 89] and will be tested as a moderator of treatment outcomes.

Temporal reproduction task[90]: Twenty presentations of a visual stimulus (i.e., a light bulb) appear on a computer screen for ½, 1, 2, 3, or 4 secs. At the end of each presentation, the participant is asked to reproduce the duration of stimulus presentation by holding down the spacebar for the same duration as the stimulus was presented. Absolute discrepancy scores are computed by comparing estimations of the interval to the actual stimulus duration. These discrepancy scores will be tested as a moderator of treatment outcomes.

Behavior Rating Inventory of Executive Function: (BRIEF)[91]: There are separate parent- and self-report versions of this questionnaire which assess executive functioning in teens. Scale scores include various aspects of executive functioning (e.g., Inhibit, Emotional Control, Working Memory, and Monitor). Baseline scores on executive functioning will be evaluated as potential moderators of treatment response.

Pittsburgh Sleep Quality Index (PSQI)[92]: The PSQI is a self-rated questionnaire which assesses sleep quality and disturbances. Several aspects of sleep are assessed by this scale including sleep latency, duration, sleep disturbances, use of sleeping medication, and subjective sleep quality. We will evaluate sleep quality and quantity as a potential covariate in our outcome analyses.

Services Use in Children and Adolescents-Parent Interview (SCA-PI); Service Barriers and Attitudes[93]: This brief structured interview conducted with the parent captures adolescent services use across mental health, primary care, school, and community settings. Medication use data acquired from this interview will be entered as a covariate into our statistical modeling.

Consumer satisfaction questionnaire: Teens and parents will complete a consumer satisfaction questionnaire asking them about their own opinions of the intervention. Questions will focus on the following domains: 1) appreciation of intervention format including length, setting, computer interface, etc.; 2) perceptions of whether they felt that the intervention might help them drive better; and 3) whether they would recommend this intervention to other teens.

Driving simulation (**primary outcome measure**): *In addition to testing at baseline and each of the major assessment points, a driving simulation assessment will also occur for participants in both intervention groups immediately preceding each of the weekly training sessions. This will allow an examination of the number of weekly training sessions that are needed to reduce extended glances away from the roadway to levels seen among experienced drivers. Note that in order to reduce overlap between the FOCAL+ simulator training and simulator assessments, the driving scenarios will differ across these two situations.*

To assess driving performance, participants will complete a simulated drive in a driving simulator with an integrated eye-tracking system (see Facilities and Resources page). Participants will complete a 5-minute practice drive consisting of a highway drive with both straight and curving road sections with other vehicles present. After acclimating to the driving simulator, participants will complete two 15-minute drives. During each drive, the participant will engage in one secondary task per minute for a total of 28 secondary tasks. The secondary task will consist of searching for correct change akin to finding correct change for a toll booth. The driver will be alerted by an on-screen sign identifying the amount of change needed. Drivers will search through a fixed container with identically shaped coins, though with different amounts written on each coin, for the correct change amount. *Throughout the drive, a variety of situations known to increase the risk for MVCs (e.g., poor weather, car unexpectedly pulling out in front of driver) will occur intermittently.*

Eye gaze, driving speed and lateral position will be sampled continuously. Using ISO 15007-2[94] and SAE J-2396[95] criteria which standardize definitions and metrics related to the measurement of driver visual behavior, we will identify eye glances away from the roadway. Eye gaze data will be summarized by calculating the number of extended (≥2 secs) glances away from the roadway, which will be our primary outcome for visual behavior during driving.

Using driving simulator data, we will calculate number of MVCs, average speed, SD speed, and SDLP. Note that SDLP has high test-retest validity (r=.80) as it does not differ across AM or PM driving nor does it differ significantly as a function of traffic or weather[53]. Importantly, SDLP is sensitive to treatment effects[53]. Lane position variability is highly correlated with leaving one's lane of traffic[96], and leaving one's lane significantly increases risk for MVCs[8]. Some studies have shown correlations as high as .96-.99 between SDLP and the risk of having a traffic accident[20]. In our own data we found that SDLP in the driving simulator correlated .38 (p<.05) with self-reported MVC among ADHD teens. Hence, SDLP is a critical driving performance outcome[97] and will be our primary driving performance outcome. Simulated driving performance

explains over two-thirds of the variability in actual on-road driving[98] suggesting that driving simulation is a valid method for assessing driving performance.

Road Test (secondary outcome measure): We have contracted with a local driving school (see letter in Appendix) to use their instrumented vehicle and Certified Driver Rehabilitation Specialists (CDRS). The instrumented vehicle has a "student driver" sign on top of the vehicle and is outfitted with dual foot pedal brakes. A CDRS has completed comprehensive training and education programs in order to plan, develop, coordinate and implement driver rehabilitation services for individuals with disabilities. The CDRS will be seated in the passenger seat and will intervene with braking if necessary. The teen will be seated in the driver's seat and will be instructed by the CDRS to traverse a fixed 10-mile set course consisting of urban and suburban environments. At five points during the drive, the teen will be prompted by the instructor to engage in a variety of safety-critical tasks (e.g., turning on window defroster; see Protection of Human Subjects 6.a).

The vehicle also has a "Five-Camera Mobile Lab" system (termed iHERE) that digitally records the views to the front, left and right of the vehicle using three roof-mounted cameras and the view of the two front tires using two cameras mounted on the side mirrors. The outputs of all five cameras are run into a video multiplexor that combines and time-stamps the video signals into one split screen image. This combined signal is then recorded on digital videotape using a MiniDV video recorder. The system is entirely mobile and is configured to be installed in any vehicle within minutes using high-powered magnets (see Facilities). The indicator of driving performance is the number of lane crossing events excluding purposeful lane changes (e.g., changing to the right-hand lane to make a right turn). *We will use standard operating procedures for conducting the measurement of SDLP using data gathered from the road test as described by Verster & Roth (2011) [53]. Importantly, these procedures have been applied in psychopharmacological research for over 30 years[53]. In addition, the number of lane crossings will be divided by the number of miles (i.e., 10 miles) to arrive at an indicator of number of lane crossings as an additional indicator of driving performance on the on-road test.*

In addition, the teen will wear Tobii eye-tracking glasses while driving during the road test in order to measure eye movements. The Tobii glasses consist of binocular eye tracking sensors and are outfitted with a scene camera and audio recording capabilities. The resulting interleaved video is stored on the same on-board digital video recorder that will store the iHERE video. Labstreaminglayer software (Swartz Center for Computational Neuroscience) will unify the separate video streams and will time-synchronize and time-stamp the multiple streams into a single video file. Also, the Tobii software will convert the Tobii eye-tracking data into a separate digital video file which can be played back with a view of the driving scene (as seen through the driver's point of view) with the driver's gaze represented by crosshairs superimposed on the video. Similar to the driving simulator eye gaze data, we will use ISO 15007-2[94] and SAE J-2396[95] criteria to identify extended (≥2 secs) glances away from the roadway and will use the total number of these extended glances as an indicator of eye gaze activity during the road test drive. *Note that this road test was developed by co-I Fisher and has demonstrated sensitivity to FOCAL intervention effects[19].*

DriveCam event recording (secondary outcome measure): The DriveCam device is an event-triggered palm sized pair of cameras that are mounted to the rear view mirror of the participant's car. The device has a forward-road facing camera and another camera that faces the driver. Both cameras continuously record but only save to memory when a built-in accelerometer exceeds a set g force threshold. When the accelerometer detects a motion that exceeds this threshold, the device automatically records the 10 secs before and 10 secs after the triggered event. The external research division at DriveCam has agreed to work with us, as they have with other research groups[99], to lower the g-force threshold for this study in order that we can obtain snippets surrounding extreme g-force incidents (i.e., swerving or hard braking resulting in a g-force of .6 or higher) as well as routine driving events such as making a turn or changing lanes (i.e., events that produce g-forces in the range of .4-.5). The DriveCam will be installed at the time of training and will remain in the car for 1 year.

All video is time- and date-stamped and transferred to our servers daily through wireless communication. The DriveCam technology will also be programmed to record the onset and offset of driving. In addition, global positioning capability within DriveCam will allow tracking of miles driven for each drive. Using this information, we will be able to determine how many hours and miles the car was driven by the teen. We will also be able to determine from this video whether other people (e.g., parents, other adults, or friends) were present in the car during each driving episode. We will also use an established coding system[8] to record general background (e.g., time of day) and environmental (e.g., weather, road type) variables surrounding the MVC.

Any g-force event that exceeds .6 g-force will be coded using three primary codings: 1) incidents (i.e., a threshold exceedance in which the driver's action, either intentional or unintentional, was responsible for a safety-relevant event), 2) crashes (i.e., collision with another vehicle or object), and 3) near-crashes (i.e., an evasive maneuver performed to avoid a MVC). Video recordings of the driver will be coded for whether an

extended glance away from the roadway preceded the event, along with the length of the glance away from the roadway and the temporal proximity of that glance to the actual event. Also, since most incidents will be preceded by an extended glance away from the roadway, incident-related video recordings will not provide an adequate sample for examining typical eye glance behavior. Hence, we will also collect and code an additional 60 randomly-selected 20-second clips from low threshold events.

The primary outcomes we will obtain from these data will include the number of incidents, crashes, and near-crashes per hour driven. Also, we will be able to determine the number of incidents preceded by ≥ 2 sec glance away from roadway per hour driven as well as a general number of extended glances away from the roadway from the random clips.

In addition, since we will NOT be asking teens to terminate medication during this naturalistic assessment of driving, we will need to record information about ADHD medication use including medication type and dosage. Families will be queried about ADHD medication prescriptions at each clinic assessment using the SCA-PI interview (see above). Further, families will use a medication event monitoring system (MEMSCAP™) over the course of the year to electronically track date and time of medication administration.

Review of driving records: Participants' driving records from the Bureau of Motor Vehicles dating back from licensure and extending until 1-year post randomization will be obtained. We will record the number and type of traffic violations, incidents of driving while intoxicated, license suspensions and revocations, and MVCs.

Table 1: Schedule of measures

					Post-Randomization			
Measure	**Done By**	**Purpose**	**Time to complete**	**Screening/ Baseline**	**4-week training**	**1-, 4- 8-, and 12 month assessments**		
K-SADS	A,P	IN,M	90 m	X				
VAPRS	P,T	M	5 m	X				
Conners-3 Self-Report	A	M	5 m	X				
WASI-II	A	IN,M	30 m	X				
Driving Ability Quest.	A	M	10 m	X				
Temporal Reproduction	A	M	15 m	X				
Go/No-go task	A	M	30 m	X				
BRIEF	A, P	M	10 m	X				
PSQI	A	M,C	10 m	X		X	X	X
SCA-PI	P	C	20 m	X		X	X	X
Driving Simulator	A	M,O	30 m	X	WEEKLY	X	X	X
Road Test	A	M,O	20 m	X	1st SESSION	X	X	X
DriveCam	A	M,O	N/A	X	← CONTINUOUS →			
Driving Records	N/A	O	N/A	X	← X			
Consumer Satisfaction	A	S	5 m			X	X	X

Notes: A=Adolescent; P=Parent; T=Teacher; IN=inclusion measure; M=moderator measure; C=covariate measure; O=outcome measure; S=Satisfaction measure

Note about driving measures: Four different driving outcomes will be utilized for assessing driving performance. There are trade-offs for each measure in terms of its use during training (e.g., raising concerns about training to the task), whether the driving environment can be controlled (e.g., assigning distracting secondary tasks), whether eye glance behavior can be measured during driving, and each tasks ecological validity. These trade-offs are outlined in Table 2. No single measure is ideal. However, by including all four measures, we feel that we are comprehensively assessing driver's visual behavior and driving performance.

Table 2: Driving measure trade-offs

	Not used during training	Can control environment	Able to measure eye glances	Ecologically valid
Simulator		X	X	
Road test	X	X	X	
DriveCam	X		X	X
Driving records	X			X

5.f Analyses

5.f.1 Missing Data: Although every effort will be made to avoid having missing data when a teen withdraws from the study or a data point is missed, missing data due to attrition is common in longitudinal studies. *However, as noted in Section 5.a.6, we have demonstrated high rates (>90%) of retention in other*

ADHD treatment studies. That said, if a participant drops from the study, we will replace that participant with a new participant in order that we are adequately powered to test our study hypotheses. Moreover, we will utilize maximum likelihood estimation to address data assumed missing at random. A missing data attrition analysis will be performed using SAS PROC MI to identify potentials for non-random or systematic attrition (MNAR) related to key independent and dependent variables. In cases of MNAR missing data, selection and pattern mixture models will be used to appropriately address non-random attrition.

5.f.2 Analyses

5.f.2.a Analytic Plan to Address Aims 1 & 2

Aim #1: Examine short- and long-term efficacy of FOCAL+ intervention on decreasing rates of extended glances away from the roadway among teens with ADHD

Hypothesis #1*: Teens with ADHD assigned to the FOCAL+ intervention will evidence fewer extended glances away from roadway immediately following initial training, and 1-, 4-, 8- and 12-months post randomization compared to teens with ADHD assigned to the sham intervention.*

Aim #2: Examine short- and long-term efficacy of FOCAL+ intervention on improving driving performance among teens with ADHD

Hypothesis #2*: Teens with ADHD in FOCAL+ will exhibit more improvements in driving performance immediately following initial training, and 1-, 4-, 8- and 12-months post randomization than teens with ADHD in the sham intervention group.*

The *hypotheses listed above will use the same statistical modeling. For each analysis, every randomized teen will be kept in the analyses (i.e., intent-to-treat approach). Mixed factorial ANCOVAs will be used to analyze the data. The two independent variables in the analyses will be Intervention (FOCAL+ vs. Sham Intervention) and Time (immediately after initial training, and 1-, 4-, 8- and 12-months post- randomization). Months of driving experience will be covaried. To test Hypotheses 1, the primary dependent variable will be the number of extended (>2 sec) glances away from the roadway during driving simulation. Secondary analyses testing Hypotheses 1 will focus on other visual attention outcomes across the intervention groups including number of extended glances away from the roadway during the road test.*

To test Hypotheses 2, the primary dependent variable will be SDLP during driving simulation. Secondary outcomes for Hypotheses 2 include 1) number of MVCs and reaction time to unexpected events during driving simulation, 2) number of lane crossings and proportion of time out of lane during the road test, 3) number of incidents, near-crashes, and crashes per hour during DriveCam monitoring; and 4) rates of MVCs from teen's driving records. When examining DriveCam outcomes, we will add a time-varying covariate indicating medication use to account for the effects of medications on driving outcomes.

For each statistical model, the term of interest is the main effect of Intervention. A significant main effect of Intervention would indicate that the FOCAL+ intervention significantly impacted eye glance and driving outcomes. A significant Intervention effect will be followed up with post-hoc comparisons to determine the direction and locus of the effect, including whether intervention effects were maintained at 4-, 8-and 12-months post-training. Though we expect intervention effects to be strongest immediately following training (1-month), we predict that FOCAL+ will be more effective than the sham intervention for ADHD teens at each time point.

