Software Treatment for Actively Reducing Severity of ADHD as Adjunctive Treatment to Stimulant

(STARS-ADHD-Adjunctive)

Protocol Number: AKIL-05

Principal Investigator/Medical Monitor: Daniel Laskowitz, MD

Co-Principal Investigator: Scott H. Kollins, PhD

Sponsor: Akili Interactive Labs, Inc.

Version Number: 2.0

27 February 2019

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STATEMENT OF COMPLIANCE

This trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- US Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

The protocol, informed consent forms, recruitment materials, and all participant materials will be submitted by the Project Leader to the institutional review board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

LIST OF ABBREVIATIONS

ACS	attention composite score
ADE	adverse device effect
ADHD	attention deficit hyperactivity disorder
ADHD-RS-IV	Attention Deficit Hyperactivity Disorder Rating Scale
API	attention performance index
APP	application
ASD	autism spectrum disorder
CGI-I	Clinical Global Impression - Improvement
CGI-S	Clinical Global Impression - Severity
CMP	clinical monitoring plan
ComSS	Commission Error Standard Score
CPT	continuous performance test
C-SSRS	Columbia Suicide Severity Rating Scale
DCRI	Duke Clinical Research Institute
DSM-V	Diagnostic and Statistical Manual of Mental Health – Fifth Edition
eCRF	electronic case report form
FDA	Food and Drug Administration
ICBT	Ishihara Color Blindness Test
ICF	informed consent form
IRB	institutional review board
IRS	Impairment Rating Scale
KBIT	Kaufman Brief Intelligence Test
LD	learning disability
MAOI	monoamine oxidase inhibitor
MFaCTs	Mathematics Fluency and Calculation Tests
MINI-KID	MINI International Neuropsychiatric Interview for Children and Adolescents
OTC	over the counter
PI	principal investigator
ROC	receiver operator curve
SAP	statistical analysis plan
SSRI	selective serotonin reuptake inhibitor
ToSREC	Test of Silent Reading Efficiency and Comprehension
TOVA-9	Test of Variables of Attention – version 9
UADE	unanticipated adverse device effect

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Software Treatment for Actively Reducing the Severity of ADHD as Adjunctive Treatment to Stimulant
Phase:	Post Registration Follow Up Trial
Description of Study Intervention & Symptom Tracking:	Intervention: AKL-T01 is digital therapeutic software for the neuromodulatory treatment of attention and inhibitory control deficits in pediatric patients with attention deficit hyperactivity disorder. AKL-T01 is an investigational medical device known as Software as a Medical Device (SaMD). Symptom Tracking: AKL-X01 (Fengo) is a mobile application (app) that provides a convenience service to caretakers to capture their routine observations of their child's ADHD symptoms and behaviors in a structured format. AKL-X01 (Fengo) captures symptoms data and provides simple graphical displays; it is not an investigational medical device.
Study Description:	The study aims to enroll (203) participants, with a confirmed diagnosis of ADHD, at approximately 15 sites and will be divided between 2 cohorts; (130) participants will be enrolled in Cohort 1, and (73) participants will be enrolled in Cohort 2. Cohort 1, the primary cohort, will have been stable (adherence to a prescribed medication schedule) on a stimulant medication, but are inadequately managed by the stimulant (in the opinion of the investigator). The stimulant is managed by their own physician for at least 30 days before baseline. This is the "stimulant cohort." Cohort 2, the secondary cohort will have been stable without any stimulant medication for at least 30 days before the baseline. This is the "no stimulant" cohort. For both cohorts, at least 7 and up to 30 days before baseline, participants' caretakers will

	begin using AKL-X01 (Fengo) to track their participants' symptoms and behaviors. During Treatment Phase 1 (Days 1 through 28) participants in Cohort 1 (stimulant) will continue to receive their current stimulant plus the addition of AKL-T01. Participants in Cohort 2 (no stimulant) will only receive AKL-T01. For both cohorts, during this time the caretakers will monitor their child's symptoms daily with AKL-X01. During the 1-Month Break (Days 29 through 56) between AKL-T01 treatment phases, participants in Cohort 1 (stimulant) will continue to receive their current stimulant. In both cohorts, AKL-T01 will be suspended during this time. For both cohorts, during this time caretakers will continue to monitor their child's symptoms daily with AKL-X01. During Treatment Phase 2 (Days 57 through 84), participants in Cohort 1 (stimulant) will continue to receive their current stimulant plus the addition of AKL-T01. Participants in Cohort 2 (no stimulant) will just receive AKL-T01. For both cohorts, during this time the caretakers will monitor their child's symptoms daily with AKL-X01
Objectives:	**Primary:** To understand the synergistic effects of combining AKL-T01 (with AKL-X01 symptom tracking) as adjunctive treatment to stimulant medication on impairment. To understand the effects of AKL-T01 (with AKL-X01 symptom tracking) treatment in participants not recently on stimulant medication on impairment. **Secondary:** To understand symptom and attentional effects of AKL-T01 (with AKL-X01 symptom tracking) in all participants (both Cohort 1 and Cohort 2). **Exploratory:** To understand sustained benefits, through reduction of ADHD impairment and symptoms, following one month of AKL-T01 treatment (with AKL-X01 symptom tracking).
Endpoints:	Primary (Cohort 1, Cohort 2):

1) Overall change in clinician-reported Impairment Rating Scale (IRS) “Overall severity of child’s problem in functioning and overall need for treatment” score from baseline to Day 28.

Secondary (Cohort 1, Cohort 2):

1) Overall change in ADHD-Rating Scale (ADHD-RS) total component score from baseline to Day 28.
2) Clinical Global Impression-Improvement (CGI-I) score at Day 28.
3) Overall change in Test of Variable Attention-Version 9 (TOVA) attention composite score (ACS) and certain constituent scores, from baseline to Day 28 (the specific constituent scores will be described in the SAP).

Exploratory (Cohort 1, Cohort 2):

1) Overall change in clinician-reported IRS “Overall severity of child’s problem in functioning and overall need for treatment” score from baseline to Day 56 and from baseline to Day 84.
2) Overall change in ADHD-RS total component score from baseline to Day 56 and from baseline to Day 84.
3) CGI-I score at Day 56 and at Day 84.
4) Overall improvement in TOVA ACS and certain constituent scores, from baseline to Day 56 and from baseline to Day 84.
5) Overall change in Test of Silent Reading Efficiency and Comprehension (ToSREC) from baseline to Day 28 and from baseline to Day 84, using the appropriate ToSREc form.
6) Overall change in Mathematics Fluency and Calculation Tests (MFaCTs) from baseline to Day 28 and from baseline to Day 84, using the appropriate MFaCTs form.

Descriptive (Cohort 1, Cohort 2):

1) AKL-X01 usage, as compared to the expected usage of 5 days per week.

2) Participant/Caregiver experience and preference questionnaires.
3) Participant demographics.
4) Reported adverse events.
5) Change in participant's medications.
6) Constituent measures of the IRS (individual questions), ADHD-RS (sub-scales and individual questions), and TOVA.

Study Population:

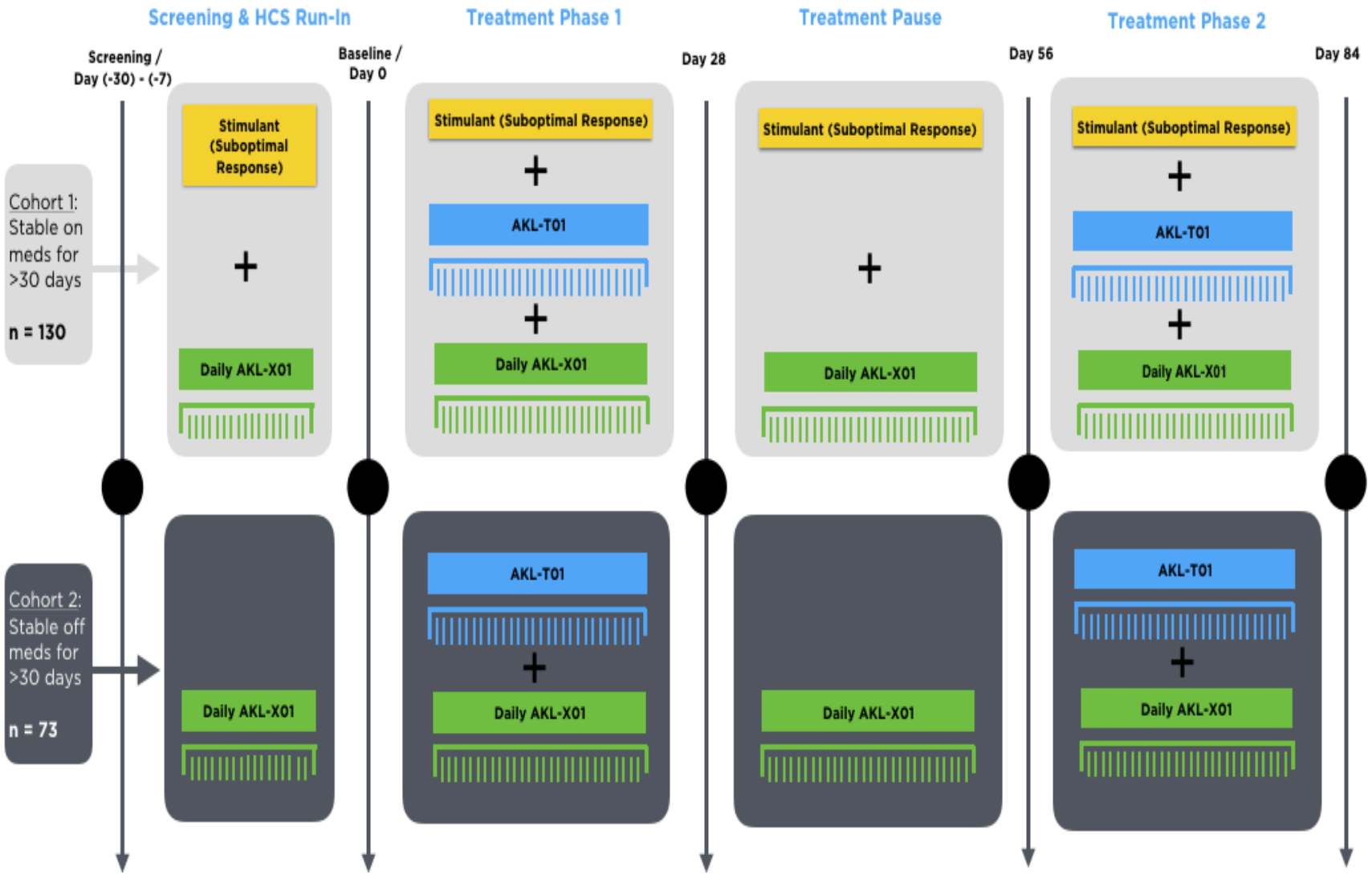
This study will enroll 203 male and female participants; ages 8 years 0 months to 14 years 9 months, inclusive; with a confirmed diagnosis of attention deficit hyperactivity disorder (ADHD), primary inattentive or combined, per the Mini-International Neuropsychiatric Interview for Children and Adolescents; Diagnostic and Statistical Manual-V. Participants must currently be experiencing sub-optimal treatment of ADHD, based upon results of the CGI-S score, and have an IRS (Parent Report) score of ≥ 3. Participants must also have an estimated IQ score of ≥ 80, as assessed by the KBIT If the participant is to be enrolled into Cohort 1 (stimulant), he/she must be consistently (i.e. stable without changes in dosing) on stimulant medication, at an approved FDA dose, for ≥ 30 days prior to enrollment and in the investigator's opinion, it is acceptable to remain on the same dose throughout the study. If the participant is to be enrolled into Cohort 2 (non-stimulant), he/she must be consistently (i.e. stable without starting and stopping medication) off stimulant medication for ≥ 30 days prior to enrollment and in the investigator's opinion, it is acceptable to remain off of stimulants throughout the study. All participants located within the continental United States.

Potential participants currently experiencing controlled (requiring a restricted medication) or uncontrolled, comorbid psychiatric diagnosis, based on MINI-KID and subsequent clinical interviews, with significant symptoms including but not limited to the following should be excluded from enrollment: post-traumatic stress disorder, psychosis, bipolar illness, autism spectrum disorder, severe obsessive-compulsive

	disorder, severe depressive disorder, severe anxiety disorder, conduct disorder, or other symptomatic manifestations that in the opinion of the Investigator may confound study data/assessments. Potential participants who are currently treated with a non-stimulant medication for ADHD (i.e., atomoxetine, clonidine, guanfacine), or who have been diagnosed with ADHD Hyperactive-Impulsive subtype (based upon score on the MINI-KID interview) will be excluded from study participation. Also, any potential participant showing no room for improvement, or those refractory to previously well-administered ADHD treatment, should be excluded.
Description of Sites/Facilities Enrolling Participants:	Approximately 15 sites (mix of institutional sites and private practice centers) located within the continental United States
Study Duration:	Approximately 13 months.
Participant Duration:	Approximately 3-4 months.

1.2 SCHEMA

The AKIL-05 study design schematic can be found on the following page.


Screening & HCS Run-In
Treatment Phase 1
Treatment Pause
Treatment Phase 2
Screening / Day (-30) - (-7)
Baseline / Day 0
Day 28
Day 56
Day 84
Cohort 1: Stable on meds for >30 days
n = 130
Cohort 2: Stable off meds for >30 days
n = 73
Stimulant (Suboptimal Response)
AKL-T01
Daily AKL-X01

1.3 SCHEDULE OF ACTIVITIES

	Screening	Baseline	Treatment Phase 1		1-Month Break		Treatment Phase 2	
	Days -30 to -8**	**Day 0****	**Days 1 to 28**	**Day 28****	**Days 29 to 56**	**Day 56****	**Days 57 to 84**	**Day 84****
Informed consent and assent	X							
Demographics	X							
Medical history/visual acuity testing	X							
Review inclusion/exclusion criteria	X	X						
Enrollment		X						
MINI-KID (administered by trained clinician)	X							
KBIT	X							
Ishihara Color Blindness Test	X							
C-SSRS	X							X
Concomitant medication review	X	X		X		X		X
Configure Fengo on caregiver's phone	X							
Caregiver tracks child's symptoms via Fengo	X	X	X		X		X	
Verify child's caretaker is using HSC (i.e. Parent shows study staff recent data entries on their phone)		X		X		X		X

	Screening	Baseline	Treatment Phase 1		1-Month Break		Treatment Phase 2	
	Days -30 to -8**	**Day 0****	**Days 1 to 28**	**Day 28****	**Days 29 to 56**	**Day 56****	**Days 57 to 84**	**Day 84****
Cohort 1: Confirm stimulant dosage		**X**	**X**		**X**		**X**	
IRS (Clinician Report) (administered by trained clinician)		X		X		X		X
IRS (Parent Report)	X							X
ADHD-RS (administered by trained clinician)		X		X		X		X
CGI-S		X						
CGI-I				X		X		X
TOVA-9		X		X		X		X
ToSREC		X		X		X		X
MFaCTs		X		X		X		X
Complete Experience & Preference Questionnaires								X
Administer AKL- T01 treatment on iPad-Mini and charger ***			X				X	
Collect the iPad-Mini				X				X
Adverse events		X	X	X	X	X	X	X
Caregiver can optionally consent to participate in a 30 to 45 min phone interview (game feature preference discussion) with Sponsor's game designers								X

****Note: All study visits for each participant should be completed during the same time of day (either AM or PM), to maintain consistent data collection and comparison of rater assessment results.**

***If the iPad and charger are not returned to the site within 7 days of visit Day 28 and Day 84, it will be noted as a protocol deviation

Conditions of Obtaining Assent vs Consent:

Visits at Day 28, Day 56 and Day 84 are allowed a window of +/-3 days, calculated based upon Baseline Visit date. (The participant should be encouraged to continue their AKL-T01 treatment during this exception period for Day 28 and Day 84 visits).

2 INTRODUCTION

2.1 STUDY RATIONALE

ADHD is one of the most common pediatric psychiatric conditions and best practice for its treatment includes both pharmacological (usually psychostimulants – methylphenidate or amphetamine) and non-pharmacological (behavioral or cognitive-behavioral therapy). These treatment modalities have demonstrated incontrovertible short-term benefits across core symptoms of ADHD and associated impairments. However, there are limitations to current best practices for the treatment of ADHD.