5.f.2.a.1 Power Analyses for Testing Hypotheses 1 & 2: *Effect size estimates from our preliminary data (Section 5.a.5) suggest a single FOCAL+ training session improves extended eye glances among teens with ADHD with an effect size (Cohen's d) of 1.19. Since this effect size will surely diminish over the course of the 1-year of assessments, we used a conservative effect size estimate of .6 to power our research hypotheses. Monte Carlo simulation power analyses were performed under the following assumptions: (a) FOCAL+ effect size of .6, (b) effect size of .10 for our sham intervention, and (c) inclusion of months of driving experience as a covariate. Power analysis with these assumptions indicate that sample sizes of N = 41 per group will result in power $\geq$ .80 to detect a significant main effect of Group indicating that the FOCAL+ intervention results in significantly fewer extended glances compared to the sham group at all post-baseline time points. We've powered our study with a larger sample size in order to detect potential moderators of treatment response (see Section* 5.f.2.c *below). Using the proposed sample size of 68 participants per group will provide use with 99% power to detect treatment effects.*

While data has been collected examining the efficacy of the FOCAL+ intervention on extended eye glances, the efficacy of the FOCAL+ intervention on driver performance has not been addressed. However, we assume a comparable intervention effect for FOCAL+ on driving outcomes based on the following pieces of evidence. Since the Pearson correlation between extended eye glances and collision events in the driving simulator is .74[42], we will assume that the effect size for intervention effects on driving outcomes will be

comparable to what has been found for extended glances and that we will have >90% power to detect intervention effects on driving performance outcomes as well.

Aim #3: *Examine how many FOCAL+ training sessions are required to normalize extended glances away from the roadway among teens with ADHD.*

5.f.2.b Analytic Plan to Address Aim #3: *The initial FOCAL+ training session as well as the 4 weekly FOCAL+ training sessions will be preceded by a 30-minute driving assessment composed of driving simulation and eye tracking. Each of these assessments will yield the number of >2 sec glances away from the roadway during the 30-minute simulated drive. With a goal of negating 2 sec glances away from the roadway to a frequency similar to that exhibited by experienced drivers (based on the performance of experienced drivers available through the University of Massachusetts Amherst Human Performance Laboratory), we will be able to determine for what percentage of teen drivers with ADHD the initial training is sufficient to achieve this criterion. Similarly, the percentage of drivers who are able to negate 2 sec glances away from the roadway can be determined for each of the weekly training sessions with the explicit goal of determining the number of training sessions required to reach this goal among teens with ADHD.*

Finally, we will be able to examine whether intervention-related improvements mediates the effects of training on driving performance outcomes. Specifically, for participants assigned to FOCAL+ training, we will have data regarding improvement in extended eye glances during weekly driving simulation. To examine whether improvement in extended eye glances during training mediates intervention effects on glance- and driving outcomes, we will compute indirect effects by multiplying the beta coefficient for the relationship between intervention and improvement in extended glances away from the roadway and the beta coefficient for the relationship between improvement in extended glances and driving outcomes[100]. Confidence intervals for these indirect effects will be estimated using bootstrapping (SAS PROC PROCESS).

Aim #4: Explore potential moderators of intervention efficacy.

5.f.2.c Analytic Plan to Address Aim #4: While we have a lengthy list of possible variables that may moderate intervention response, we have identified baseline rate of extended glances away from the roadway, intra-individual variability (IIV) in RTs, temporal reproduction task scores as the most likely moderators of intervention response. We have selected baseline rate of extended glances away from the roadway, IIV, and temporal reproduction task scores as potential moderators because we feel that teens with high rates of extended glances, poor temporal reproduction, and/or high levels of IIV at baseline may be more responsive to the proposed interventions because the FOCAL+ intervention targets the likely mechanism behind these teens' poor driving behavior. *ADHD symptom severity as rated by parent and teen will also be explored as potential moderators as some have reported that each additional ADHD symptom increases the risk for collisions by 16-17%[3]. Finally, psychiatric comorbidities such as ODD and CD will be explored as moderators since some have suggested, though our data do not support, that ODD/CD comorbidity accounts for a sizable portion of ADHD-related driving deficits[1].* Moderation will be explored using regression models including the main effect of intervention group, the main effect of the moderator variable (e.g., IIV), and the Intervention x Moderator variable interaction predicting the primary outcome measures (e.g., SDLP). *The proposed sample size provides 80% power to detect the statistical significance of the Intervention x Moderator interaction term*.

5.f.2.d Teen Satisfaction with intervention: Teen satisfaction will be analyzed descriptively and by comparing satisfaction across groups. It is expected that the overall satisfaction scores for the FOCAL+ will be higher than those observed for the sham intervention group.

5.g Alternative designs considered

5.g.1 Inclusion of non-ADHD teens: We considered this modification but since FOCAL has already been established as an effective intervention approach for non-ADHD teens[7, 18, 19], we decided that the focus of this research should be to assess a driving intervention that targets a high-risk group (i.e., ADHD teens). Investigators have called for driving interventions that focus on remediating driving risk in high-risk drivers[30].

5.g.2 Inclusion of FOCAL-only intervention arm: Our preliminary data suggest that the FOCAL intervention alone is less effective than the enhanced FOCAL+ intervention for teens with ADHD. While it would be interesting to determine whether the simpler FOCAL only intervention might work for teens with ADHD, the first step in developing this intervention should include the intervention approach that is likely to be maximally effective (i.e., FOCAL+) in teens with ADHD. Moreover, the costs of including a third intervention arm (i.e., FOCAL only) as well as including non-ADHD teens (see Section 5.g.1) would limit our ability to conduct the comprehensive multi-method, multiple time point (i.e., 1-, 4-, 8-, and 12-months post-randomization) assessment of treatment effects we now propose in this application. Also, it would limit our ability to power our test of treatment moderation (see Section **5.f.2.c**).

6. PROTECTION OF HUMAN SUBJECTS

6.a Risks to Human Subjects

Human Subjects Involvement, Characteristics, and Design

Over the 5 year study period, we will recruit 136 teens with *ADHD* between the ages of 16-19 years and one of their parents to participate. Most research participants will be current or past patients at the Center for ADHD at Cincinnati Children's Hospital Medical Center (CCHMC). Approximately 900 patients with ADHD are seen at our Center each year. We have over 2000 patients in our patient registry who have agreed to be contacted to participate in future research studies. 812 former patients within our patient registry will be in the 16-19 year old age range during the course of this study. In particular, a describing the study will be sent out to past patients and research participants at the Center for ADHD who indicated they were interested in being informed about future research studies. We also plan to recruit from the community using flyers. Finally, the study will be advertised on the CCHMC social media page using IRB approved web and flyer text. We foresee that we will be able to successfully recruit the majority of our ADHD sample using our Center's registry. However, we are also prepared to recruit participants through referrals from other specialty clinics within CCHMC (e.g., Teen Health Clinic).

We are focusing on 16-19 year olds as this population is especially vulnerable to involvement in MVCs[22]. Participants must currently meet diagnostic criteria for DSM-5 ADHD based on parent and self-report using a semi-structured interview. Given the high comorbidity rate of other mental health conditions with ADHD[101], participants will not be excluded based on the presence of comorbidity, with the exception of the presence of a condition that could impact the individual's ability to understand the intervention such as a developmental disorder or if they are taking a psychotropic medication that cannot be titrated down quickly and easily and might have some impact on driving performance. See inclusion/exclusion criteria below.

Inclusion criteria

1) Aged 16-19. **Rationale**: This age range represents the period of greatest driving risk[80].
2) Teens in ADHD group will meet DSM ADHD criteria for ADHD-Predominantly Inattentive Presentation or ADHD-Combined Presentation based on the K-SADS interview. **Rationale**: Inattentiveness - elevated in both of these ADHD subgroups - confers driving risk in teen drivers[81].
3) Possess a valid driver's license and regularly spend at least 3 hours per week engaged in unsupervised driving. **Rationale**: Must be legal for participant to drive independently since driving risk among teen drivers is greatest in absence of adult supervision[80]. Further, there is a need to collect ample DriveCam outcome data during unsupervised driving conditions to test for intervention effects. Other driving studies have used similar inclusion criteria for number of hours of independent driving[82]
4) IQ ≥80 as measured by the Wechsler Abbreviated Intelligence Scale-II (WASI-II)[83]. **Rationale**: Teens with cognitive challenges may not be able to understand intervention instructions.
5) Parent willing to participate. **Rationale**: Teens will be asked to refrain from taking medication on days of driving assessment (i.e., driving simulation). Since driving to our facility for testing without taking medication may put the teen at risk, a parent will need to agree to drive the teen to these visits. Parents will also be participating in the intervention (see Section 5.d.1).

Exclusion criteria:

1) On ADHD medication that cannot be washed out on assessment days. **Rationale**: Since we desire to test teens off medication on the assessment days, only medications with a half-life <12 hours can be allowed.
2) Drug or alcohol dependence. **Rationale**: Teens meeting criteria for drug or alcohol dependence according to K-SADS interview likely require more intensive and other interventions.
3) On psychotropic or neuroleptic medications. **Rationale**: These psychotropic medications often impact patient attention. Also, these medications cannot be titrated down quickly.
4) Require eye glasses (contacts acceptable) for driving (corrective vision restriction on driver's license). **Rationale:** The eye tracking equipment that will be used during driving simulation and the road test to measure eye glances cannot be used if the participant is wearing glasses.

At the initial evaluation, the Principal Investigator or designee will provide parents and potential participants a thorough verbal explanation of the study. The written consent form will be reviewed with families to ensure their understanding of the protocol and their rights and responsibilities. In addition, an assent form will be

reviewed with teens under the age of 18. The parent and participant will understand that refusal to participate will not influence their ability to receive treatment at CCHMC and that they are free to withdraw at any time. After signing the consent and assent form, parents will be given a copy of the signed consent/assent forms to take home with them. Parents who consent to participate will then be interviewed and complete rating scales while the teen is administered the initial assessment battery (diagnostic interview, IQ testing, etc.). Teens will also complete a simulated driving assessment and a road test. Teens meeting inclusion criteria will then be randomized to either the FOCAL+ or the sham intervention group.

The two intervention arms will be equal in sample size. Hypothesis testing will require 68 participants in each arm (see Power Analyses, Section *5.f.2.a.1*). Randomization will be stratified by gender and months of driving experience to ensure that there is equal representation of gender and months of driving experience across groups.

Teen participants and their parent will participate in an initial training and then 4 subsequent weekly trainings. At each of the 4 subsequent weekly training sessions, they will first complete a simulated driving assessment and then engage in a session of either FOCAL+ or the sham intervention training.

At the final training session 1-month post-randomization and then again at 4-, 8- and 12-months post-randomization, they will again complete the simulated driving assessment and road test. In addition, teens' naturalistic driving will be assessed using an in-car DriveCam monitoring system for a full year or their entire tenure in the study.

Participant Retention

We will gain IRB approval to implement the following retention strategies; (1) establishing trust, rapport and pride in participation by creating a study logo depicting "Driving Teens" which will be included on all measures and correspondence with families, (2) stress confidentiality with participants, (3) assess detailed information regarding names, addresses, and phone numbers of people who might know where the family is living in case they lose contact with the study, (4) adequate incentives that increase by $10 for each follow-up visit, (5) study refrigerator magnets and other materials with reminders to call the toll-free number if they move or change phone numbers, (6) interim phone contact in between sessions to acquire demographic updates and to provide reminders of upcoming study visits, (7) frequent mailings of birthday cards and holiday cards, and (8) address tracing software via Accruint®, a subsidiary of NexisLexis, to use demographic information to search for families whose phone numbers become obsolete.

Sources of Materials

Research data for all participants will be obtained from parent, teacher and self-rated behavioral rating scales, in depth parent and self-report interviews about the teen's behavior and functional status, and a comprehensive battery of cognitive and neuropsychological assessments administered directly to the participating teens. Driving will be assessed via driving simulator, a road test, recordings collected using an in-car video recorder (DriveCam) which will be installed in the identified "teen car," and official driving records obtained from the Bureau of Motor Vehicles. All data will be entered into an electronic database for storage and analysis. Information will be entered into computers by participant number, not name, in order to protect the identity of the participants and their parents. No personal identifying information will be used in conjunction with the electronic form of the generated data. The database will be accessible by password only by project personnel.

Potential Risks

The Institutional Review Board of CCHMC will be responsible for monitoring risks to human participants and assessment of ethical issues related to this study, and will an approved consent form and protocol prior to initiation of the study.

Psychological / cognitive assessments: The assessments are time consuming and may bring up sensitive emotional issues when families are asked about their teen's behavior and past life experiences. One potential risk for participants and their parents include fear or embarrassment resulting from clinical interviews or psychological testing. Most questions and measures used in the study are standard for medical or psychological evaluations and therefore have minimal risk associated with them. These questions may address issues of family psychiatric history, parental relationships, and family substance abuse. Participants and parents are free not to answer any questions to which they object. Also teens with ADHD may experience frustration when completing cognitive and neuropsychological tasks if the testing lasts longer than their

attention span or if they are being asked to complete items that are challenging for them. Our evaluators have clinical expertise in evaluating teens with ADHD and if teens are exhibiting fatigue or frustration, families will be given the option of stopping the assessments and returning at another time to complete them.

Driving simulator assessment: The simulator tasks may elicit a mild stress response. When participants are instructed to engage in a secondary task, drivers may experiences feelings of annoyance, and participants may experience minor muscle fatigue due to the length of driving time. There is a slight risk that participants may experience nausea from the simulator. In order to limit motion sickness from the simulator, there will be a fan providing air flow in the simulator room, and all participants will be provided with a SeaBand which is worn around the subject's wrist and uses acupressure to reduce nausea and motion sickness. Also, we have limited driving sessions to 5-minute lengths with breaks in between in order to reduce risks of motion sickness. To date, implementation of these safeguards has resulted in no cases of motion sickness during driving simulation with over 135 participants to date.

Road test: We have contracted with Bick's Driving School (see letter of support) to administer the road test to our research participants. The safety of our participants is of upmost importance and we will take several precautions to limit risks while driving on real roads during the road test. First, we have invested in eye tracking googles that participant's will wear while driving that do not interfere with the driver's vision. Second, we have partnered with a local professional driving school with over 40 years of experience in providing behind-the-wheel instruction to teens and other high-risk drivers. Bick's Driving School specializes in training high risk drivers and will supply Certified Driver Rehabilitation Specialists (CDRS) to accompany the research participants during the road test. *Bick's Driving School has committed to providing us with one CDRS who will serve as the road test instructor/evaluator for all of the study participants.* The CDRS will use Bick's Driving School's specially-equipped instrumented vehicle with latest in adaptive equipment including dual brakes. The CDRS will provide participants with road directions and will ask the driver to perform a variety of safety-related driving tasks (e.g., turning on the defroster). The CDRS will have ready access to a redundant braking system in order to be able to intervene if necessary. The road test will be a 10 mile set course consisting of city and suburb environments but no high speed environments (e.g., highways). The driver's task will be to follow the route defined while complying with all local traffic rules, including posted speed restrictions. In order to avoid commuter traffic, the road tests will be scheduled in the mid- to late morning or during the early afternoon. Because Bick's Driving School will be providing the vehicles and driving instructors (i.e., CDRS), Bick's Driving School will be liable for any motor vehicle incidents that occur during the road test.

Medication wash-out: Teen participants who take medication for ADHD will be asked to refrain from taking their medication on the days of simulator/road test driving assessments. Parents will be informed of the risks associated with this (i.e., driving safety, school performance, job performance, etc.). In order to limit the risk associated with a medication washout, both the teen and parent will be advised verbally and in writing that the teen is not to drive to the study appointments, and must be driven by the parent. Participants are free to resume medication immediately following the study visits.

Confidentiality: The potential for a breach in confidentiality always exists, specifically with the written research data and study databases. However, information that is obtained will be stored in locked file drawers in locked offices and data will have identifying information removed to prevent loss of confidentiality. All data will be coded by participant ID only. Data linking participants' names and their identification numbers for the study will be kept in a locked cabinet. Participant identities will only be known to the investigators and study staff. Binders with identifying information (e.g., consent forms) will be maintained separately from the evaluation, assessment and outcome data.

6.b Adequacy of Protection Against Risks

Recruitment and Informed Consent

Teens and parents who have seen the recruitment flyers and are interested in learning more about the study will be asked to contact the clinical research coordinator who will explain to them the purpose of the study and what is involved in participation. Teens calling in response to advertisements will participate a screening over the phone with IRB approved study staff. Those meeting initial phone screening criteria (age, at least 4 symptoms of DSM-5 inattention endorsed at a clinically significant level on symptom screener, and

licensure status) will be invited to attend an appointment with the PI or designee along with their parent, where the study will be explained in more detail, including risks and benefits of participation, and written parental consent and verbal teen assent will be obtained. No assessment procedures will occur until after parental consent and teen assent are obtained. For teens who are 18-19 years of age, consent will be obtained from both the teen and the parent.

Protections Against Risk

Minimizing risk of breach of confidentiality: Study procedures have been designed to protect the privacy and confidentiality of the research participants. Throughout the study, all data, including that collected during the screening and recruitment phase will only be identified by a unique identification number and participant code using letters and numbers to protect against invasion of privacy. The data will be blinded correspondingly in all data analyses. Only authorized staff will have access to participant information. All study information containing identifying information will be stored separately from the study data and will be stored in a locked filing cabinet.

Families will be informed that their confidentiality will be maintained with regard to video recorded driving behaviors during the road test. We will obtain a federal Certificate of Confidentiality in order to protect video recorded driving information collected during the road test and during DriveCam monitoring. All teen drivers will be consented in order to be protected by the Certificate of Confidentiality. Moreover, parents will be told that we will not be disclosing any information collected about the teen during the video recorded driving, including illegal behavior, with parents. Families will be explicitly told that video recordings collected using an in-car video recorder (DriveCam) will be collected on anyone driving the identified “teen car”. Moreover, a sign will be hung in each car so that anyone who drives the car or is a passenger in the car is aware that they will be video recorded[102, 103]. However, research staff will immediately destroy all video in which the teen participant is not the driver. Further, families will be informed that all video recordings will be destroyed immediately after the study period. The plan for maintaining confidentiality of driving video recordings was derived in collaboration with our institutional IRB.

A similar policy will be used in regard to self-reported substance use reported by the teen. Again, we will inform families at the outset that any information about teen substance use will not be reported to the parents. The Certificate of Confidentiality will protect this information from getting released upon subpoena. We feel that non-disclosure of teen substance use to parents is needed in order to get unbiased reports of substance use.

All data will be entered into an electronic database for storage and analysis. Information will be entered into computers by participant number, not name, in order to protect the identity of the participants and their parents. No personal identifying information will be used in conjunction with the electronic form of the generated data. The database will be accessible by password only by project personnel. Research papers will be based on analyses of group data with no identifying information about any participant used in these reports.

Minimizing risk of medication wash-out: As previously described, parents will be instructed verbally and in writing during the consent process to drive their teen to the appointment as driving without medication could be dangerous. In addition, the study coordinator will make a reminder phone call prior to the driving assessment. During this time the coordinator will remind parents and teens that parents are to drive un-medicated teens to their appointment.

Disclosure of Abuse: We are very familiar with the assessment, management, and reporting of child maltreatment as this is considered part of standard clinical care in pediatric psychology and psychiatry. These incidents are common during clinical trials, and we have standards for both managing and reporting these incidents

Disclosure of Suicidality: We are also very familiar with the assessment and management of suicidality. Specifically, prior to any clinical interview, confidentiality is discussed with the participant and family during the consent process. This includes state guidelines for reporting suicidality. If suicidality is disclosed during the interview, the interviewer will conduct a thorough suicide assessment assessing for the following: 1) specificity of the suicide plan, 2) means to execute the plan and 3) lethality of plan. This is immediately reported to the PI who will make the ultimate decision regarding next steps. In all cases, the teen’s parent will be informed of the teens’ risk and a safety contract will be completed in writing with both the teen and parent. Further, the parent will be counseled on safety precautions within the home. If the teen is unwilling to contract, then CCHMC hospital protocol will be followed. Specifically, the family will be referred to the Psychiatry Department at CCHMC for an assessment for in-patient psychiatric hospitalization.

Adverse events: If participants experience any adverse events, investigators will follow-up participants and provide treatment until the event has subsided. Investigators will be available 24-hours via pager.

Education in Protection of Human Subjects. All personnel will participate in training on protecting the rights and welfare of human participants in research. Personnel will all complete an online tutorial and satisfactorily complete an electronically-administered examination testing knowledge and application of the ethical principles and Federal regulations protecting human participants in research as described in the Belmont Report and Title 45 Code of Federal Regulations Part 46.

6.c Potential Benefits of the Proposed Research to Human Subjects and Others

Potential benefits to individual participants and their families include improved visual attention during driving and potentially improved driving performance for those assigned to the FOCAL+ group. Participants will also receive a diagnostic evaluation as a part of their participation in the study. Study assessments and treatment will be administered free of charge. Moreover, the information gained from this study has the potential to directly impact the treatment of all teen drivers including those with ADHD.

Participants will be compensated for their time completing assessments. In order to increase participant retention, the amount of compensation will increase across study visits. Specifically, compensation for the baseline visit will equal $40, $50 for the 1-month visit, $60 for the 4-month visit, and $70 for the 1-year visit. Teachers will be compensated $10 for completing baseline questionnaires.

6.d Importance of the Knowledge to be Gained

We believe that the benefits of the project greatly outweigh any risk involved. The results of this study are likely to result in an enriched understanding of the driving of teens with ADHD. This study will provide information about the efficacy of a non-pharmacological driving-focused intervention for teens with ADHD. If the intervention is efficacious in improving driving behavior of teens with ADHD, this intervention could be used in driver's education courses.

6.e Data and Safety Monitoring Plan

The PI will continuously evaluate the project's performance, safety, treatment fidelity, and need to stop. Performance will be monitored by examining subject recruitment, comparison with targeted recruitment retention, protocol adherence, and quality of data collection procedures. This will primarily be accomplished in weekly staff meetings attended by the PI. Any deviation in achieving recruitment targets will be reported to the NIMH program officer. In order to assure intervention fidelity, the PI will randomly attend training sessions. In order to assure the accuracy of data entry, all data will be verified by double entering all data into our Microsoft Access database. Inaccuracies will be addressed by double-checking the report forms. If inaccuracies cannot be resolved by checking the source forms, we will review that patient's chart again at the next data collection visit in order to resolve the query.

Should any adverse event occur, we have established a set of protocols and procedures to manage the handling/reporting of such events. Adverse event monitoring will occur at each assessment visit. Participants will be asked if they have had any adverse experiences since the last visit. Adverse events leading to discontinuation will be documented. All serious adverse events (SAEs) will be reported to the CCHMC Institutional Review Board (IRB) according to the regulations set forth by this IRB, as well as to the NIMH. All staff will be trained to identify adverse events and on procedures for handling them (e.g., reporting of child abuse, suicidality, HIPPA training, human subjects training, etc.).

The PI, Dr. Epstein, is ultimately responsible for ensuring the safety of participants enrolled in the protocol. Following baseline evaluation, Dr. Epstein will be ultimately responsible for making the decision for particular participants to continue or discontinue in the protocol.

6.f ClinicalTrials.gov Requirements

This clinical trial will be registered with ClinicalTrials.gov.

INCLUSION OF WOMEN AND MINORITIES

The primary subjects for this research study are teens of both male and female gender with ADHD between the ages of 16-19 years inclusive. Parents / primary caregivers of the teen enrolled in the study will also participate by accompanying their children to the study visits, completing parent interviews and behavioral rating scales at baseline and throughout the study. We expect to have a higher rate of males than females in our study since ADHD occurs at higher rates in males than in females with approximately a 3:1 ratio. It should be noted that since parents will be participating, and our experience in previous clinical trials is that the parent who most often participates in the intervention is the mother, we will likely have a larger proportion of adult women participating in the study than men.

The ethnic make-up of the proposed sample will roughly mirror that of the Greater Cincinnati and Northern Kentucky metropolitan area; 81% White, 15% African American, 2% Asian American, and 2% Hispanic. The racial composition of our clinical population is similar to these rates. Also, another recently completed NIH-funded research study (n=151) in our Center for ADHD that used similar recruitment methods produced the following rates: 75% White, 17% African American, 1% American Indian, and 2% Hispanic[63]. In the event that minority rates do not emulate local distributions and those achieved in previous research, we will respond by focusing our recruitment efforts on local urban high schools, which are attended primarily by minorities.

OMB Number: 0925-0002

Planned Enrollment Report

Study Title: Improving ADHD Teen Driving by Targeting Visual Inattention to the Roadway

Domestic/Foreign: Domestic

Comments:

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/Alaska Native	0	0	0	0	**0**
Asian	1	2	0	0	**3**
Native Hawaiian or Other Pacific Islander	0	0	0	0	**0**
Black or African American	5	15	0	0	**20**
White	26	82	1	1	**110**
More than One Race	1	1	0	1	**3**
Total	**33**	**100**	**1**	**2**	**136**

Study 1 of 1

Funding Opportunity Number: PA-13-302. Received Date: 2015-07-02T13:16:59.000-04:00

INCLUSION OF CHILDREN

Our study population includes children 16-19 years old with ADHD (plus their parents / caregivers). We are focusing on 16-19 year olds as this population is especially vulnerable to involvement in motor vehicle crashes (MVC)[22]. The knowledge gained from this research will provide evidence of an intervention that could improve the driving safety of teens with ADHD who are at increased risk for adverse driving outcomes; therefore, it is essential that our study population include children.

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Statistical Analysis Plan

Trial of Training to Reduce Driver Inattention in Teens with ADHD

STATISTICAL ANALYSIS PLAN

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Supported By:
Eunice Kennedy Shriver National Institute of Child Health & Human Development
Project Number: 5R01HD084430

September 20, 2022

1 SAP Signatures

I give my approval for the attached SAP entitled "Trial of Training to Reduce Driver Inattention in Teens with ADHD" dated September 20, 2022

Statistician:
Name: James Peugh, PhD

Signature: _____

Date: _____

Principal Investigator
Name: Jeffery N. Epstein, PhD

Signature: _____

Date: _____

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3 Abbreviations and Definitions

AE	Adverse Event
ADHD	Attention-Deficit/Hyperactivity Disorder
AMAP	Attention Maintenance Assessment Program
CCHMC	Cincinnati Children's Hospital Medical Center
CD	Conduct Disorder
CNS	Crashes and near crashes
Co-I	Co-Investigator
CRF	Case Report Form
DSM-5	Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition
FOCAL	FOcused Concentration and Attention Learning
FOCAL+	Enhanced FOcused Concentration and Attention Learning
GEE	Generalized Estimating Equations
GPS	Global Positioning System
GTSSSS	Georgia Tech Simulator Sickness Screening Survey
IQ	Intelligence Quotient
IRB	Institutional Review Board
K-BIT	Kaufman Brief Intelligence Tests-2
K-SADS-PL	Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version
MVC	Motor Vehicle Crash
NICHD	National Institutes of Child Health and Human Development
ODD	Oppositional Defiant Disorder
PI	Primary Investigator
RCT	Randomized Control Trial
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SSI-AOD	Simple Screening Instrument for Alcohol and Other Drugs
SSQ	Simulator Sickness Questionnaire
ST	Secondary Task
VAPRS	Vanderbilt ADHD Parent Rating Scales

4 Introduction

4.1 Preface

Glances away from the roadway, especially those longer than 2 seconds, significantly increase one's risk for a motor vehicle crash (MVC). Teen drivers evidence far more extended glances away from the roadway than experienced drivers. Further, teens with a diagnosis of Attention Deficit/Hyperactivity Disorder (ADHD) emit 3-times more extended glances (defined as $\geq$ 2 seconds) away from the roadway than neurotypical teens. Driving deficits, such as difficulty maintaining lane

position, observed among teen drivers with ADHD are mediated by elevations in the number of extended glances away from the roadway. Hence, there is a clear need for interventions, particularly one that targets extended glances away from the roadway, to address the driving deficits of teens with ADHD. The randomized controlled trial (RCT) described in this Statistical Analysis Plan (SAP) will test the efficacy of an enhanced FOcused Concentration and Attention Learning (FOCAL) intervention (FOCAL+), which targets reducing the number of extended glances away from the roadway, among teens with ADHD. The public health impact of improving the driving behavior of teens with ADHD cannot be overstated. MVCs are the leading cause of death among teens. The 2- to 3-fold increased risk of MVCs among teens with ADHD significantly contributes to these figures. By targeting teens with ADHD, we are targeting one of the highest risk groups of drivers on the road. Were our interventions to normalize driving among teens with ADHD, the potential impact on rates of MVC injuries and deaths would be substantial.

4.2 Scope of the analyses

This SAP describes the planned analyses for the Improving ADHD Teen Driving study (National Institutes of Child Health and Human Development (NICHD) grant # 5R01HD084430). These analyses will empirically test the effectiveness of the FOCAL+ intervention in comparison to a sham placebo intervention at reducing the frequency of extended eye glances and driving performance during simulated driving and real-world driving outcomes captured by in-car technology.

The planned analyses identified in this SAP will be submitted at the study completion as part of the Final Study Report and future manuscripts.

5 Study Objectives and Endpoints

5.1 Study Objectives

The goal of the proposed research is to empirically test the effectiveness of the FOCAL+ intervention in comparison to a sham intervention at improving visual attention and driving performance in teens with ADHD. Specifically, we will conduct a randomized controlled trial using 152 teens diagnosed with ADHD. Teens will be randomized to receive 5 training sessions of the FOCAL+ intervention or a sham intervention. 1-month and 6- months post-training, teens' driving skills, including frequency of extended eye glances, will be assessed during driving simulation. In addition, at the conclusion of training, a DriveCam camera system in their car will record naturalistic driving. The DriveCam will remain in their car until 12-months post-training. Finally, we will acquire the teen's driving records for the period they are in the study.

Primary Objective: We will examine the effectiveness of the FOCAL+ intervention versus sham intervention at decreasing rates of extended glances away from the roadway and improving driving performance among teens with ADHD at 1-month post-training, and 6-months post-training.

Secondary Objective: We will examine the effectiveness of the FOCAL+ intervention versus sham intervention in decreasing rates of extended glances away from the roadway, frequency of driving events, crashes, and crashes/near crashes as measured by in-car technology (DriveCam) during the 12-months post-training.

5.2 Endpoints

Primary Endpoint

Two primary endpoints will be used to compare the immediate effectiveness of interventions at 1-

month and 6-months after the last training session. The driving simulator will be integrated with an eye tracking system and gyroscope. After acclimating to the driving simulator, participants will complete two 15-minute drives. The following are the two primary endpoints assessed during driving simulation:

1) Number of Extended Glances Away from Roadway during Driving Simulation: During the two 15-minute drives, the participant will engage in one secondary task per minute for a total of 28 secondary tasks. The secondary task, each lasting 20 secs, will consist of searching for streets on a simulated GPS map. Using visual mapping from the Tobii eyetracking, a forward roadway gaze area will be defined. Tobii analyses software (Tobii Glasses 2, Tobii Pro, Reston, VA) will determine for each 20 msec epoch whether the visual gaze was off the forward roadway, and the number of ≥2 secs glances during secondary task periods will be computed at 1-month and 6-months post- training.