Pharmacological interventions are accompanied by adverse events in many children, do not normalize functioning, and adherence rates over time are generally low. The latter aspect is likely because longer-term benefits of medication for ADHD are modest. Longitudinal studies have shown that acute improvements in ADHD symptoms and functioning are not maintained beyond 24-36 months.

With respect to non-pharmacological interventions, access to such services can be a challenge for several reasons, including the number of qualified providers and coverage by third-party payers.

Given these limitations to current standards of care, there is a strong need for the development of additional interventions for ADHD that can be easily and widely disseminated. Given the central role of attention and other aspects of cognition in the pathophysiology of ADHD, interventions that specifically target these constructs in safe and effective ways are particularly needed.

While a previous pivotal (FDA Registration) trial demonstrated efficacy and safety of AKL-T01 in children not currently taking psychostimulants, much is still unknown about the effect of AKL-T01 on symptoms and impairments of children currently treated with psychostimulants. Specifically, it is unknown whether AKL-T01 offers additional clinical benefit to patients who are treated with stimulants. In addition, little is known about the sustained effects of AKL-T01 in either stimulant-treated or untreated children. Examining the durability of treatment effects of AKL-T01 will be important for patients and their families, providers, and payers. Relatedly, it is not currently known how additional treatment cycles with AKL-T01 following the initial 28-day regimen will affect outcomes. Addressing this issue will also be critically important for developing long-term treatment plans with AKL-T01 in pediatric populations.

The current study seeks to address these unanswered questions. Specifically, this study aims to determine the effect of AKL-T01 in children with ADHD who are currently treated – but inadequately managed – with psychostimulants. Participants will receive AKL-T01 for approximately 25-30 minutes per day, 5 days per week, over a 4-week treatment period, for two treatment periods separated by a one-month break. Change in Baseline on the IRS (Clinician Report) will serve as the primary outcome variable and will allow for a determination of whether AKL-T01 significantly improves impairments in pediatric patients with ADHD. Secondary measures will include measures of ADHD symptoms, objective measures of attention, and measures of participant and parent/caregiver experience and preference.

2.2 BACKGROUND

Front-line treatment for ADHD includes the use of stimulant medications, which is effective in reducing core symptoms of the disorder but are associated with well-documented side effects. In addition, there is recent evidence that pharmacological treatment may not show optimal benefits in some cognitive domains (Biederman, et al 2015). Computerized cognitive training programs have shown some promise in improving working memory and attention in ADHD populations (Klingberg, et al 2005). Further research is needed to validate the effectiveness of currently available computerized cognitive interventions as well as consumer-grade gamified therapies that are still being developed.

This protocol will evaluate the effects of a novel, highly-immersive, videogame-based intervention for ADHD as adjunctive treatment to stimulants while also providing a mobile app to track symptoms. AKL-T01 was derived from a comparable cognitive training program shown to have robust effects on working memory, attention, and related constructs in older adults (Anguera, et al 2013). AKL-T01 is deployed on mobile devices (i.e. tablets) and incorporates adaptive, simultaneous cognitive tasks in a consumer-grade action videogame-like platform with high-quality graphics and reward mechanisms.

Novel, cost-effective, non-pharmacological interventions for ADHD which are easy to implement and disseminate could be helpful for many participants given the limitations of other approved interventions.

Most relevant to the current protocol is the recently-completed pivotal study STARS-ADHD; a multi-center, randomized, double-blind, active-controlled study comparing AKL-T01 treatment to the use of EVO Words active control in 348 pediatric participants (180 participants were randomized into AKL-T01, and 168 into the control group EVO Words) ages 8-12 diagnosed with ADHD. The study was conducted across 20 sites that were geographically distributed nationwide. Study participants must either have been (a) currently off ADHD medication or (b) currently receiving ADHD medication but inadequately managed on their current stimulant dose per investigator's judgment and willing to discontinue ADHD medication for the study.

Participants were asked to engage in AKL-T01 treatment at home for 25 minutes per day, 5 days per week, for 4 weeks. Participants were assessed using the TOVA, ADHD-RS, IRS, and BRIEF.

The study successfully demonstrated a statistically significant improvement (p=0.006) between AKL-T01 and EVO Words on the primary endpoint (TOVA-API change from Baseline to Post-Treatment) (STARS-ADHD, in progress). This improvement in TOVA-API score based upon treatment is indicative of a clinically meaningful benefit for AKL-T01 participants. This conclusion is supported by the results of the study secondary endpoints, which all consistently trended towards improvement. In this study, AKL-T01 demonstrated a favorable safety profile, with no serious adverse events observed.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

The risks to a participant taking part in this study are minimal. The study involves completing some computerized tests, game-based digital therapies, and answering some questions. It is possible that the participant could become frustrated by some of the tasks. The participant could become fatigued by the computer tests or therapeutic play. If the participant becomes frustrated or fatigued, they may stop at any time. There are no other risks to taking part in this study of which we are aware.

2.3.2 KNOWN POTENTIAL BENEFITS

Based on preliminary data obtained in several studies including a recent registration trial in children with ADHD, the potential benefit of the AKL-T01 game-based treatment for this population is to increase attentional functioning. Given the central role of attention in the pathophysiology of ADHD, this benefit is substantial.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

To date, there have been no serious adverse events reported across several studies with the device. The risk/benefit ratio for use is favorable.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
Cohort 1: To understand the synergistic impairment effects when combining AKL-T01 (with AKL-X01 symptom tracking) as adjunctive treatment to stimulant medication. Cohort 2: To understand the impairment effects of AKL-T01 (with AKL-X01 symptom tracking) treatment in participants not recently on stimulant medication.	Cohort 1, Cohort 2: 1) Overall change in clinician-reported Impairment Rating Scale (IRS) "Overall severity of child's problem in functioning and overall need for treatment" score from baseline to Day 28.	Cohort 1: The overall change in Impairment Rating Scale (Clinician Report) from baseline to Day 28, in participants on stimulant medication, will demonstrate the overall effect that AKL-T01 has on ADHD related impairments when administered in addition to stimulant medication. The IRS score measures the effects on individualized functional impairments. Cohort 2: The overall change in IRS (Clinician Report) from baseline to Day 28, in participants not currently on stimulant medication, will demonstrate the overall effect that AKL-T01 has on ADHD related impairments when administered without stimulant medication. The IRS score measures the effects on individualized functional impairments.
Secondary		
To understand symptom and attentional effects of AKL-T01 (with AKL-X01 symptom tracking) in all participants (both Cohort 1 and Cohort 2).	Cohort 1, Cohort2: 1) Overall change in ADHD-Rating Scale (ADHD-RS) total component score from baseline to Day 28. 2) Clinical Global Impression-Improvement (CGI-I) score at Day 28. 3) Overall change in Test of Variable Attention-Version 9 (TOVA) attention composite score (ACS) and certain constituent scores, from baseline to Day 28 (the specific constituent scores will be described in the SAP).	Measuring and analyzing the overall change in ADHD-Rating Scale and Test of Variable Attention-Version 9 from baseline to Day 28, and the Clinical Global Impression – Improvement score at Day 28, will assist with assessing the impact of AKL-T01 on ADHD symptoms within the short-term following treatment administration.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Exploratory/Descriptive		
Sustained benefits, through reduction of ADHD impairment and symptoms, following 1-Month of AKL-T01 treatment (with AKL-X01 symptom tracking) (both Cohort 1 and Cohort 2).	Exploratory (Cohort 1, Cohort 2): 1) Overall change in clinician-reported IRS "Overall severity of child's problem in functioning and overall need for treatment" score from baseline to Day 56 and from baseline to Day 84. 2) Overall change in ADHD-RS total component score from baseline to Day 56 and from baseline to Day 84. 3) CGI-I score at Day 56 and at Day 84. 4) Overall improvement in TOVA ACS and certain constituent scores, from baseline to Day 56 and from baseline to Day 84. 5) Overall change in Test of Silent Reading Efficiency and Comprehension (ToSREC) from baseline to Day 28 and from baseline to Day 84, using the appropriate ToSREc form. 6) Overall change in Mathematics Fluency and Calculation Tests (MFaCTs) from baseline to Day 28 and from baseline to Day 84, using the appropriate MFaCTs form. Descriptive (Cohort 1, Cohort 2): 1) AKL-X01 usage, as compared to the expected usage of 5 days per week. 2) Participant/Caregiver experience and preference questionnaires. 3) Participant demographics. 4) Reported adverse events. 5) Change in participant's medications. 6) Constituent measures of the IRS (individual questions), ADHD-RS (sub-scales and individual questions), and TOVA.	Measuring the overall change from baseline to Day 84 will examine the sustained effects of AKL-T01 on ADHD symptoms after 1-Month of treatment and 1-Month break, and a follow-on month of treatment in both Cohorts 1 and 2 (analyzed individually). Measuring the overall change from baseline to Day 56 will examine the sustained effects of AKL-T01 on ADHD symptoms after 1-Month of treatment and 1-Month break in both Cohorts 1 and 2 (analyzed individually).