2) Standard Deviation of Lateral Position during Driving Simulation: The standard deviation of lateral lane position will be computed using lane position recorded every 17 msecs for the secondary task periods at 1-month and 6-months post-training. Lane position variability is highly correlated with MVCs (Owens & Ramaekers, 2009).

Every effort will be made to ensure that participants attend all 5 training sessions. However, should participants fail to complete all training sessions, the last completed training session will be used as the start of the post-training period.

Secondary Endpoint

Two secondary endpoints will use DriveCam event-triggered device (Model#: DC3; Lytx, Inc.). This data will be used to compare the long-term (12-months post the final training session) effectiveness of the interventions in a naturalistic setting.

The DriveCam device has two integrated cameras. One facing the forward roadway; the other facing the driver. If the built-in accelerometer detects a ≥.6 forward or lateral g-force event, the device records the 8 secs before and 4 secs after the triggered event. Four events will be randomly selected for coding if a teen had >4 events in a week. Trained coders will code the onset and offset of visual glances away from the roadway such that a count of extended eye glances (≥2 seconds) will be obtained. Additionally, coders will record whether the event captured a crash (i.e., contact between the vehicle and another object) or near crash (i.e., an evasive maneuver performed to avoid a MVC). The two secondary endpoints that will be used from the DriveCam video events will be as follows:

1) Events that Included an Extended Eye Glance: During the 5-seconds preceding the event until the 1-second after the g-force event, if a glance away from the roadway was ≥2 seconds, the event will be identified as having a long glance. Events that do not include a glance away from the roadway ≥2 seconds during the 5-seconds preceding the event until the 1-second after the g-force event will be identified as not having a long glance.

2) Events that Included Crashes and Near Crashes: Coders will make a determination after viewing each event whether the event included or did not include a crash or near-crash. Crashes and near crashes (CNC) will be combined due to low crash rates and near-crashes are an established surrogate for crashes (Guo, Klauer, Hankey, & Dingus, 2010).

6 Study Methods

6.1 General Study Design and Plan

Recruitment

We will target our study advertisements to parents of teen drivers with ADHD or attention problems. It is not required that participants have an existing diagnosis of ADHD as the research team will conduct a comprehensive ADHD assessment. Most of our research participants will be current or past patients at the Center for ADHD at Cincinnati Children's Hospital Medical Center (CCHMC). We will also identify patients with an ADHD diagnosis who have indicated interest in being informed about future research studies who have been seen at CCHMC (outside of the Center for ADHD) to whom a letter will be mailed to advertise more broadly as needed. This letter will be sent along with a postcard indicating whether they would "not wish to be contacted about the study" or "wish to be contacted at a future date". Families not returning the postcards will be called by research staff to share more about the study and invite participation. The study will be advertised on the CCHMC social media page using IRB (Institutional Review Board) approved web and flyer text.

We will also recruit from the community including distributing flyers (see advertisement text) to local schools, driving schools, the Department of Motor Vehicles, local physicians, and through advertising (e.g., flyers, CCHMC outlook emails). Additionally, the study will be advertised through brief IRB approved audio clips and digital flyers on local radio stations as well as internet radio services (e.g., Pandora). We also plan on using multiple online participant recruitment services (Truventis, Fusion Media), to promote our research study on social community pages such as Facebook, Twitter, Instagram, and Pinterest and through search engines such as Google, Bing, and Yahoo. Truventis and Fusion Media will create recruitment materials including a study flyer and a brief video. These recruitment materials will direct potential participants to either a study website created by Truventis or to a REDCap e-screener page where potential participants will be directed to provide contact information so that study staff may contact the participants to inform them about the study. Finally, we will recruit participants through the SONA system (psychology subject pool). Participants recruited using this approach will complete screening measures online via Qualtrics survey software in a single session lasting approximately 15 minutes. These subjects will be enrolled at University of Cincinnati, Xavier, or Northern Kentucky University as undergraduates. Students in Psychology courses visit the SONA website to see descriptions of all experiments currently being offered. Once they find an experiment that interests them, they will follow a link that provides directions for completing the study via Qualtrics. Once participants follow the link to the study on Qualtrics, they will also be required to read the recruitment statement. After completing the survey, participants will automatically receive course credit in SONA for their participation. The survey questions will be those currently asked during the phone screening process for participants recruited using alternative methods (i.e., questions regarding ADHD symptoms, driving history and habits, and motion sickness) and will also incorporate the driving history questionnaire. We foresee that we will be able to successfully recruit the majority of our sample using our Center's registry. Additionally, we will using radio, social media, and print advertisements.

Screening

Interested families will be screened over the phone for inclusionary and exclusionary criteria (See Inclusion-Exclusion Criteria and General Study Population section) including a screening of ADHD symptoms using a behavioral rating scale (ADHD Vanderbilt Rating Scale-Parent Report). This screening is expected to take no longer than 15 minutes. Families meeting screening eligibility criteria will attend an eligibility study visit at the Center for ADHD at CCHMC where they will be consented and assented, and parents and teens will complete a structured interview with a graduate

student, post-doctoral fellow, or psychologists. In addition, the teen will be administered an abbreviated intelligence measure, and complete self-report measures assessing ADHD symptoms. Finally, the teens will complete some drives in the driving simulator. If participants are taking stimulant medication at the time of assessment, then they will be instructed to not take the medication the day of their initial visit (See 11.1 Adverse Events for safety procedures regarding medication wash-out). We will ask that the teen be off their medication because we are interested in assessing teens' driving abilities off medication, given that most teens drive in the mornings and evenings when ADHD medication may not have yet taken effect or may be wearing off. Moreover, it is common practice for teens not to take medication on weekends or during summer when school is out. For safety reasons, parents of children with ADHD who are not taking medication on the day of their assessments will be required to drive their child to and from these visits. Lastly, although it would be ideal for the teen to be off medication for their first visit and should reduce participant burden, we can work with the family to schedule multiple appointments as necessary (i.e., some families may opt to not have their teen refrain from taking medication at the initial visit and may opt for two initial visits; only the latter simulator visit being off medication).

Eligibility Assessment

Each potential participant will undergo a complete comprehensive assessment. The assessments are intended to establish a clinical research diagnosis of ADHD. Participants must meet full DSM-5 (Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition) (American Psychiatric Association, 2013) criteria for ADHD as determined by a semi-structured interview (Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version; K-SADS-PL) (Kaufman, Birmaher, Brent et al., 1997). Both the parent and teen will be administered the Behavior Disorders—ADHD, Oppositional Defiant Disorder (ODD), Conduct Disorder (CD)—section of the interview, in addition to a review of anxiety and mood disorders. Reliability and validity for this measure are good to excellent, and the interview takes about 60 minutes to complete. Teens can have comorbid diagnoses as long as ADHD is their primary diagnosis. Participants will be recruited and ascertained by trained personnel at the CCHMC ADHD Program. The assessment visit is expected to take approximately 4 hours.

If during the evaluation, suicidal ideation or more serious psychopathology is uncovered, the patient will immediately be referred to an appropriate mental health provider or emergency room facility (See 11.2 Adverse Events for safety procedures for more information about psychological/cognitive assessments). Further, any participants who do not meet study criteria will be referred to appropriate referrals within CCHMC or within the community depending on patient preference and physician availability.

Interventions

This is a randomized clinical trial testing the superiority of the FOCAL+ intervention over the sham control intervention. The sham control intervention is an active control and is described below in greater detail. All teens who take ADHD stimulant medication will be instructed to refrain from taking ADHD medication for all intervention sessions and post-intervention assessment visits. Parents of these teens were instructed to drive their teen to the visits.

FOCAL+ Intervention: Initially, and then once a week for the next training sessions after the initial training, teens with ADHD randomized to the FOCAL+ intervention will participate in FOCAL+ training sessions (total of 5 sessions). FOCAL training begins with the Attention Maintenance Assessment Program (AMAP). AMAP is a computerized desk-top program designed to assess visual attention. During AMAP, the computer screen is split horizontally in order to simulate distracted driving. Participants can either view a windshield-view video of driving in the top portion of the

screen (primary task) or view a map on the bottom portion of the screen (secondary task). Participants toggle between views by pressing the spacebar on the keyboard. Only the top or bottom view is visible at any one time with the non-selected portion of the screen blacked out. Although blacked out when viewing the map, the video of the drive continues to progress in real time while the map is being viewed. During AMAP, the participant is given three street names. By toggling between the views of the top and bottom halves of the display, they are asked to identify street signs in the driving video (top portion) while concurrently determining whether the street names exist on the map (bottom portion).

After AMAP, feedback and training includes five separate steps. (1) Participants learn to appreciate how long they looked away from the driving scenario during AMAP by viewing their own AMAP performance. During this viewing the top portion of the screen (simulated video drive) is blacked out for as long as the participant viewed the map during the AMAP testing. For example, if the teen diverted his attention to the map for 3.8 secs during the initial driving task, the screen is blacked out for the same 3.8 secs during video playback. (2) In a subsequent feedback period, the AMAP video is played back again with a blacked-out screen during times the teen was looking away. In addition, a timer is added to the screen to show the teen how long they looked away during each instance. (3) Next, the video is re-played again with a timer during blacked-out sections to demonstrate the length of long-glances. (4) Next, a new drive is played with the same street name search task; however, a warning tone sounds when glances at the map are $\geq$3 secs. Participants repeat the drive until all long-glances at the map $\leq$3 secs. Finally, (5) Step 4 is repeated with a 2 sec threshold.

Due to concerns that teens with ADHD might have decreased ability to generalize the visual glance skills they learn during FOCAL training to actual driving conditions, we have enhanced the FOCAL intervention to specifically train generalization to a driving environment (Abikoff, 2009; Barkley, 1997). Immediately following each FOCAL training session, teens will enter the driving simulator equipped with eye tracking technology. They will complete two 5-minute drives. During the drives, approximately once per minute, the driver will be alerted with an auditory tone and a visual cue indicating that they need to search for a symbol within a 6x6 array of symbols on the screen located within a computer monitor situated within a virtual dashboard. They will need to inform the research assistant of how many times the target symbol appears in the stimulus array. They will be given 20 secs to complete the search. During the FOCAL+ drive, the eye tracker will monitor eye glances and teens will be provided with real time immediate auditory feedback when a visual glance away from the roadway exceeds 2 secs. Specifically, an auditory alarm will sound when the glance duration exceeds 2 secs and will continue to sound until visual gaze returns to the roadway. All teens will complete two 5-minute drives under these conditions. However, if a teen is still demonstrating any glances away from the roadway that are ≥2 secs or <50% accuracy in responses, they will complete additional 5-minute drives under the same conditions until they succeed in having no ≥2 secs glances and having > 50% accuracy in responses during the 5-minute drive up to a maximum of 3 extra 5-minute drives. Each training session lasts approximately 1.5 hours.

During the initial training session, as teens are completing the FOCAL+ training, parents will complete the FOCAL training in a separate room so that they can learn the skills being taught to the teen and can thereafter provide feedback to the teen regarding extended visual glances during supervised driving. Parents will also be given a short 5-minute refresher at the fifth and final training session.

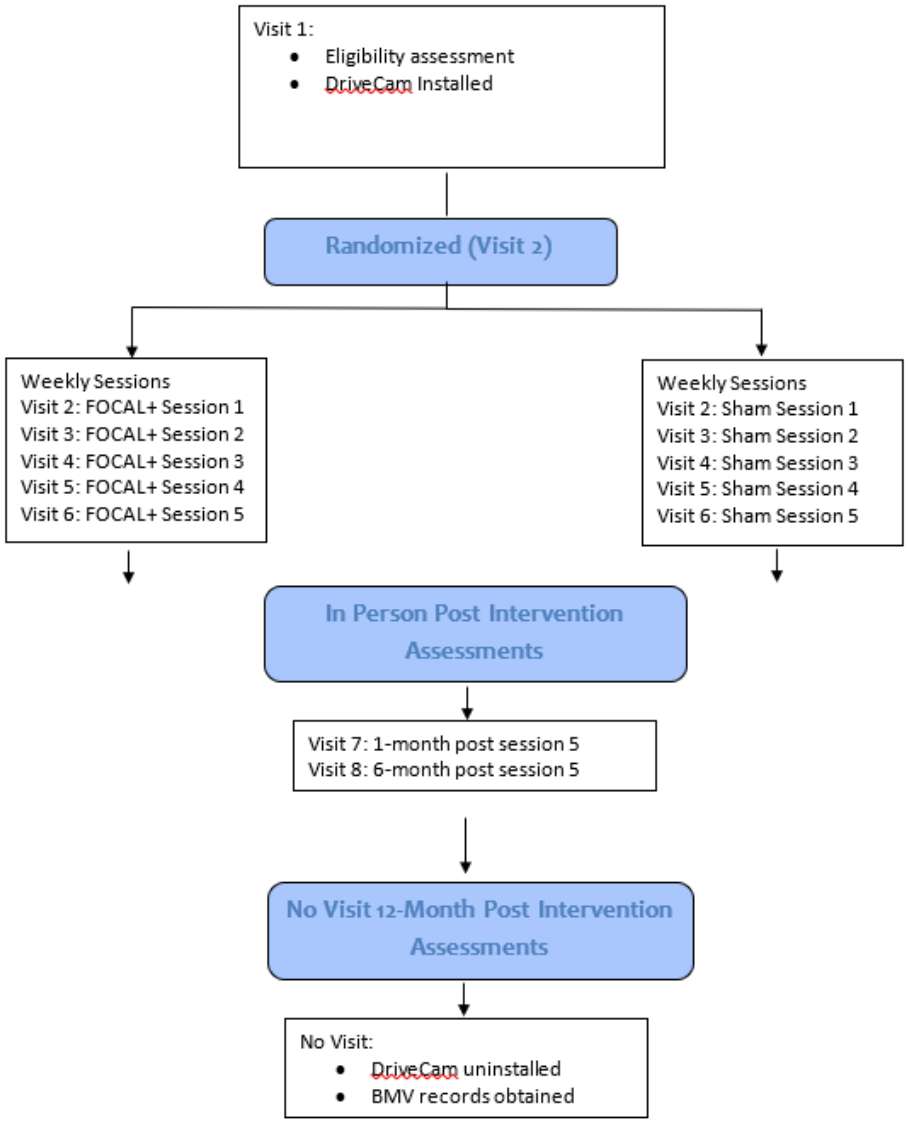
Sham intervention: Like teens randomized to the FOCAL+ intervention, teens with ADHD randomized to the sham intervention will engage in sham training initially and then once a week for the next 4 training sessions after the initial training (total of 5 sessions). The first hour of each training session will consist of computer-based training about the rules of the road based on an

abbreviated established driver training curriculum from the American Driver & Traffic Safety Education Association (ADTSEA). Teens will learn about traffic codes, laws, and rules of the road. To control for the extra time that teens assigned to FOCAL+ will spend in the driving simulator during FOCAL+ training, teens in the sham intervention will also drive in the driving simulator after each training session for a comparable length of time (i.e., two 5-minute sessions). This time in the driving simulator will be contextualized as a time for them to practice the rules of the road they learned during training. Importantly, teens in the sham intervention group will NOT receive any feedback regarding their eye gaze during simulated driving. The number of additional 5-minute drives beyond the initial two 5-minute drives will be kept equal across groups by yoking each control participant to an intervention participant. The number of training drives completed by controls was determined by matching each control to a FOCAL+ participant ensuring equal numbers of training drives across groups. Parents will also participate in the training by receiving materials on the information their teen learned at their initial and fifth training visits.

Post Intervention Assessments

At 1-month post-training and 6- months post-training, teens' driving skills and frequency of extended eye glances will be assessed using a driving simulator. In addition, we will install a DriveCam camera system in the car that the teen most often drives and leave this in their car until 12-months post-training. Finally, we will acquire the teen's driving records for the period they are in the study.

Below is a study flow-chart.



Study Timeline

The project will take place over a 5-year time-period. Years 01-04 of the study will be used to

(1) recruit, phenotype, and consent teens with ADHD and their families,
(2) randomize participants to treatment groups,
(3) conduct FOCAL+, and sham intervention trainings (5-sessions, 1 week apart),
(4) conduct driving simulation assessments at baseline, 1-, and 6-months post-training,
(5) collect information about medication use at baseline, 6-months, and 12-months post-training,
(6) install and collect driving data using DriveCam cameras,
(7) collect driving records,
(8) conduct data entry and coding.

Since we forecast that recruitment will take 4 years to complete, we expect that some post-intervention data collection will continue into Year 05. However, most of Year 05 will be devoted to data cleaning, analyses, and preparation of study findings for publication and dissemination.

6.2 Inclusion-Exclusion Criteria and General Study Population

Inclusion Criteria

Participants for the study must meet all the following criteria:

a. Consent: The family must provide signature of informed consent by parents or legal guardians. Eighteen-year-old adolescents must provide their own consent.
b. Assent: Adolescents under the age of 18 must provide a signature indicating assent to participate in the study
c. Aged 16-19.
d. Teens in ADHD group will meet DSM ADHD criteria for ADHD-Predominantly Inattentive Presentation or ADHD-Combined Presentation based on the K-SADS interview. For research purposes, we will utilize criteria specified in the DSM-5 for older adolescents (i.e., a teen will qualify for an ADHD diagnosis with 5 or more inattentive and/or 5 or more hyperactive impulsive symptoms with related impairment across multiple settings) for all teens.
e. Possess a valid driver's license and regularly spend at least 3 hours per week engaged in unsupervised driving. **Rationale**: Must be legal for participant to drive independently since driving risk among teen drivers is greatest in absence of adult supervision (Williams, 2003). Further, there is a need to collect ample DriveCam outcome data during unsupervised driving conditions to test for intervention effects. Other driving studies have used similar inclusion criteria for number of hours of independent driving (Nichols, 2012).
f. Participant has an IQ (Intelligence Quotient) $\geq$ 80 on at least one standard score or composite score as determined by the Kaufman Brief Intelligence Test—2nd edition. **Rationale**: Teens with cognitive challenges may not be able to understand intervention instructions.
g. Parent willing to participate. **Rationale**: Teens will be asked to refrain from taking medication on days of driving assessment (i.e., driving simulation). Since driving to our facility for testing without taking medication may put the teen at risk, a parent will need to agree to drive the teen to these visits. Parents will also be participating in the intervention.
h. Participants are permitted to be on medication except for those participants taking medication prescribed to manage ADHD symptoms that cannot be washed out on days they use the simulator, and neuroleptic medications. For participants taking stimulant medications for their ADHD, they will not take that medication on the days they complete simulator tasks.
i. Successful calibration on eye tracker: All participants must receive ≥80% of data captured during Georgia Tech Simulator Sickness Survey 2-minute pre-test drive.

Exclusion Criteria:

Participants will be excluded from the study if they meet any of the following criteria:

a. Understanding level: The participant and parent cannot understand or follow instructions given in the study as determined by study staff discretion at primary visit.
b. On neuroleptic medications or medications for ADHD that cannot be washed out on assessment days.
c. Risk for alcohol or drug abuse. **Rationale**: Teens engaging in significant abuse behaviors as assessed using the Simple Screening Instrument for Alcohol and Other Drugs (SSI-AOD) (Winters & Zenilman, 1994) likely require more intensive and other interventions. Participants with a score of 4 of higher on the SSI-AOD will be excluded from the study.

d. Cannot see the secondary task stimuli without the use of glasses (contacts acceptable). **Rationale:** The eye tracking equipment that will be used during driving simulation to measure eye glances cannot be used if the participant is wearing glasses

j. Risk for motion sickness in driving simulator: During phone screening, participants will be asked a series of questions on the Simulator Sickness Questionnaire that are designed to measure propensity for motion sickness. If the participant indicates that they "Nearly Always" get motion sickness in at least 4 of the situations, they will be excluded from the study. In addition, at the baseline visit, each participant will complete the Georgia Tech Simulator Sickness Screening Survey (GTSSSS) (Gable & Walker, 2013). After they complete the survey, they will complete a 2-minute practice drive in the driving simulator. After the practice drive, they will complete the GTSSSS a second time. If any single rating on the post-drive survey is greater than or equal to 5 more than pre-drive survey, or if any three of the ratings on the post-drive survey are above a 3 as compared to the pre-drive survey, the participant will be excluded.

e. Participants must not have a history of moderate to severe head trauma, neurological disorder, or any other organic disorder that could possibly affect brain function. Moderate to severe head trauma will be defined as having lost consciousness for over 30 minutes or having multiple instances of traumatic brain injury irrespective of severity. Participants who have had head trauma that are not excluded from the study will be required to wait 30 days after their head trauma before participating in the study, in order to allow sufficient time to pass that negative sequelae do not develop.

Measures used referenced above for establishing inclusion/exclusion criteria are listed below:

1) Simulator Sickness Questionnaire (SSQ) (Kennedy, Lane, Berbaum, & Lilienthal, 1993): The SSQ has been used extensively in studies of simulator sickness. The SSQ asks how often the person experiences feelings of nausea, headaches, or dizziness in a series of situations using a 4-point Likert scale (0=never; 3=Nearly Always). Situations include automobile driving, amusement rides, air travel, ship travel, computer usage, and simulators. If the parent responds that the teen "nearly always" gets nauseous/headaches/dizziness in 4 or more situations, the teen will be excluded from the study.
2) Demographic Questionnaire: A laboratory developed questionnaire assessing for covariates such as sex and age will be completed by participants. In addition, the questionnaire enquires about the family psychiatric history. The purpose of this questionnaire is to obtain information for inclusionary/exclusionary criteria and relevant covariates.
3) Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL; Kaufman, et al, 1997): The KSADS is a semi-structured diagnostic interview and has been used in a number of clinical and epidemiological studies of child psychiatric disorders. This measure consists of 82 screening items, and 5 diagnostic supplements, and can generate 32 DSM-5 diagnoses. Both parent and adolescent will be administered the Behavior Disorders (ADHD, ODD, CD) section of the interview, in addition to a review of anxiety and mood disorders. Reliability and validity for this measure are good to excellent, and the interview takes about 60 minutes to complete.
4) Vanderbilt ADHD Parent Rating Scales (VAPRS) (Wolraich, Lambert, Doffing, Bickman, Simmons, & Worley, 2003): This DSM-based checklist allows parents to rate the teen on each of the 18 ADHD core symptoms. Parents also rate the teen on a variety of domains of functional impairment. Internal consistency and reliability are excellent (Wolraich et al., 2003).

5) Georgia Tech Simulator Sickness Screening Survey (GTSSSS) (Gable & Walker, 2013): Participants complete the GTSSSS prior to driving in the simulator. The participant drives through the scenario as they would in a regular vehicle, observing all traffic laws. Following completion of the driving scenario participants return to the post-drive survey.
6) Simple Screening Instrument for Alcohol and Other Drugs (SSI-AOD) is a 16-item screening instrument including yes/no questions about the respondent's experience with alcohol and other drugs in the past 6 months (Winters & Zenilman, 1994). It covers drug use, preoccupation and loss of control, adverse consequences, problem recognition, and tolerance and withdrawal. This questionnaire will be administered during the in-person visits at Baseline and 6-months. In addition, this questionnaire will be sent as a REDCap survey for teens to complete at the 12-month time point.
7) Kaufman Brief Intelligence Test-2 (K-BIT; Kaufman & Kaufman, 2004): The K-BIT is a culturally-sensitive standardized assessment that estimates verbal and non-verbal and overall intelligence. This test has good reliability and validity and will be administered to assess each child's intelligence and rule out possible intellectual disability.
8) Driving History Questionnaire (Laboratory Developed): The Driving History Questionnaire is a brief laboratory developed questionnaire assessing relevant driving history such as date of licensure. This questionnaire will be administered during the in-person visits at Baseline and 6-months. In addition, this questionnaire will be sent as a REDCap survey for teens to complete at the 12-month time point.

6.3 Randomization and Blinding

Randomization will be done according to a 1:1 ratio. The randomization scheme will be done using blocks of 10 so that for every 10 participants, 5 will be randomized to each group. A data manager (John Simon, MA) will generate the allocation sequence using the Microsoft Excel random number function. At study outset, each assignment for the full sample will be placed in sequentially numbered sealed envelopes. When participants show up for the initial training visit, the randomization envelope for that participant will be opened at which time the participant's randomized group will be revealed to the individual conducting the participant's training.

Participants will know which intervention they are assigned to (FOCAL+ or sham intervention) but will be blind as to which intervention was the active intervention (FOCAL+). Research assistants who implement the intervention will not be blind to participant randomization; however, research assistants who code the DriveCam data (onset and off set of eye glance duration and crashes/near crashes) will be blind to participant randomization.

6.4 Study Assessments

Frequency and Timing of Relevant Assessments:

	Baseline/Randomization	1-month follow-up assessment	6-month follow-up assessment	12-month follow-up
Diagnostic and Clinical Assessment	X			
Driving Simulation Assessment		X (2 runs)	X (2 runs)	
DriveCam Recording	X (Installation)	**CONTINUOUS**		
Driving Records		**CONTINUOUS**		
Adverse event monitoring		**CONTINUOUS**		

Analysis Time Windows:

Visit (target day)	Lower bound (days)	Upper bound (days)
Baseline/Diagnostic and Clinical Assessment (-7)	-14	-7
Randomization/Training 1 (0)	N/A	N/A
Training 2 (7)	4	10
Training 3 (14)	11	17
Training 4 (21)	18	24
Training 5 (28)	25	31
Month 1 (30 post-training 5)	30	45
Month 6 (180 post-training 5)	180	195
Month 12 (360 post-training 5)	Not in person	Not in person

Study Variables:

Primary Endpoint Variables Collected During Secondary Task (ST) Performance Portion of Driving Simulation:

1) Extended eye glances: This variable will be a frequency count of the number of ≥2 secs glances. Extended eye glances of interest are those occurring during the ST portions of the drive. The range for this variable could range from 0 to 100.

2) Standard Deviation of Lane Position (SLDP): Standard deviation of lane position will be calculated during the ST portions of the drive. An average of 0 indicates that an individual maintained consistent lane position. The range for this variable is from 0 to 3

Secondary Endpoint Variables Collected using DriveCam:

1) Extended eye glances: As has been done in previous research, the number of $\geq$2 sec eye glances away from the roadway occurring between -5 secs before to 1 sec after the event causing a .6 g-force will be calculated (Dingus, Klauer, Neale et al., 2006). For each event video, we will code the onset and offset of glances away from the roadway. Based on the onset and offset times, we will calculate whether the video clip contains a continuous eye glance away from the roadway that lasts for 2-seconds or longer between -5 secs before to 1 sec after the event. It is possible that some participants will not contribute any data at all to this outcome variable due to not experiencing any .6 g-force events during the 12-month observation. The lower end of the range for this variable for participants who do experience at least 1 .6 g-force event during the observation period is 0. There is no upper limit to this variable.

2) Crashes and near crashes (CNC): Like the extended eye glance endpoint, this variable is only calculated when participants experience a g-force event $\geq$ .6. Coders will record whether the event captured a crash (i.e., contact between the vehicle and another object) or near crash (i.e., an evasive maneuver performed to avoid a MVC). Some participants may not contribute data due to not having any events. These participants will not be included in analyses. The lower end of the range for this variable, for participants who do experience at least 1 .6 g-force event during the observation period is 0. There is no upper limit to this variable.

7 Sample Size

Our initial protocol proposed to randomize 136 participants; however, this randomization goal did not account for attrition at the 1- and 6-month driving simulations—the source of our primary endpoints. When we reached a sample size of 136, we estimated how many additional participants would be required to achieve 136 participants with completed driving simulation data at 1- and 6-months post-training. The calculation suggested that we needed to recruit a randomized sample size of 152 to achieve 136 participants with 1- and 6-month simulator outcomes (primary endpoints). (See Section 16 for date of this protocol change).

8 General Analysis Considerations

8.1 Timing of Analyses

- The final analyses of the driving simulation data will be performed after the final randomized participant has completed their 6-month driving simulation assessment.
- The final analyses of the DriveCam data will be performed after both a) all events from all participants have been recorded and b) all events from all participants have been coded and resolved for any discrepancies.
- The final analysis will be performed on datasets compiled by John Simon, MA after having been documented as having been cleaned and finalized.

8.2 Analysis Populations

8.2.1 Full Analysis Population (or Intention to Treat or Modified Intention to Treat)

- All subject who were randomized.
- Driving simulation outcomes: All participants will have baseline driving simulation. Missing driving simulation data at the 1-month and 6-month timepoints will be assumed to be missing at random and handled using multiple imputation.
- Demographic characteristics: All participants who are randomized will be included in the report of demographic characteristics of the sample.

8.2.2 Per Protocol Population

- DriveCam outcomes: All participants who produce any DriveCam events during the period beginning at post-training through 1-year post-training. For any participants with missing DriveCam 'long-glance' data, data will be assumed to be missing at random and handled using multiple imputation.

8.2.3 Safety Population

All subjects who have a DriveCam installed in their car will be monitored for safety as described in 8.5 Interim Analyses.

8.3 Covariates and Subgroups

For all analyses:

- Driving experience: Defined as baseline date minus the date that the teen received their graduated or full unrestricted license. Computed in months.

Specific to driving simulation analyses:

- Driving runs: Included in order to be able to include primary outcomes from the two driving runs conducted at the baseline, 1-month post-training assessment, and the 6-month post-training assessment. Generalized estimating equation (GEE) analyses allowed driving simulation data from the two "runs" nested within each of the three "drive types" nested within each participant to be modeled as correlated response variable data, but main or interaction effects for "runs" were not of theoretical interest.

Specific to DriveCam analyses:

- To account for variability in the length of time the DriveCam camera was installed in each participants' automobile during the 1-year post-training period was included as a covariate in addition to months of driving experience as detailed above.

Supplemental Analyses (Requested by New England Journal of Medicine reviewers, editor, and/or statistical expert)

- Moderation Effects—These analyses are post-hoc; thus, effects (adjusted mean difference or relative risk and 95% CI) will be reported rather than significance testing. Note that the widths of confidence intervals are not adjusted for multiple comparisons and no definite conclusions can be drawn from these results.

- Medication status dichotomized based on whether the teen reported taking ADHD medication at any point during the 12-months of naturalistic driving.