4 STUDY DESIGN

4.1 OVERALL DESIGN

This study is a multi-center, open label trial to determine the effect of AKL-T01 treatment (with AKL-X01 mobile app-based symptom tracking) on ADHD symptoms and impairments in children currently on or off stimulant.

Two hundred and three participants (203) at multiple sites will be enrolled into 2 cohorts. 130 participants will be recruited into cohort 1 and 73 participants will be recruited into cohort 2.

Cohort 1 will have been stable** on stimulant(s) for at least 30 days before baseline. At screening (at least 7 and up to 30 days before baseline), participant caregivers will be instructed to download AKL-X01 on to their smartphone. Caregivers will use AKL-X01 for tracking participants' symptoms and behaviors beginning between days -30 and -7, through day 84. During Treatment Phase 1, Days 1 through 28, participants will continue receiving stimulant and will also receive AKL-T01 treatment. During the 1-month treatment pause, Days 29 through 56, participants will continue receiving stimulant but will discontinue AKL-T01. During Treatment Phase 2, Days 57 through 84, participants will continue receiving stimulant and will also receive AKL-T01 treatment.

****Note:** Medication stability is defined as:

- Moderate response on stimulant, but still room for improvement
- Dose unchanged within past 30 days, but other doses have been tried previously without improvement
- Currently taking stimulant, but parent and/or caregiver wishes not to increase dosage for any reason
- Taking consistent stimulant dose on weekdays, but not on weekends

The hypothesis for Cohort 1 is that children receiving stimulant plus AKL-T01 treatment will improve in ADHD symptoms and impairments from Day 0 to Day 28.

Cohort 2 will have been stable without any stimulant for ≥30 days before baseline. At screening (at least 7 and up to 30 days before baseline), participant caregivers will be instructed to download AKL-X01 on to their smartphone. Caregivers will use AKL-X01 for tracking participant symptoms and behaviors beginning between days -30 and -7, through day 84. During Treatment Phase 1, Days 1 through 28, participants will receive AKL-T01 treatment. During the 1-month treatment pause, Days 29 through 56, participants will discontinue AKL-T01. During Treatment Phase 2, Days 57 through 84, participants will receive AKL-T01 treatment.

The hypothesis for Cohort 2 is that children receiving AKL-T01 treatment will improve in ADHD symptoms and impairments from Day 0 to Day 28.

All study visits for each participant should be completed during the same time of day (either AM or PM), to maintain consistent data collection and comparison of rater assessment results.

4.2 SCIENTIFIC RATIONALE STUDY DESIGN

The Akili-001R trial focused on randomizing participants, into the blinded study, who were not currently being prescribed a stimulant medication regimen for the treatment of ADHD. Participants were evaluated for changes in ADHD symptoms after 28 days of treatment with AKL-T01. The results of the Akili-001R trial showed a marked improvement in ADHD symptoms in participants, ages 8-12 years, who were not currently prescribed stimulant medication(s).

Four post-hoc analyses were of interest in the Akili-001R trial. First, an analysis using the Wilcoxon signed-rank test was used to determine whether the baseline and 28-day API were different within each treatment group. The resulting p-value was less than 0.0001 for AKL-T01 (EVO: Multitask) and 0.67 for placebo (EVO: Words). This result supports the observation that the mean improvement is higher for treatment than the control group. The second post-hoc analysis was to investigate whether there was an interaction between treatment and ADHD type (inattentive vs combined). There was no evidence of a clinically relevant interaction between treatment and either subgroup (all p-values were > 0.13), indicating a consistency of response irrespective of ADHD type. The third analysis using the Wilcoxon signed-rank test was used to determine whether the baseline and 28-day API were different within each treatment group for the ADHD inattentive subgroup. The resulting p-value was 0.0003 for AKL-T01 and 0.40 for placebo. This supports the observed means for the ADHD inattentive subgroup. Lastly, an alternative responder analysis was performed where a responder was a 30% reduction in API. The analysis showed there was an absolute 14.2% more responders in the treatment arm than the control arm ($p = 0.0038$).

The responder results from the Akili-001R trial led to interest in the hypothesis that AKL-T01 administered adjunctively with stimulant medication(s) in participants (ages 8 years 0 months-14 years 9 months) with ADHD may also improve the symptoms of ADHD.

4.3 JUSTIFICATION FOR DOSE

The therapeutic play regimen for the current study (typically 25 minutes per day; 5 days per week; 4 weeks) was established based on previous work with AKL-T01 digital treatment. Specifically, a recent pivotal trial of AKL-T01 demonstrated that this regimen resulted in significant improvements in TOVA API scores in a sample of children with similar characteristics as proposed in this study. The mean compliance for this regimen is 86% (STARS-ADHD).

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit, at Day 84.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all the following criteria:

1) Male or female, ages 8 years 0 months to 14 years 9 months (inclusive), at the time of parental informed consent.
2) Confirmed ADHD diagnosis (primarily inattentive or combined subtype), at Screening based on DSM-V criteria and established via the MINI-KID administered by a trained clinician.
   Note: Co-morbid diagnoses on the MINI-KID are acceptable provided that ADHD is the primary diagnosis and the co-morbid diagnoses will not confound study data (per the Investigator's judgment and documented in source note).
3) Currently experiencing sub-optimal treatment of ADHD, based upon results of Clinical Global Impression-Severity score.
4) Impairment Rating Scale (Parent Report) score of ≥ 3, for #8 Overall Impairment, at Screening.
5) Ability to follow written and verbal instructions (English), as assessed by the PI and/or study coordinator.
6) Estimated IQ score ≥ 80 as assessed by the Kaufmann Brief Intelligence Test, Second Edition (KBIT-II). KBIT assessment performed within 12 months at site prior to screening visit can be used for this study and is not required to be repeated, as long as assessment documentation is available and filed with participant source.
7) Ability to comply with all testing, requirements, study procedures, and availability for the duration of the study.
8) Provision of signed and dated parental informed consent form and assent form.
9) Participant's parent and/or caregiver has access to any of the following Apple™ or Android™ smart phone and/or mobile devices (for accessing AKL-X01 application): Apple iPhone 6, 6+, 7, 8, 10; Android Samsung Galaxy S7, S7 Edge, S8, S8+, S9, S9+; Android Samsung Note 8; Android LG G6, G7, V30, K20. Apple mobile devices must be running iOS 11.2+. Android mobile devices must be running Nougat or Marshmallow.
10) **For Cohort 1 (stimulant),** participant must be stable**** on stimulant medication, at an approved FDA dose, for ≥ 30 days prior to enrollment (may also be one stimulant plus a booster, provided that the dose is stable and does not change throughout the course of the trial).

    ****Note:** Medication stability is defined as:

    - Moderate response on stimulant, but still room for improvement
    - Dose unchanged within past 30 days, but other doses have been tried previously without improvement
    - Currently taking stimulant, but parent and/or caregiver wishes not to increase dosage for any reason
    - Taking consistent stimulant dose on weekdays, but not on weekends
11) **For Cohort 2 (non-stimulant),** participant must be stable off stimulant medication for ≥ 30 days prior to enrollment.

5.2 EXCLUSION CRITERIA

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

1. Current, controlled (requiring a restricted medication) or uncontrolled, comorbid psychiatric diagnosis, based on MINI-KID and subsequent clinical interviewing, with significant symptoms including but not limited to:
    a. post-traumatic stress disorder
    b. psychosis
    c. bipolar illness
    d. autism spectrum disorder
    e. severe obsessive-compulsive disorder
    f. severe depressive
    g. severe anxiety disorder
    h. conduct disorder
    i. other symptomatic manifestations that in the opinion of the Investigator may confound study data/assessments.

Participants with clinical history of learning disorders will be allowed to participate, provided the disorder does not impact their ability to participate in the trial based on PI judgment.

2. Participants who are currently treated with a non-stimulant medication for ADHD (i.e., atomoxetine, clonidine, guanfacine).
3. Participants diagnosed with ADHD Hyperactive-Impulsive subtype, based upon score on the MINI-KID interview.
4. Participants showing no room for improvement, or those refractory to non-intensive ADHD treatment.
5. Initiation within the last 4 weeks from the time of consent of behavioral therapy. Participants who have been in behavior therapy consistently for more than 4 weeks may participate provided their therapy frequency and intensity is unchanged during the course of the study. Participants planning on changing or initiating behavior therapy during the course of the study will be excluded.
6. Participant is currently considered a suicide risk in the opinion of the Investigator, has previously made a suicide attempt, or has a prior history of, or is currently demonstrating active suicidal ideation or self-injurious behavior as measured by C-SSRS at Screening.
7. Motor condition (e.g., physical deformity of the hands/arms; prostheses) that prevents playing the digital treatment as reported by the parent/caregiver or observed by the investigator.
8. Recent history (within the past 6 months) of suspected substance abuse or dependence
9. History of seizures (exclusive of febrile seizures), or significant motor or vocal tics, including but not limited to Tourette's Disorder)
10. Has participated in a clinical trial within 90 days prior to Screening.
11. Diagnosis of or parent-reported color blindness (Confirmed in-clinic via ICBT)
12. Uncorrected visual acuity (confirmed via ability of participant to log-in to T01 app and complete in-clinic game play, at Baseline)
13. Regular use of psychoactive drugs (non-stimulant) that in the opinion of the Investigator may confound study data/assessments.
14. Any other medical, behavioral, or developmental condition that in the opinion of the investigator may confound study data/assessments.
15. Has a sibling also enrolled/currently participating in the same study. Siblings may participate in the study sequentially, but not at the same time.
16. Has previously been randomized in a study of Akili’s videogame-like digital treatment.

5.3 LIFESTYLE CONSIDERATIONS

During this study, participants and parents/caregivers will be asked to:

- Remain on an unchanged dosage of stimulant medication (and stimulant booster, if applicable) during participation in the trial, (Cohort 1).
- Refrain from beginning any treatment with medication during participation in the trial, (Cohort 2).
- Complete gameplay of AKL-T01 for 25 minutes (consecutively) per day, for 5 days each week during the treatment periods.
- Return to the in-clinic visits (Day 28 and Day 84) with the iPad Mini (and iPad charger) that was programmed with their AKL-T01 treatment. Note: On Day 28 the clinical site will return the iPad to Akili for the 1 month break period and will receive the same device from Akili in advance of Day 56 for redistribution to the participant for Treatment Phase II.

During this study, parents and/or caregivers of participants are asked to:

- Complete evaluation of the participant's ADHD symptoms daily (5 days per week) using the AKL-X01 smartphone app. Efforts should be made so that the evaluations are completed at the end of each day, to capture behavior(s) from the entire day. All parents and/or caregivers of participants (study-wide) should complete these evaluations at the same time each day.
- Return to the in-clinic visits with their smartphone and demonstrate they are using the AKL-X01 symptom tracker as described above to the study staff.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently enrolled into the study or administered study treatment. A minimal set of information is required to ensure transparent reporting of participant screen failures, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, and eligibility criteria.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

The following strategies and tools will be utilized to recruit participants for this trial. Recruitment initiatives utilized will be up to the discretion of each individual trial site:

- Newspaper advertisements
- Radio and Television advertisements
- StudyKik website
- Recruitment flyers
- Social media advertisements (trial site initiated and/or Truventis; social media vendor)
- ADDitude Magazine
- Trial site patient databases.

The following strategies and tools will be utilized to maintain participant retention for this trial:

- Appointment reminder cards
- Clinical site contacts parents / caregivers if child isn't using AKL-T01 regularly
- Fengo compliance reminders
- AKL-T01 built-in reminders.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

AKL-T01 multitasking digital treatment was designed to incorporate the fundamental features of Neuroracer into a state-of-the-art mobile video game-like platform, which deploys modern videogame graphics, engaging reward loops, and real-time adaptive mechanics to dynamically personalize difficulty based on the user's ability. AKL-T01 multitasking treatment employs perceptual discrimination attention/memory task as well as a continuous motor "driving" task. Performance on these tasks are assessed in isolation and when performed together to calculate a performance index for each individual user. A personalized multitask treatment regimen is automatically configured and delivered to the user and is optimized adaptively to increase multitasking performance. As players proceed through the treatment periodic recalibration occurs to maintain an optimal difficulty level.

AKL-T01 treatment will be loaded by the sponsor (Akili Interactive Labs) onto iPad Mini 4 tablets. The iPads are configured to minimize the participants' ability to utilize non-study related applications. Features such as browsing the internet, downloading apps, deleting apps, and messaging are restricted. The study devices are not intended to be used for any purpose other than that outlined in this protocol. Site staff will instruct participants and parents on intended and unintended use, as outlined in this protocol. The iPads, along with chargers, will be provided by the sponsor to the clinical sites. In a separate document, a list of login credentials (participant usernames and passwords) will be provided.

Participants will be assigned one iPad Mini 4 loaded with AKL-T01 and login credentials at baseline for use during Treatment Phase I. At Day 28, participants will return the study device to the clinic. On Day 56, the participant will be assigned one iPad Mini 4 with the same login credentials for Treatment Phase II.

6.2 MEASURES TO MINIMIZE BIAS

In an effort to minimize the bias of clinical raters completing subjective clinical outcome measures, every effort should be made to restrict clinical raters' access to participant compliance data reports. Sites should identify a separate staff member to receive and review participant compliance data reports.

Additionally, bias opportunities should be minimized by the removal of rater variability. Every effort should be made, throughout the course of the trial, to maintain the consistency of rating staff among participants.

Also, to minimize the unintentional bias of study data and to maintain data consistency, clinical rater assessments for each participant should be completed at the same time of day throughout the course of the study. Also, all attempts should be made to ensure that the same parent/caregiver completes

the outcome measures. Also, all attempts should be made to ensure that the same study staff administers the subjective clinical outcome measures (ADHD-RS, CGI, and IRS).

All parents and/or caregivers of participants should complete the daily Fengo app assessment five days per week, at the end of each day, to ensure that the entire day's behavior(s) are captured. All parents and/or caregivers of participants (study-wide) should complete the Fengo assessment at the same time of day each day.

All ADHD-RS, MINI-KID and IRS-Clinician clinical assessments **MUST** be completed by a trained clinician, to maintain data consistency.

6.3 STUDY INTERVENTION COMPLIANCE

AKL-T01 automatically captures gameplay compliance and uploads these data directly to a central server when connected to WiFi. The server will automatically push daily compliance emails to the clinical sites (the format of which is described in a separate document). Based on these emails, study staff can then reach out to parents/caregivers (via the preferred contact method captured in the demographic collection) to troubleshoot technical problems and/or encourage more play. The rule for compliance outreach follow:

1. Participants that fail to play any sessions of AKL-T01 over two consecutive days will be contacted to troubleshoot potential WiFi connection problems. These participants will be highlighted in yellow in the daily compliance emails.
2. Participants that fail to play at least 35 sessions of AKL-T01 over 53 days will be contacted and reminded to play more. These participants will be highlighted yellow in the daily compliance emails.
3. Participants that fail to play any sessions of AKL-T01 over 7 consecutive days will be contacted a second time and reminded to play more. These participants will be highlighted red in the daily compliance emails.
4. Participants that fail to play at least 12 sessions of AKL-T01 over 14 days will be contacted a second time and reminded to play more. These participants will be highlighted red in the daily compliance emails.

Additionally, AKL-T01 contains built-in features that remind the participant to play each day.

6.4 CONCOMITANT THERAPY

- **If the participant is enrolled into Cohort 1 (stimulant):** Stimulant medication prescribed for the treatment of ADHD symptoms, provided that the participant's dosage has been stable** for ≥ 30 days prior to Baseline. Participant's stimulant medication dosage should remain stable during the course of the trial, as much as possible. Any titrations (including switching medications) of the participant's stimulant medication during the course of their participation in the trial will be documented within the eCRFs.