- COVID-19 Sensitivity Analysis
  - For 56 (FOCAL+: n=29 teens; Control: n=27 teens) of the 152 participants, their 1-year of naturalistic driving included days beyond March 15, 2020 when COVID restrictions were put into place. We will conduct a sensitivity analyses of our naturalistic driving results by re-running our primary and secondary analyses but including only the 96 teens (FOCAL+ n=47; Control n=49) whose 1-year of naturalistic driving ended prior to COVID restrictions.

8.3.1 Multi-center Studies

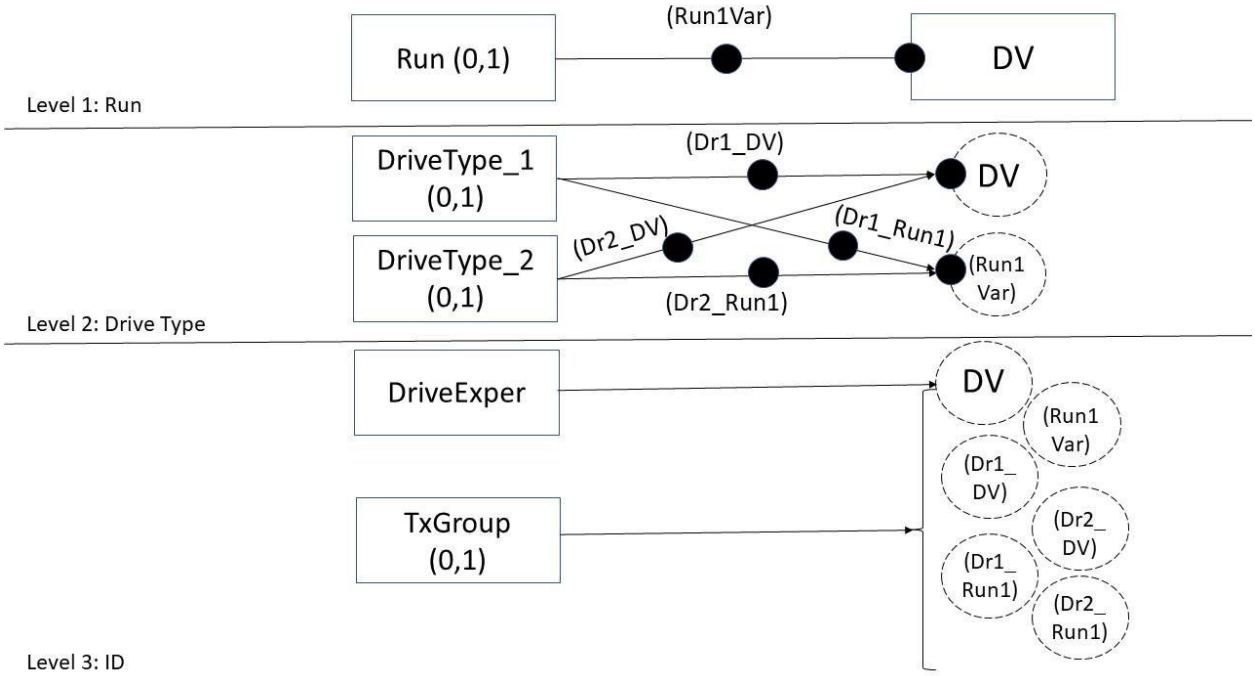
Participants for this study will be recruited from a single site: Cincinnati Children's Hospital Medical Center.

8.4 Missing Data

Although every effort will be undertaken to eliminate missing data, driving simulator and DriveCam equipment failures could occur, and the possibility exists that participants may not complete follow up assessments even after prompting from the research team. Missing data will be assumed to be minimal (< 15%), missing at random (MAR), and consistent with Intent-to-Treat analyses handled via multiple imputation in all primary outcomes analyses (see below for multiple imputation models description).

Primary Analyses

Two different types of multiple imputation models, data analysis model-based imputation, and fully-conditional specification imputation (Enders, 2010; Graham, 2012; Muthén & Muthén, 1998-2017, p. 576), were used to handle primary analysis missing data because the two primary outcomes were measured on two different scales. Missing data for standard-deviation of lane-position, a continuous response variable, was handled using model based imputation assuming a normal distribution. Specifically, a model in which specific driving simulator "runs" (level 1) nested within drive types over time (level 2) across participants (level 3) formed the foundation of the missing data imputation model. A binary indicator of the specific driving simulator "run" was the sole level 1 predictor of standard-deviation of lane-position ("DV"), and that effect was allowed to vary across driving types at level 2 (i.e., slope variance; "RUN1VAR"). Binary indicators of 1-month ("DriveType_1") and 6-month ("DriveType_2") predicted both standard-deviation of lane-position ("DV") and the variation in the effect of specific "run" as a predictor of standard-deviation of lane-position ("RUN1VAR") at level 2, and all four of those predictive effects (shown as "Dr1_DV", "Dr2_DV", "Dr1_Run1", "Dr2_Run1") were allowed to vary across participants at level 3. Randomization ("TxGroup") was entered as a level 3 predictor of all 5 sources of variance ("Run1Var", "Dr1_DV", "Dr2_DV", "Dr1_Run1", "Dr2_Run1"). Driving experience, a level 3 covariate, was included in the model as a predictor of standard-deviation of lane-position ("DV") variance across participants. The standard-deviation of lane-position multiple imputation model is represented graphically in the figure below.



Missing data for long-glances, a Poisson-distributed count response variable, could not be imputed with the same 3-level model used to impute missing standard-deviation of lane-position data. Currently, there is no statistical analysis software package capable of imputing missing 3-level count response variable data. In fact, only Mplus (version 8.8) is capable imputing missing multilevel count data, but only under two conditions: 1.) the imputation model can have no more than two levels, and 2.) missing count of long-glances data can only be imputed with a fully conditional specification (or H_A:) model. As such, the multiple imputation model used to handle missing long - glance data is different from the imputation model used to handle missing standard-deviation of lane-position data in two ways: 1.) a 2-level imputation model, where long-glances variation in driving "runs" nested within post-baseline "drive types" constituted the level 1 model, and long-glances variation across participants constituted the level 2 model, and 2.) all available analysis variable information (i.e., means, variances [where applicable], and covariances [where applicable]) at both levels was used to impute missing long-glances data.

M = 100 imputed datasets were generated for all multiple imputation models. Imputed standard-deviation of lane-position and long-glances primary outcomes data were analyzed using generalized estimating equations (GEE) allowing response variable data non-independence from "runs" nested within "drive types" across participants to be modeled. Specifically, the standard-deviation of lane-position GEE model was specified using a normal distribution assumption with an identity link function. The GEE for long-glances, a count variable, was modeled specifying a Poisson distribution and a natural logarithmic link function. All primary and secondary GEE analyses of imputed data pooled the estimates based on Rubin's rules, and all standard errors were computed based on the average standard errors across imputations and the parameter estimate variation across imputations (Rubin, 1987; Schafer, 1997).

Secondary Analyses

The two outcomes for the secondary analyses, off-road glances and crash/near crash were both measured on a binary scale. Some participants did not have any events either due to the DriveCam not being installed in their car or they did not have any events. Such missing data was not imputed, and we conducted non intent-to-treat analysis using those participants with event data. There was no missing data for the 'crash/near crash' secondary outcome across events for those with a DriveCam installed. The GEE analysis for the 'crash/near crash' outcome was performed using all

participants with DriveCam event data available. However, long glance data was missing for some events due to unforeseen circumstances (e.g., DriveCam view obstruction or participant driver was wearing sunglasses). Missing data for the 'long-glance' outcome was imputed using GEE model-based imputation. Specifically, a logistic link function was used within a missing data imputation model that allowed the effect of random assignment to predict the presence (=1) or absence (=0) of long-glances nested within participants while controlling for months of driving experience and days DriveCam was operational in vehicle.

8.5 Interim Analyses and Data Monitoring

8.5.1 Purpose of Interim Analyses

The only planned interim analysis involves safety monitoring of DriveCam incident data. We will designate a researcher (Stephen Becker, PhD) independent of the present study who will be unblinded to treatment randomization. This researcher will examine the monthly report for events where trigger type = shock [indicative of a collision] and review those clips. Clips containing a crash will be recorded and frequencies by treatment group will be examined. The purpose of these interim safety analyses is to ensure that the FOCAL+ training is not associated with a greater proportion of crashes. If so, we will terminate the study.

8.5.2 Planned Schedule of Interim Analyses

The safety monitoring will occur monthly when we receive the event reports from Lytx.

8.5.3 Stopping Rules

Should participants in the FOCAL+ group experience disproportionately greater numbers of crashes, the independent researcher will inform the PI to determine whether the study will need to end early.

8.5.4 Analysis Methods to Minimize Bias

Generalized estimating equations allows data from driving simulation "runs" (2) within each of the three drive "types" (baseline, 1-month, & 6-month) for all participants to be modeled as correlated responses in analyses even though none of the potential effects for "runs" are of theoretical interest. Risk ratio effect sizes for secondary DriveCam response variables with 95% confidence intervals will be computed based on GEE analysis results.

8.5.5 Adjustment of Confidence Intervals and p-values

Because we have two primary endpoints (number of extended glances away from the roadway and SDLP during driving simulation) that are collected at 2 primary endpoints (1-month post-training and 6-months post-training), we have 4 statistical tests for our primary hypotheses. In order to control for potential Type 1 error, we will use a Bonferroni-corrected alpha of .0125 for testing statistical significance.

Confidence intervals for relative risk ratios effect sizes for the secondary DriveCam data analyses will be obtained based on GEE analysis results. Note that the widths of confidence intervals are not adjusted for multiple comparisons and no definite conclusions can be drawn from these results.

8.5.6 Interim Analysis for Sample Size Adjustment

Our initial protocol included a plan to randomize 136 participants; however, this randomization goal did not account for attrition at the 1- and 6-month driving simulations—the source of our primary endpoints. We were unsure what our level of attrition would be, especially since our sample population was teens with ADHD who can have difficulty following through on commitments.

Hence, our plan was to assess attrition when we reached our sample size of 136 to determine how many additional participants we would need to recruit in order to account for attrition. When we reached our sample size of 136, our calculations suggested that we needed to over-recruit to a randomized sample size of 152 to achieve 136 participants with 1- and 6-month simulator outcomes (primary endpoints) (See 16 Summary of Changes to the Protocol and/or SAP).

8.5.7 Practical Measures to Minimize Bias

To minimize bias, all investigators will remain blinded to participant random assignment until all study measures are completed. The only interim analysis that will be performed concerns safety monitoring to ensure that the FOCAL+ intervention does not result in higher rates of crashes (see section 8.5.1). The person that will view these interim analyses is not a study investigator.

8.5.8 Documentation of Interim Analyses

Monthly, the designated safety reviewer will receive two tables for interim safety monitoring analyses: one summarizing the number of MVC for each randomized group for that month and a second table summarizing the number of cumulative MVCs for each randomized group. Within each table we will specify the number of events with a shock value (i.e., indicative of a MVC). See the templates below:

Current Month: November 2021
Number of Motor Vehicle Accidents for Each Randomized Group

	FOCAL+ (intervention)	Sham Control
Number of motor vehicle accidents		

Cumulative
Number of Motor Vehicle Accidents for Each Randomized Group

	FOCAL+ (intervention)	Sham Control
Number of motor vehicle accidents		

8.6 Multiple Testing

See Section 8.4.5 for statistical adjustments for multiple testing.

9 Summary of Study Data

All continuous variables will be summarized using the following descriptive statistics: mean, standard deviation, median, maximum and minimum. The frequency and percentages of observed levels will be reported for all categorical measures. In general, all data will be listed, sorted by intervention group and subject, and when appropriate by visit number within subject. All summary tables will be structured with a column for each treatment in the order (Full Sample, FOCAL+, Sham Control) and will be annotated with the total population size relevant to that table/treatment, including any missing observations.

9.5 Subject Disposition

Operational definitions used to establish how many subjects reached the various stages of the trial are listed below:

1) Number Screened: Screening for the study will be defined as any contact between an interested individual who queries about the study and is screened for potential eligibility as

described in 6.1 Recruitment. We will track the number of individuals who are screened for the study.

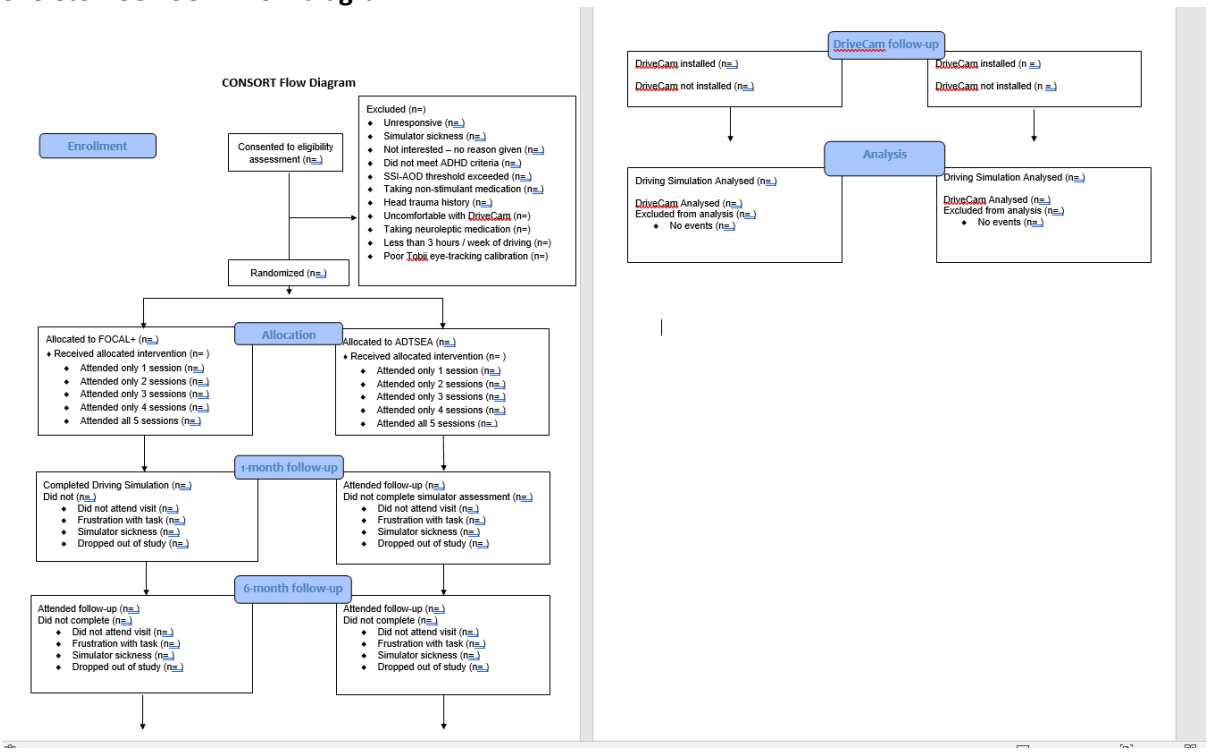
2) Consent: Consent will occur during the first study visit (also known as Baseline/Diagnostic and Clinical Assessment).
3) Number Eligible: Of those who consented to the study, the number who met all eligibility criteria and who showed up for the initial training visit (when randomization occurred).
4) Randomized: Randomization will occur at the second study visit. A sealed envelope will contain the participant's randomization
5) Completed intervention/training visits 1-5: Participants will be considered to have completed the intervention/training visit if they complete at least 1 training.
6) Completed study 1-month post-training follow-up: Participants will be considered to have completed the 1-month post-training follow-up visit if they complete at least one of the two assessment drives.
7) Completed study 6-month post-training follow-up: Participants will be considered to have completed the 6-month post-training follow-up visit if they complete at least one of the two assessment drives.
8) Completed DriveCam follow-up: Participants will be considered to have completed the DriveCam follow-up if we are able to obtain DriveCam data within the previously specified analysis time window (See 6.4 Study Assessments section).