****Note:** Medication stability is defined as:

- Moderate response on stimulant, but still room for improvement
- Dose unchanged within past 30 days, but other doses have been tried previously without improvement
- Taking stimulant, but parent and/or caregiver wishes not to increase dosage for any reason
- Taking consistent stimulant dose on weekdays, but not on weekends.

Note: Stimulant medication(s) are expected to be managed by non-study clinicians (unless the site PI/Sub-I is the participant's provider).

- With the exception of common over the counter (OTC) (e.g. ibuprofen, acetaminophen, non-sedating antihistamines to treat seasonal allergies) and prescription medications (e.g. antibiotics) for minor transient ailments, regular use of concomitant medications is not permitted during the study. Daily use of some medications (i.e., non-sedating antihistamines to treat seasonal allergies) may be permitted on a case-by-case basis with PI review/approval documented. Families should advise the study staff if it becomes necessary to use other types of medication. Study investigators can approve short-term use of other medications that are not anticipated to confound study assessments.
- Initiation of or significant changes in non-pharmacological treatment for ADHD is not permitted during the course of the study. Participants actively engaged in non-pharmacological treatment at Screening may be eligible if they meet all inclusion criteria and do not undergo changes to their treatment during the course of the study.

Allowed Medications:

1) Stimulant medication(s), including formulaic variants of amphetamines and/or methylphenidates, which are currently FDA approved for prescribed treatment of pediatric ADHD **(if participant is enrolled into Cohort 1)**.
2) Non-sedating antihistamines
3) Analgesics, including acetaminophen and ibuprofen
4) Antibiotics required for the treatment of minor illnesses
5) Vitamins
6) Melatonin, provided that use is intermittent and not every day and is only taken at night

Prohibited Medications, taken 30 days prior to Baseline visit and throughout the duration of the trial include:

1) Amphetamines **(if participant is enrolled into Cohort 2)**
2) Methylphenidates **(if participant is enrolled into Cohort 2)**
3) SSRIs (e.g., fluoxetine, paroxetine)
4) MAOIs (monoamine oxidase inhibitors)
5) Mood stabilizers (e.g., lithium, valproate, quetiapine)
6) Antipsychotics (e.g., risperidone, olanzapine)
7) Anticonvulsants (e.g., phenobarbital, phenytoin, primidone)
8) Anticoagulants
9) Dextromethorphan
10) Halogenated anesthetics

11) Tricyclic antidepressants
12) Atomoxetine
13) Guanfacine
14) Clonidine
15) Phenylbutazone
16) Sedating antihistamines
17) Decongestants with stimulant properties

7 STUDY TREATMENT DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY TREATMENT

Participants may withdraw at any time during the study without prejudice or be discontinued from study treatment at the discretion of the investigator if medically necessary or if any untoward effects occur. In addition, a participant may be withdrawn by the investigator (in consultation with the sponsor as necessary) if the participant is noncompliant with their assigned treatment (as described below) or otherwise violates the study plan, or for administrative and/or other safety reason.

The investigator or designee will notify the sponsor or their designee immediately when a participant has been discontinued or withdrawn from study treatment because of an adverse event. When a participant discontinues or is withdrawn from treatment before study completion, all applicable activities scheduled for the final study visit should be performed at the time of discontinuation. Any adverse events that are present at the time of discontinuation/withdrawal should be reported and followed up in accordance with the safety requirements outlined in Section 8.3 (Adverse Events).

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Significant study treatment non-compliance, defined as <50% compliance with study treatment
- If any clinical adverse event (AE), or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression worsening, which requires discontinuation of the study treatment
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant unable to receive AKL-T01 for 25 minutes per day, 5 days per week, as prescribed per protocol.

The reason for participant discontinuation or withdrawal from the study will be recorded on the trial's electronic Case Report Form (eCRF). Participants who sign the informed consent form and are enrolled but do not receive the study treatment will not be replaced. Participants who sign the informed consent form, and are enrolled and receive the study treatment, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for one study visit and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within a one week window of the missed visit and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFECTIVENESS ASSESSMENTS

Effectiveness assessments will include the following instruments:

- Impairment Rating Scale
- ADHD-RS-IV
- CGI-I
- TOVA-9
- ToSREC
- MFaCTs

Every effort must be made to ensure that raters of all rating scales/assessments are kept consistent among participants throughout trial participation. Each rating scale/assessment for the participant should be administered by the same rater for the duration of the trial. If a rater leaves a clinical site for any reason the site should replace the rater as quickly as possible, and this replacement rater will also be expected to complete rater training (if not previously trained). The replacement rater should review the participant's source documents for previously completed rating assessments, in an effort to become familiar with the former rater's evaluations.

8.2 SAFETY AND OTHER ASSESSMENTS

Safety assessments will include the evaluation of adverse device events (ADEs).

8.3 ADVERSE DEVICE EFFECTS, SEVERITY, AND REPORTING

8.3.1 DEFINITION OF ADVERSE DEVICE EFFECTS (ADE)

An ADE is an adverse event related to the use of an investigational medical device. This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implementation, the installation, the operation, or any malfunction of the investigational medical device. This also includes any event that is a result of a user error or intentional misuse.

8.3.2 DEFINITION OF UNANTICIPATED ADVERSE DEVICE EFFECTS (UADE)

Per 21 CFR 812.3, an Unanticipated Adverse Device Effect is any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of participants.

Unanticipated Adverse Device Effects will include events meeting BOTH A and B as stated below:

A. Events meeting ALL of the following criteria:
    1) Not included in the list of Anticipated Events (refer to protocol Section 8.3.3)

2) Possibly, probably, or definitely related to the investigational device (per the sponsor)

B. Serious (meets any of the following criteria):
   1) Is life-threatening illness or injury
   2) Results in permanent impairment of a body structure or a body structure
   3) Necessitates medical or surgical intervention to prevent permanent* impairment of a body function or a body structure. (***Permanent*** is defined as irreversible impairment or damage to a body structure or function, excluding trivial impairment or damage)
   4) Leads to fetal distress, fetal death or a congenital abnormality or birth defect
   5) Leads to death.

8.3.3 PREVIOUSLY KNOWN ADVERSE DEVICE EFFECTS

AKL-T01 (instructions for use)....The expectedness of an ADE shall be determined according to the specified reference document containing safety information (e.g., Instructions for Use) and the expected ADEs listed below. Any ADE that is not identified in nature, severity, or specificity in the current investigational product reference documents is considered unanticipated.

Adverse Device Effects expected for this device are as follows:

- Dizziness
- Nausea
- Headache
- Decreased frustration tolerance
- Emotional reaction

8.3.4 CLASSIFICATION OF AN ADVERSE DEVICE EFFECTS

8.3.4.1 SEVERITY OF EVENT

The following guidelines will be used to describe the severity of an ADE:

- **Mild**: Awareness of sign, symptom, or event, but easily tolerated.
- **Moderate**: Discomfort enough to cause interference with usual activity and may warrant intervention.
- **Severe**: Incapacitating, with an inability to do usual activities or significantly affects clinical status and warrants intervention. **Please note: the term "severe" is not the same as "serious".**

8.3.4.2 RELATIONSHIP TO STUDY TREATMENT

All ADEs must have their relationship to study treatment assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. In a clinical trial, the investigational device must always be suspect. The degree of certainty of causal relationship of an adverse device effect of either study treatment will be rated as follows:

- **Possible:** An event that might be due to the use of the study device. An alternative explanation - e.g., concomitant drug(s), concomitant disease(s) - is inconclusive. The relationship in time is reasonable; therefore the causal relationship cannot be excluded.
- **Probable:** An event that might be due to the use of the study device. An alternative explanation is less likely - e.g., concomitant drug(s), concomitant disease(s). The relationship in time is suggestive.
- **Definitely:** An event that is due to the use of the study device. The event cannot be reasonably explained by an alternative explanation - e.g., concomitant drug(s), concomitant disease(s).

8.3.4.3 EXPECTEDNESS

The DCRI Safety Medical Monitor will be responsible for determining whether an ADE is expected or unexpected for events meeting serious criteria. An ADE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study treatment.

8.3.5 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an ADE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All ADEs including local and systemic reactions will be captured on the appropriate case report form (CRF). Information to be collected includes the event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All ADEs occurring while in the study will be documented appropriately regardless of relationship. All ADEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an ADE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an ADE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. ADEs characterized as intermittent require documentation of onset and duration of each episode.

The Site Principal Investigator will record all reportable events with start dates occurring from the time of enrollment through the final study visit (Day 84). At each study visit, the investigator will inquire about the occurrence of ADEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.6 ADVERSE DEVICE EFFECTS REPORTING

It is understood that complete information about an event may not be known at the time the initial report is submitted. The investigator must assess the relationship of the event to the investigational

device (including rationale for assessment) and should make every attempt to obtain as much information as possible concerning the event. Additional information pertaining to an event should be reported in the EDC as it becomes available.

The investigator must report, via IBM Clinical Development EDC database, all adverse device effects (anticipated or unanticipated) that meet serious criteria occurring from the time of enrollment through the final study visit (Day 84) within 24 hours of knowledge of the event. If the EDC database is temporarily unavailable, the event, including investigator-determined causality assessment, should be reported to DCRI via a paper back-up ADE form. Upon return of the availability of the EDC database, the ADE information must be entered into the eCRF.

The investigator must report, via IBM Clinical Development EDC database, when important follow-up information (final diagnosis, outcome, results of specific investigations, etc.) becomes available after submission of the initial ADE form and information. Follow-up information should be submitted according to the same process used for reporting the initial event as described above (i.e., within 24 hours of knowledge, via IBM Clinical Development EDC database). All adverse device effects will be followed through resolution.

DCRI Safety Surveillance will report all adverse device effects to specified trial personnel (sponsor, protocol principal investigator [PI] and project leader) within 1 to 2 business days of receipt.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

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

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.
- Unanticipated adverse device effect, any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of participants
- Examples of potential Unanticipated Problems include, but are not limited to:

1) Unanticipated misuse of device hardware
2) Unanticipated misuse of device software
3) Unanticipated hardware issues
4) Unanticipated software issues.

8.4.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing IRB and to the DCRI Safety Surveillance/lead principal investigator (PI). The UP report will include the following information:

- Protocol-identifying information: protocol title and number, PI's name, and the IRB project number
- Detailed description of the event, incident, experience, or outcome
- Explanation of the basis for determining that the event, incident, experience, or outcome represents an UP
- Description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

An investigator shall submit to the sponsor and to the reviewing IRB a report of any unanticipated device problem occurring during an investigation as soon as possible, but in no event later than 10 business days after the investigator first learns of the effect. A sponsor who conducts an evaluation of an unanticipated adverse device effect under 812.46(b) shall report the results of such evaluation to the Food and Drug Administration (FDA) and to all reviewing IRBs and participating investigators within 10 business days after the sponsor first receives notice of the effect. Thereafter, the sponsor shall submit such additional reports concerning the effect as FDA requests.

9 STATISTICAL CONSIDERATIONS

This section provides a brief overview of the statistical analyses, both quantitative and qualitative in nature that will be used during this study. In addition to what follows in this section, further details will be provided in a separate statistical analysis plan (SAP).

The primary objectives of this study are to (1) understand the synergistic impairment effects when combining AKL-T01 (with app-based symptom tracking, AKL-X01) as adjunctive treatment to stimulant medication, and (2) understand the impairment effects of AKL-T01 (with app-based symptom tracking, AKL-X01) treatment in participants not recently on stimulant medication. Within both the medicated and non-medicated cohorts, a change in Impairment Rating Scale (IRS) (Clinician Report) from baseline to Day 28 will demonstrate the overall effect that AKL-T01 treatment has on ADHD symptoms.

The secondary objective of this study is to understand the symptom and attentional effects of AKL-T01 (with app-based symptom tracking AKL-X01) treatment in all participants. There is an additional exploratory objective which focuses specifically on sustained benefits, through reduction of ADHD symptoms and impairment, experienced by participants following (a) 1-month of treatment with AKL-T01, and (b) an additional 4 weeks of AKL-T01 treatment.

9.1 STATISTICAL HYPOTHESES

The aim of the primary objective is to demonstrate a statistically significant difference on mean change in IRS "Overall severity of child's problem in functioning and overall need for treatment" score, defined for each participant as the score measured on Day 28 minus the score measured at the baseline visit. In both the medicated and non-medicated cohorts, the statistical significance of the primary efficacy analysis will be assessed using a 2-sided paired *t*-test evaluated at the 95% level of confidence. The formulation of the null (H_0) and alternative (H_a) hypotheses are stated below, where μ_d refers to the true mean difference:

- H_0: $\mu_d = 0$
- H_a: $\mu_d \neq 0$.

If, within a particular cohort, the upper bound of the 95% confidence interval around the sample difference is smaller than 0, we will have sufficient evidence to reject H_0 and conclude that AKL-T01 plus Fengo improves ADHD symptoms in that cohort.

If the set of sample differences is non-normal, defined here as skewness larger than 1.5 in magnitude, the efficacy analysis will proceed as a non-parametric Wilcoxon signed rank test. Significance will be determined by evaluating the W-statistic at the 95% level of confidence.

9.2 SAMPLE SIZE DETERMINATION

Sample size estimates were computed by hand and verified with PASS (Machin, Campbell, Fayers, & and Pinol, 1997) (Zar, 1984). Assuming a standard deviation of 1, we determined that an effective total of at least 117 medicated participants (Cohort 1) would be needed to demonstrate an effect size of 0.30 with 90% power at the 95% level of confidence using a within-group *t*-test. Similarly, at least 66 non-medicated participants (Cohort 2) would be needed to demonstrate an effect size of 0.40 with 90% power and 95% confidence. Incorporating a 10% dropout requires that at least 130 + 73 = 203 patients are enrolled in the study. See Table 1 below for more details.

Table 1. Sample size estimates for various combinations of differences and standard deviations. In all cases, we assume 90% power and 95% confidence. The rows used to inform enrollment size for this trial have been highlighted in gray.

Absolute difference between follow-up and baseline	SD	Effect Size	Effective n
0.30	1.00	0.30	117
0.30	1.50	0.20	263
0.30	2.00	0.15	467
0.35	1.00	0.35	86
0.35	1.50	0.23	193
0.35	2.00	0.18	343
0.40	1.00	0.40	66
0.40	1.50	0.27	148
0.40	2.00	0.20	263
0.45	1.00	0.45	52
0.45	1.50	0.30	117
0.45	2.00	0.23	208
0.50	1.00	0.50	42
0.50	1.50	0.33	95
0.50	2.00	0.25	168

9.3 POPULATIONS FOR ANALYSES

There are 3 populations defined for this study: intention-to-treat (ITT); per-protocol (PP); and, safety. The ITT and PP populations will be used for efficacy analyses, and the safety population will be used for the safety analysis. The success of the primary and secondary efficacy analyses will be determined within the ITT population.

9.3.1 INTENTION-TO-TREAT (ITT)

This population is defined as any participant enrolled in the study who receives a device. In the event that a medicated participant's clinician deems it necessary to end medication treatment (or vice versa), no correction will be made to that participant's cohort. Unless otherwise indicated, the ITT population will be used for all statistical analyses, tabular summaries, and data listings.

9.3.2 PER-PROTOCOL

This population is defined as any participant enrolled in the study who began AKL-T01 treatment, completed both the baseline and follow-up IRS assessments, and met a minimum level of compliance. Within both cohorts, an episode of play is approximately 25 minutes once per day, prescribed 5 days per week through the duration of the first treatment phase until Day 28. Compliance is defined as playing at least 50% of all possible episodes in the first treatment phase and is automatically monitored and transmitted back to sites by the device (see Section 6.3 of this document for additional details).

Additionally, the following participants will be excluded from the PP population:

- Participants in Cohort 1 who discontinue medication (or changed medication dosing/type) and participants in Cohort 2 who begin medication after the baseline visit but before Day 28 (i.e., crossovers)
- Participants who used prohibited/exclusionary medication or other treatments for ADHD during the course of the trial.

9.3.3 SAFETY

This population is defined as any participant enrolled in the study who receives a device. At any time during the study, if a participant's clinician deems it necessary to end medication treatment, or, conversely, to begin treatment, that participant's cohort will be determined based on where the participant spent the majority of the first treatment phase (the tiebreaker will be cohort the participant belonged to on Day 28).

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

All continuous variables will be summarized as means (standard deviations), medians (25^{th} and 75^{th} percentiles), minimum and maximum. The number and percentage of participants in each category will be presented for categorical variables. Shift tables may be used to compare baseline and post-baseline assessments involving categorical variables.