We will track many subjects reached the various stages of the trial, how many dropped out and for what reasons (death, treatment failure, withdrew consent).

Resolving multiple or ambiguous visit dates

Research assistants will be trained to keep detailed logs of each study visit noting any deviations in the study visit protocol (e.g., visit rescheduled because teen took their stimulant medication). If there is any ambiguity arising from multiple sources of visit date, we will examine research visit logs to understand the reason for multiple visits. Using this information, we will decide which visit data to use in final analyses.

Skeleton CONSORT flow diagram



9.6 Derived variables

- **Participant Age**: (moderator for supplemental analyses). Age will be measured in years (using decimals; range 16.00-19.99) and will be calculated by subtracting the participant's date of baseline visit from their date of birth
- **Stimulant medication status**: dichotomized based on whether the teen reported taking ADHD medication at any point during the 12-months of naturalistic driving.

9.7 Protocol Deviations

All protocol deviations will be documented in accordance with IRB requirements in a 'Protocol Deviation Log'. We will evaluate the deviation log at the end of the study and determine if any of the deviations require statistical consideration or adjustment.

9.8 Demographic and Baseline Variables

The data set will be summarized by treatment groups with respect to important confounders. The distributions of categorical variables will be tabulated by treatment group and overall. Continuous variables will be summarized as mean, median, and standard deviation by treatment group and for the overall sample.

- Age in years
- Age at licensure
- State of licensure
- Gender
- Race
- Ethnicity (Latino/a; Not Latino/a; Unknown)

- Maternal/Paternal education (highest level)
- Family income
- License Type (Graduated driver's license; full unrestricted license)
- Driving experience (calculated as months since licensed)
- Full Scale IQ
- Number on stimulant medication at baseline
- Number on stimulant medication during 1-year of post-training driving
- VAPRS scores (Inattention, Hyperactivity/Impulsivity, and Total Score)
- K-SADS ODD diagnosis
- K-SADS Anxiety Disorder diagnosis
- K-SADS Mood Disorder diagnosis

9.9 Concurrent Illnesses and Medical Conditions

Relevant concurrent illnesses, medical conditions, and mental health diagnoses will be assessed as part of the screening and/or the Baseline/Diagnostic and Clinical Assessment. Relevant concurrent illnesses, medical conditions and mental health diagnoses are below along with the methods for assessing them:

Exclusionary concurrent illnesses, medical conditions, and mental health diagnoses:

Concurrent Illness/Medical Condition/Mental Health Diagnosis	**Time Point Assessed**	**Method of Assessment**
High-Risk Substance Use	Baseline	Simple Screening Instrument for Alcohol and Other Drugs (SSI-AOD) score $\geq$ 4
History of moderate to severe head trauma	Screening	Self-report of having lost consciousness for over 30 minutes or having multiple instances of traumatic brain injury irrespective of severity

Non-exclusionary concurrent illnesses, medical conditions, and mental health diagnoses:

Concurrent Illness/Medical Condition/Mental Health Diagnosis	**Time Point Assessed**	**Method of Assessment**
Comorbid mental health diagnosis (e.g., oppositional defiant disorder)	Baseline	Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL)—semi-structured interview with parent and teen
History of head trauma not meeting criteria for moderate to severe head trauma	Screening	Self-report of head trauma that did not meet criteria for moderate to severe. Participants will be required to wait 30 days after their head trauma before participating in the study, to allow sufficient time to pass that negative sequela do not develop.

9.10 Treatment Compliance

The number of treatment sessions attended will be used to assess treatment compliance.

10 Efficacy Analyses

10.5 Primary Efficacy Analysis

Generalized estimating equations (GEE) will be used to analyze the two primary endpoint driving simulator outcome measures: standard deviation of lane position and number of long off-road glances. Missing data will be handled as discussed above (8.4 Missing Data). GEE with an independent correlation structure and accounting for clustering within participants will be conducted for each outcome. Group (FOCAL+ vs. Sham Control), driving timepoint (baseline, 1-month post-training, 6-months post-training), and the two relevant interaction terms: 1) Group x Timepoint (baseline vs. 1-month) and 2) Group x Timepoint (baseline vs 6-month) terms will be tested. Standard deviation of lane position will be analyzed as a continuous variable assuming a normal distribution with a identity link function and an independent correlation matrix. Prior sensitivity analyses showed number of long off-road glances could be analyzed assuming a Poisson distribution with a natural logarithmic link function. Adjusted mean differences for between-group comparisons of standard deviation of lane position (a continuous variable) will be reported by specifying a 'multiple group' option allowing for the two outcome measures to be predicted by months of driving experience separately for the two treatment groups in the same analysis. The resulting intercepts for the outcomes are, by definition, covariate adjusted means. Exponentiated incidence rate ratio for count of long glances during driving simulation will be computed and reported. Note that we will report the exponentiated incidence rate ratio rather than adjusted mean difference for count of long glances because this is the statistic we have seen used for comparing two group counts (Zou, 2004). Confidence intervals for both adjusted mean difference and exponentiated incidence rate ratios will be computed.

10.6 Secondary Efficacy Analyses

All analyses of secondary endpoint DriveCam data will be analyzed using GEE. GEE analyses assuming a Poisson distribution and natural logarithmic link function will be used to analyze individual DriveCam events per participant (random effect) and assess the relative risk of each dichotomous outcome (i.e., presence/absence of long-glance, crash/near crash per event). For these secondary analyses, relative risk ratios with 95% confidence intervals will be computed rather than testing statistical significance (Zou, 2004). Note that the widths of confidence intervals will not be adjusted for multiple comparisons and no definite conclusions can be drawn from these results.

11 Safety Analyses

The PI (Epstein) will be responsible for detecting, documenting, and reporting events that meet the definition of an Adverse Event (AE) or Serious Adverse Event (SAE). Safety data will be tracked and reported as required by Clinicaltrials.gov. Three tables summarizing adverse events will be created:

- All-Cause Mortality: A table of all deaths due to any cause, with number and frequency of such events in each arm/group of the clinical study.

- Serious Adverse Events: A table of all serious adverse events with number and frequency of such events in each arm/group of the clinical study. See Serious Adverse Events definition

below.

- Other (Not Including Serious) Adverse Events: A table of events within any arm of the clinical study with number and frequency of such events in each arm/group of the clinical study. See Adverse Events definition below.

These events will be analyzed and reported for All Randomized Study Participants and by treatment group at the end of the study period. The only SAE that will be analyzed in the interim is events with a shock value (i.e., indicating a collision) as recorded by DriveCam technology (See 8.5 Interim Analyses for more information).

11.5 Adverse Events

Anticipated AE and possible precautions and responses to these events include:

1) **Discomfort caused by completion of survey questions.** Most questions and measures used in the study are standard for medical or psychological evaluations and therefore have minimal risk associated with them. These questions may address issues of family psychiatric history, parental relationships, significant depression/self-harm, and family substance abuse. Participants and parents are free not to answer any questions to which they object. Also, teens with ADHD may experience frustration when completing cognitive and neuropsychological tasks if the testing lasts longer than their attention span or if they are being asked to complete items that are challenging for them. Our evaluators have clinical expertise in evaluating teens with ADHD and if teens are exhibiting fatigue or frustration, families will be given the option of stopping the assessments and returning at another time to complete them.
2) **Identification of high-risk substance use.** If a 16- or 17-year-old is excluded because of their score on the SSI-AOD indicating that they are at risk for substance abuse, we will follow these steps:

    1. A clinician will meet with the 16- or 17-year-old child and provide them with resources for substance use assessment and treatment in the community so that they may seek help. We will give the teen the opportunity to insert the information into their phone or have the information emailed to their private email in order that this remains private health information. The family will be informed that the research staff has determined that the teen does not meet our inclusion/exclusion criteria with no specifics about which criteria were not fulfilled.
    2. Further, the SSI-AOD will be checked to see if the 16- or 17-year-old responded affirmatively to critical items on the SSI-AOD reflecting that the teen's substance use may be putting him/her or others at risk for significant harm ("been injured after drinking or using", "been arrested or had other legal problems (such as driving while intoxicated)", or "When drinking or using drugs, are you more likely to do something you wouldn't normally do, such as break rules, break law, sell things that are important to you, or have unprotected sex with someone?"). If so, a clinician will meet with the 16- or 17-year-old to further interview the teen about these items and make a clinical determination if the child is at risk of significant harm to self or others. If so, the parents of the minor will be notified of the issue and the family will be given resources for substance use assessment and treatment in the community.
    3. The SSI-AOD substance use measure will also be collected at the 6-month assessment point. If the teen has a score of 4 or more indicating "Moderate to high substance use and possible need for further assessment", a clinician will meet with

the 16- or 17-year-old child and provide them with resources for substance use assessment and treatment in the community so that they may seek help. We will give the teen the opportunity to insert the information into their phone or have the information emailed to their private email in order that this remains private health information.

At the 12-month timepoint, we will again collect the SSI-AOD but since there is no in-clinic visit, the SSI-AOD will be collected via REDCap survey. The REDCap survey will be programmed so that if the teen has a score of 4 or more indicating "Moderate to high substance use and possible need for further assessment", the teen will be presented with text indicating that they have scored in the problematic range and providing them with resources for substance use assessment and treatment in the community so that they may seek help.

3) **Simulator sickness including nausea and headache.** The simulator tasks may elicit a mild stress response. When participants are instructed to engage in a secondary task, drivers may experience feelings of annoyance, and participants may experience minor muscle fatigue due to the length of driving time. There is a slight risk that participants may experience nausea from the simulator. In order to limit motion sickness from the simulator, there will be a fan providing air flow in the simulator room, and all participants will be provided with a SeaBand which is worn around the subject's wrist and uses acupressure to reduce nausea and motion sickness. Also, we have limited training driving sessions to 5-minute lengths with breaks in between in order to reduce risks of motion sickness.
4) **Negative impact of medication wash-out on teen driving.** Teen participants who take medication for ADHD will be asked to refrain from taking their medication on the days of simulator driving assessments. Parents will be informed of the risks associated with this (i.e., driving safety, school performance, job performance, etc.). In order to limit the risk associated with a medication washout, both the teen and parent will be advised verbally and in writing that the teen is not to drive to the study appointments and must be driven by the parent. In addition, the study coordinator will make a reminder phone call prior to the driving assessment. During this call, the coordinator will remind parents and teens that parents are to drive un-medicated teens to their appointment. Participants are free to resume medication immediately following the study visits.
5) **Breach of confidentiality.** The potential for a breach in confidentiality always exists, specifically with the written research data and study databases. Study procedures have been designed to protect the privacy and confidentiality of the research participants. Throughout the study, all data, including that collected during the screening and recruitment phase will only be identified by a unique identification number and participant code using letters and numbers to protect against invasion of privacy. The data will be blinded correspondingly in all data analyses. Only authorized staff will have access to participant information. All study information containing identifying information will be stored separately from the study data and will be stored in a locked filing cabinet. Binders with identifying information (e.g., consent forms) will be maintained separately from the evaluation, assessment and outcome data. All data will be entered into an electronic database for storage and analysis. Information will be entered into computers by participant number, not name, in order to protect the identity of the participants and their parents. No personal identifying information will be used in conjunction with the electronic form of the generated data. The database will be accessible by password only by project personnel. Research papers will be based on analyses of group data with no identifying information about any participant used in these reports. For students who complete the Qualtrics Survey via the SONA system, all

electronic data will be kept on password-protected computers and protected by a firewall. Only the researchers will have access to the data.

6) **Incriminating DriveCam recordings.** Driving will be assessed using an in-car video recorder (DriveCam) which will be installed in the identified "teen car." There is a risk that the video recordings could capture video that could be used to incriminate the driver of the car and/or another driver in terms of driving behavior or other illegal behavior. We have obtained a federal Certificate of Confidentiality in order to protect video recorded driving information collected with DriveCam monitoring. All teen drivers will be consented in order to be protected by the Certificate of Confidentiality. Moreover, parents will be told during consent that we will not be sharing the recorded video footage with anyone. If the teen or parent(s) later request to view the footage (e.g., following a driving incident or MVC), the study staff will review the footage and provide the family with a summary of incident-related information visible in the recorded footage (e.g., number of passengers present, driver engagement in another task, etc.). If the family further presses to view the driving footage, the PI will contact the family to discuss Certificate of Confidentiality stipulations prior to releasing any footage information. Additionally, families will be explicitly told that video recordings collected using an in-car video recorder (DriveCam) will be collected on anyone driving the identified "teen car". Moreover, an information card will be provided each family to keep in the car so that anyone who drives the car or is a passenger in the car is aware that they will be video recorded. However, research staff will immediately destroy all video in which the teen participant is not the driver. Further, families will be informed that all video recordings will be destroyed immediately after the study period.
7) **MVC involvement.** Please see 8.5 Interim Analyses for information regarding safety monitoring.

Unanticipated AE: An adverse event whose nature, severity or frequency is inconsistent with the underlying disease, disorder, or condition of the subject, and is not identified in the informed consent document.

11.6 Deaths, Serious Adverse Events and other Significant Adverse Events

A serious adverse event (SAE) is defined as any untoward medical occurrence that at any dose: results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity or is a congenital anomaly/birth defect.

Expected SAE and responses to these events include:

1) **Disclosure of intent to self-harm or harm others and/or disclosure of child abuse.** Teens will also be questioned about depression/self-harm on the K-SADS-PL interview. Consistent with procedures established in several ongoing studies at the Center for ADHD, we will follow a formal process to identify, document, and manage risky behaviors. All K-SADS-PL interviewers will be responsible for identifying and reporting whether the teen is experiencing suicidal ideation or is currently being abused/neglected. If any risk is identified during the K-SADS-PL interview, the interviewer will page the PI or other co-Is to discuss the situation and determine what additional information is necessary to ascertain risk and engage in safety planning, including considering hospitalization, CPS reporting, etc. Teens will be notified at the beginning of the interview (and in the assent form) that anything they discuss during the interview will be kept confidential except if they report any behaviors that place themselves at risk; in those cases, their parents will be informed on the day of the interview and will be part of safety planning. A critical items checklist will be completed

immediately after the interview. Any safety plans will be documented on the critical items checklist.

11.7 Prior and Concurrent Medications

A medication interview conducted with the teen and parent that captures current prescribed medication usage and past prescribed medication usage for attention, learning, emotional, or behavioral difficulties since driving. This questionnaire will be administered during the in-person visits at Baseline and 6-months. In addition, this questionnaire will be sent as a REDCap survey for teens to complete at the 12-month time point.

The summary statistics for who was taking stimulant medication at baseline and during the 1-year of naturalistic driving for the whole sample and separately for each intervention will be produced.

12 Reporting Conventions

P-values ≥0.001 will be reported to 3 decimal places; p-values less than 0.001 will be reported as "<0.001".

13 Quality Assurance of Statistical Programming

All primary analyses will be performed in SPSS (version 27) and SAS (version 9.4) using the generalized linear model function. All secondary analyses will be performed using *Mplus* (version 8.8) and SAS (version 9.4) on a Windows operating system. All analyses will be performed by James Peugh, Ph.D. All analyses code and results will be double-checked by Jeff Epstein, Ph.D.

14 Summary of Changes to the Protocol and/or SAP

The changes from the protocol-specified definitions of aims, outcomes and statistical analytic approaches are outlined below. Changes to the study procedures are also included here. These changes reflect 1) budget cuts that impacted our study design and 2) advances in our knowledge and experience with research methods in recruiting adolescents with ADHD, driving, and human factors.

14.5 Aims Changes

None.

14.6 Outcomes Changes

5/9/2016

1) **No longer collecting and coding randomly selected clips from low threshold events collected from DriveCam technology**. Initially, we were informed that the DriveCam would have a "canary" feature that would randomly record events irrespective of the g-force thresholds. These events would allow us to assess eye-glance behavior that was not tied to g-force events. The "canary" feature did not work with the DriveCams we purchased. Hence, we set the threshold for g-force events at a lower level (i.e., >.45 g-force) than the planned >.6 g-force threshold that would be used for defining events. However, this lower threshold began to produce so many events among our randomized participants that our

servers could not keep up with the number of videos produced. Moreover, the coding demand was too great and unmanageable. It was decided by the research team on 3/26/19 to modify the g-force thresholds back to >.6 g-force and to only save and code those events.

6/1/2016

1) We received our notice of grant award for grant #R01HD084430. The proposed budget was cut by approximately 17%. We needed to modify the scope of some of the proposed work to accommodate the 17% budget reduction. The following outcomes and assessment changes were approved by our NICHD program officer:
    a. Due to the reductions in effort to the investigators and staff and to reduce subject payment costs, we reduced the number of outcome assessments we had originally proposed. The original application proposed collection of baseline, 1-month, 4-month, 8-month, and 1-year post-randomization assessments. We now propose to conduct in-person assessments at baseline, 1-month, and 6-month post-training.
    b. We also made changes to the types of assessments we will include in the study. We will no longer include a road-test assessment. Excluding the road test still allows us to assess driving performance using our remaining three driving measures. That is, use of driving simulation, DriveCam monitoring, and driving records will allow us to assess teen's driving behavior. Hence, we feel that even in the absence of the road test, we will continue to possess the scope of driving assessment necessary to detect between-group differences on driving outcomes.
    c. Due to the cost, the MEMSCap Medication Event Monitoring System was dropped from the study protocol. We replaced daily monitoring of ADHD medication use using self-reported measure of medication administered at baseline and each follow-up visit.

10/30/2019

1) **Increase in sample size based on attrition for 6-month driving simulator visit.** Our initial protocol proposed to randomize 136 participants; however, this randomization goal was based on successfully collected data from 136 at the 1- and 6-month driving simulations—the source of our primary endpoints. When we reached 136 recruited participants, we have estimated a new attrition rate based on data collected thus far. This calculation suggests that we need to over-recruit to a randomized sample size of 152 to achieve 136 participants with 1- and 6-month simulator outcomes (primary endpoints).

1/11/21

1) **BMV records no longer an outcome of interest.** Once all BMV records were collected, we examined the frequency of BMV-reported MVCs. We also compared these rates to the frequency of behaviorally coded MVCs captured by DriveCam technology. The frequency of MVCs according to BMV records was 19 total MVCs across the entire sample over the course of 1-year of driving. According to DriveCam codings of collisions, there were >100 crashes across the entire sample over the course of 1-year of driving. Thus, the research team decided that BMV crashes were not an accurate outcome measure and therefore it would no longer be used as an outcome measure.

14.7 Statistical Changes

6/1/2016

1) **Changes were made to the protocol to reduce the budget with one having implications for the statistical analysis (See Protocol Changes 6/1/2016).** Specifically, the MEMSCap Medication Event Monitoring System would have allowed us to continuously track daily use of medications during the study period. This measurement of medication was being replaced with an administration of self-reported measure of medication use. This measure asks about medication use over the 6 months rather than daily use. Thus, we cannot meaningfully include medication status as a time-varying covariate in analyses as originally intended.

12/1/2016

1) **Changes were made to the protocol to address subject burden which caused us to reconsider the statistical approach (See Protocol Changes 12/1/2016).** In particular, rather than having a single 30-minute run of driving simulator data, we had two 15-minute runs. We made a decision to compute driving simulation outcomes for each run and then include run in the model. Hence, run would be nested within assessment time point (baseline, 1-month, & 6-month) and would create a double repeated measure (i.e., 2 driving "runs" nested within 3 repeated measurements). Generalized linear equations (GEE) handle double repeated measure data better than the originally proposed ANCOVA analysis. In addition, GEE models a) provide a more stringent test of significance; b) are more amenable to analyzing binary and count outcomes; c) and use a long database format which allows us flexibility in handling missing data. Hence, we modified our statistical approach to use GEE rather than ANCOVA models.

   Further, statistical models for examining intervention effects on DriveCam outcomes were modified to allow us to use multilevel mixed longitudinal linear models. Specifically, each participant will have repeated measures response variable data collected over time (i.e., level 1), and within each participant, these responses are not independent but correlated. However, the interest is between-participant variation (level 2) as explained by random assignment. This means within-participant (level-1) variation is not of interest to answering the treatment effect research question, but such variation must be either modeled or controlled appropriately to avoid Type-1 inferential errors. To do so, participant will be declared as the level 2 clustering variable, and specific commands in Mplus ('Type = Complex') will be used to: 1) estimate the intra-class correlation (ICC), which quantifies the non-independence of response variable data, 2) compute the design effect (= C -1 * ICC), which is the multiplier needed to be applied to standard error estimates to avoid Type-1 errors, and 3) test the effect of randomization on binary indicators of crash/near-crashes (1=yes, 0=no) and presence of 2-second off-road glances (1=yes, 0=no). Further, it is well-known that analytic techniques such as 'Type=Complex;' will only accurately correct parameter estimate standard errors if the number of clusters at level 2 is greater than 20. By declaring participant as the level 2 clustering unit, and N (or, in this case, C), which is more than sufficient to accurately correct standard errors to obtain an accurate treatment effect estimate.

06/23/2022

The following statistical changes were made based on New England Journal of Medicine reviewer, statistical expert, and editor feedback.

1) **Changes to primary analyses.**

   a. **Reporting adjusted mean differences for Standard Deviation of Lane Position.** Reviewers noted that we should report adjusted mean differences rather than raw mean differences for standard deviation of lane position at 1-month and 6-months post-training.

b. **Reporting exponentiated incidence rate ratio for comparing group differences in eye glance data.** We now report exponentiated incidence risk ratio for count of long glances during driving simulation. We computed an exponentiated incidence rate ratio which is the appropriate statistic for comparing two counts.

c. **Change in correction for type I error.** We initially proposed to use false discovery rate to control for type I error. However, the statistical expert reviewer indicated that Bonferroni corrected alpha is more a more appropriate type I error control in confirmatory studies of a small number of pre-specified hypotheses. Accordingly, we used a Bonferroni corrected alpha threshold of 0.0125 for assessing statistical significance of the four primary outcome measures at 1-month and 6-months.

d. **Change in covariate**. Rather than use years since licensure as a covariate, we now use months of driving experience instead of years of experience in all our analyses.

e. **Change in handling of missing data**. Multiple imputation was used (See 8.4 Missing Data for more details) to handle missing data rather than maximum likelihood estimation.

2) **Addition of supplemental analyses.**

a. **Sensitivity analysis of naturalistic driving results including only teens whose 1-year of naturalistic driving ended prior to COVID restrictions.** Of the 152 participants, 56 (FOCAL+: n=29 teens; Sham Control: n=27 teens) participants had a portion of their 1-year of naturalistic driving that included days beyond March 15, 2020, when COVID restrictions were put into place. We conducted a sensitivity analysis of our naturalistic driving results including only the 96 teens (FOCAL+ n=47; Sham Control n=49) whose 1-year of naturalistic driving ended prior to COVID restrictions.

b. **Moderator analyses.** We ran a moderator analysis examining age and medication status as moderators of FOCAL+ training effects. For the driving simulation outcomes, we examined whether the improvements from baseline to 1-month post-training and baseline to 6-months post-training were moderated by baseline age or medication status. We ran GEE models like those conducted for the primary analyses as described in 10.1 Primary Analysis, however we inserted the moderator variable in the model, analyzed a fully factorially crossed 4-way interaction model, but assessed the significance of the relevant 3-way interactions (Group x Drive Timepoint: baseline vs. 1-month; baseline vs. 6-months x [Moderator Variable]). For DriveCam outcomes, we examined whether group differences on long glances and crash/near-crashes were moderated by baseline age or medication status. We ran multi-level generalized linear mixed models with a logit link function similar to those conducted for the secondary analyses as reported in the manuscript, however we inserted the moderator variable in the model and assessed the significance of the 2-way interaction between Group x [Moderator Variable].

08/15/2022

The following statistical changes were made based on New England Journal of Medicine statistical expert and editor feedback.

1) Supplemental analyses were trimmed to analyses for which we could provide a strong rationale. Specifically, we will only report moderation analysis of the medication on training outcomes and COVID-19 sensitivity analyses.

a. **Medication Moderation**. For the driving simulation outcomes, we examined whether the improvements from baseline to 1-month post-training and baseline to 6-months post-training were moderated by medication status. These analyses were not intent-to-treat since only the 140 teens for whom we had information about medication status during the 1 year of follow-up were included in these analyses. Adjusted mean differences for standard-deviation of lane-position and natural logarithmic incident rate ratios for count of long glances were computed

using multiple group analysis methods. Specifically, conditional on months of driving experience, training group difference statistics were computed separately across binary medication status.

For DriveCam outcomes, relative risk statistics for binary indicators of long glances and crash/near crash were computed conditional on both months of driving experience and days of DriveCam installation. Specifically, relative risk statistics were computed separately across binary medication status

b. **COVID-19 Sensitivity.** For 56 (FOCAL+: n=29 teens; Control: n=27 teens) of the 152 participants, their 1-year of naturalistic driving included days beyond March 15, 2020 when COVID restrictions were put into place. We conducted a sensitivity analyses of our naturalistic driving results by re-running our primary and secondary analyses but including only the 96 teens (FOCAL+ n=47; Control n=49) whose 1-year of naturalistic driving ended prior to COVID restrictions.

14.8 Protocol Changes

12/1/2016

1) While creating the driving simulation protocols and piloting with our staff, we realized that having participants complete a continuous 30-minute simulated drive for the simulated assessment drives completed at baseline, 1-month, and 6-month time points was too long and might increase risk of motion sickness in our participants. Hence, we made a decision to break the 30-minute assessment drive into 2 15-minute drives with a short break between the drives.

3/09/2017

1) Modifying recruitment procedures to also include recruitment from the SONA system (the psychology research participation system). Plan is to allow students to do initial screening via SONA for course credit (15 minutes) and, for those that appear to qualify, to provide additional information regarding the study and ask them if they are interested in being contacted regarding participation in the larger study.

3/21/2017

1) Revised recruitment language to indicate that recruitment will be broader than the ADHD registry and will include a more general query of hospital electronic medical records.

10/16/2017

1) Added section regarding protocol-specific definition of adverse events for this study within “Potential risks, discomforts, inconveniences, and precautions” section.

11/27/2017

1) Added a section about using the company Truventis for recruitment in “Research Participant Recruitment.”

3/23/2018

1) Added Fusion Media to be used as a recruitment service.
2) Added that a REDCap e-screener will be used when recruiting through recruitment services.
3) Clarified how participants and their parents will sign for consent/assent in the “Obtaining Informed Consent”.
4) Clarified requirements for successfully completing training drives in “Description of Intervention Groups and Control Group” and “Study Measures”.

5) Changed DriveCam g-force threshold to accurately reflect current study procedures.
6) Clarified what DriveCam footage is able to be shared with participant families in order to maintain the Certificate of Confidentiality.

10/10/2018

1) Letters sent from the Center for ADHD may include an opt out option such that families sent letters will send in a post-card opting out from further contact or opting to be contacted on a future date.
2) Modified protocol language to state that the 5 trainings will be completed in 5 sessions scheduled approximately 1 week apart rather than within 5 consecutive weeks to reflect our efforts to better accommodate participant schedules.

3/19/2020

1) Revised protocol to state data safety and monitoring procedures related to coding DriveCam videos remotely during the period of COVID-19 restrictions.

11/17/2020

1) Edited the protocol to indicate that the DriveCam may stay in teens' car beyond one year. This is to account for the fact that some teens have not yet scheduled a de-installation visit, and that we postponed scheduling both install and de-install visits during the shelter in place order related to the COVID pandemic.

Study Documentation Changes

1/23/2017

1) Added risks related to the DriveCam installation/de-installation to study risks portion of consent/assent forms due to previous participant experiencing these risks in the study.
2) Added that the DriveCam contains a GPS but that we would not access these data on the consent/assent form.

2/28/2017

1) Revised Teen Driving History Questionnaire to reflect accurate licensure requirements.
2) Revised compensation in flyer text, recruitment letter, and web text.
3) Revised recruitment contact form to include field stating that the teen would be willing to come off medication for days of visits, as stated in the protocol.
4) Revised recruitment phone script to include new compensation amount and include question to clarify that the teen would need to come off their medication for days of visits, as stated in the protocol.
5) Revised Clinic Recruitment Letter to include additional study opportunity.

3/09/2017

1) Revised adult consent and parent permission form to clarify the section "WHAT IF WE LEARN NEW INFORMATION DURING THE RESEARCH?" with reasons a participant might be excluded from the study.
2) Added materials related to Qualitrics survey (recruitment description, recruitment statement, survey questions, and debriefing script).
3) Modified recruitment script and phone contact form to include questions regarding traumatic brain injury.

3/21/2017

1) Uploaded a general recruitment letter for use with EPIC query.

3/23/2018

1) Consent form change: Removed "Your child's medical problem remains unchanged or becomes worse" from the "What If We Learn New Information During the Research" section as it is not applicable to the study.
2) Parental permission form change: Removed "Your child's medical problem remains unchanged or becomes worse" from the "What If We Learn New Information During the Research" section as it is not applicable to the study.

8/08/2018

1) Added a statement in "Facilities" about sharing data with co-investigators at institutions other than CCHMC to be consistent with the language in our consent forms.

10/10/2018

1) Modified recruitment letter to include a postcard with delayed communication or opt-out options.

Smartform Changes

1/23/2017

1) Edited the second field of recruitment in the Plan of Informed Consent, Assent, and Parental Permission tab to include that we will be using recruitment services. Participants will be able to find information about our study through search engines (e.g., Google, Bing, and Yahoo) and social community pages (e.g., Facebook, Twitter, Pinterest).

2/28/2017

1) Edited the second field of recruitment in the Plan of Informed Consent, Assent, and Parental Permission tab to include that we will be using other media platforms (e.g., Radio and/or Television) for recruitment. Any information that is presented in these advertisements will be IRB approved. If changes to previously IRB approved scripts are needed, we will re-submit all changes prior to posting.

Recruitment Materials

11/27/2017

1) Due to recent lull in recruitment numbers, we plan to use Truventis, a recruitment service that recruits through social media platforms. For this, Truventis has created recruitment materials to display on these platforms.

3/12/2019

1) Added radio ad campaign as a recruitment method in protocol.
2) Added digital flyer to be used with internet radio ad (e.g., Pandora).

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