Statistical comparisons of continuous variables within each of the two cohorts will be performed using a paired *t*-test, with a Box-Cox transformation applied to induce normality if necessary; comparisons of categorical variables will be performed using the Pearson's chi-square test or Fisher's exact test depending on expected cell sizes. Statistical normality will be assessed using a Shapiro-Wilk test, and will be confirmed by examining the corresponding diagnostic figures. Unless otherwise indicated, comparisons will always use a two-sided significance test at the 95% level of confidence.

All analyses will be conducted using a complete case analysis. In no situation will missing data be imputed.

Analyses will be performed using SAS software version 9.2 or higher (SAS Institute, Inc., Cary, NC).

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

The primary efficacy endpoint for each participant is the change in IRS score from baseline to Day 28, defined as the score on Day 28 minus the score at baseline. Missing data will not be imputed. If a participant is missing either the baseline or Day 28 IRS assessment, that participant will be excluded from the analysis. Within each cohort, the ITT population is the primary efficacy analysis population. Additional per-protocol analyses will be performed on the per-protocol population.

Statistical significance of the change in IRS will be determined using a paired *t*-test. No adjustment for covariates will take place for the primary efficacy analysis, although additional analyses may be requested at the discretion of the investigators. Details will be provided in the SAP.

The results of the primary efficacy analysis will be summarized by cohort as mean change (95% confidence interval) and p-value. If the upper bound of the 95% confidence interval is smaller than 0 in a particular cohort, we will conclude that significance is achieved within that cohort.

Outliers will be determined clinically and identified by an independent third party, with confirmation coming from the PI. If outliers are identified for a given endpoint, a sensitivity analysis will be performed without the outlier.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

The following secondary efficacy endpoints will be tested using the same technique outlined for the primary efficacy analysis: (1) change in sum of ADHD-RS component scores from baseline to Day 28; (2) CGI-I score at Day 28; and, (3) change in TOVA ACS and certain constituents, from baseline to Day 28. The ITT population will be used for all secondary efficacy endpoints with the same analyses being repeated on the per-protocol population.

Family-wise error rate will be controlled using a hierarchical testing strategy. Within each cohort, the maximum allowable Type I error rate will be set to 0.05.

If the primary efficacy endpoint is significant at the 0.05 confidence level, the secondary efficacy endpoints will be tested sequentially in the order in which they appear above, starting with (1) change in autocalculated sum of ADHD-RS Total. If the test for (1) is significant at the 0.05 confidence level, the test for (2) CGI-I score at Day 28 will proceed. If the test for (2) is significant at the 0.05 confidence level, the test for (3) change in TOVA constituents from baseline to Day 28 will proceed, starting with Ex-Gaussian Tau Total, and then to API/ACS, Commission Errors Standard Score H2, RT Variability Standard Score Total, RT Mean Standard Score H1, D-Prime Standard Score H2, and Omission Errors Standard Score H2, in this order. At any point, if the test of a secondary efficacy endpoint fails to achieve significance at the 0.05 confidence level, only nominal p-values will be reported for that endpoint and for all subsequent secondary efficacy endpoints.

If the primary efficacy endpoint is not significant at the 0.05 confidence level, only nominal p-values will be reported for all secondary efficacy endpoints.

9.4.4 SAFETY ANALYSES

Serious adverse device events for both cohorts will be presented. Any adverse events occurring during any phase of the study judged by clinical site primary investigators (PIs) to be related to the device will be recorded and presented in a listing using the safety population. A tabular summary of adverse events by system organ class and preferred term will also be provided using the safety population. The severity of each event will be evaluated by the site PI and presented in the listing and table.

9.4.5 DESCRIPTIVE STATISTICS

Tabular outputs and/or listings will be provided at all available timepoints (baseline, Day 28, Day 56, Day 84) for the following outcomes: (1) AKL-T01 and AKL-X01 actual usage; (2) participant preference surveys and questionnaires; (3) participant demographics; (4) reported adverse events; and, (5) concomitant medications.

9.4.6 PLANNED INTERIM ANALYSES

Tabular outputs and/or listings will be provided at all available timepoints (baseline, Day 28, Day 56, Day 84) (1) participant preference surveys and questionnaires; (2) participant demographics; (3) reported adverse events; and, (4) concomitant medications.

Additionally, an interim analysis will be conducted after the Day 28 visit data has been collected for approximately 50% of participants in each of Cohorts 1 and 2. The interim analysis will include the following assessments data:

1. IRS
2. ADHD-RS
3. TOVA
4. CGI-I

9.4.7 SUB-GROUP ANALYSES

Details of the sub-group analyses will be provided in the SAP.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Tabular outputs of descriptive statistics at each available timepoint (baseline, Day 28, Day 56, Day 84) will be provided for the following assessments: IRS, (all components), ADHD-RS (all components), CGI-Severity, CGI-I, TOVA-9, (attention composite score [ACS] and the constituents of the ACS, including reaction time and prime score), ToSREC, and MFaCTs. Listings may also be provided at the request of the investigators. The ITT population will be used for tables and listings described in this section.

9.4.9 EXPLORATORY ANALYSES

The following exploratory analysis endpoints will be investigated and descriptive statistics will be summarized in the medicated and non-medicated cohorts using the ITT population:

1) Overall change in clinician-reported IRS “Overall severity of child’s problem in functioning and overall need for treatment” score from baseline to Day 56 and from baseline to Day 84.
2) Overall change in ADHD-RS total component score from baseline to Day 56 and from baseline to Day 84.
3) CGI-I score at Day 56 and at Day 84.
4) Overall improvement in TOVA ACS and certain constituent scores, from baseline to Day 56 and from baseline to Day 84.
5) Overall change in Test of Silent Reading Efficiency and Comprehension (ToSREC) from baseline to Day 28 and from baseline to Day 84, using the appropriate ToSREc form.
6) Overall change in Mathematics Fluency and Calculation Tests (MFaCTs) from baseline to Day 28 and from baseline to Day 84, using the appropriate MFaCTs form.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study treatment, study procedures, and risks are given to the participant, and written documentation of informed consent is required before starting treatment/administering study treatment.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent will be obtained from all participants (or their legally authorized representatives; LAR) per 21 CFR Part 50. Informed consent is a process that is initiated before the individual agrees to participate in the study and continues throughout the individual's study participation. Consent forms will be IRB approved, and the participant will be asked to read and review the document. The informed consent process will be conducted and documented in the source document (including the date), and the form signed before the participant undergoes any study-specific procedures. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the sponsor to regulatory authorities, investigators, and study participants as applicable. If the study is prematurely terminated or suspended, the site principal investigator (PI) will promptly inform study participants, their reviewing IRB, and will provide the reasons for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

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

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance with protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA).

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor. The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB, and regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's caregiver contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements (see Section 10.1.8).

The study participant's caregiver email address will also be securely stored in Auth0 as part of the Fengo Single Sign On platform.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the Duke Clinical Research Institute. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by Duke Clinical Research Institute's research staff will be secured and password protected. At the end of the study, all study databases will be coded and archived at the Duke Clinical Research Institute. Any data transferred from the Duke Clinical Research Institute to Akili Interactive will also be coded.

10.1.4 FUTURE USE OF STORED DATA

Data collected for this study will be analyzed and stored at the Duke Clinical Research Institute. After the study is completed, the coded, archived data will be transmitted to and stored at the Duke Clinical Research Institute, for use by other researchers including those outside of the study. Permission to transmit data to the Duke Clinical Research Institute will be included in the informed consent.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	**Co - Principal Investigator**	**Medical Monitor**	**Project Leader**
Daniel Laskowitz, MD	Scott Kollins, PhD	Daniel Laskowitz, MD	Kelly Mundy, MSCR, CCRP
Duke Clinical Research Institute	Duke Clinical Research Institute	Duke Clinical Research Institute	Duke Clinical Research Institute
Duke University Medical Center Duke Box 2900 Durham, NC 27710	Duke ADHD Clinic Pavilion East at Lakeview 2608 Erwin Road, Suite 300 Durham, NC 27705	Duke University Medical Center Duke Box 2900 Durham, NC 27710	Duke Clinical Research Institute 300 West Morgan Street Durham, NC 27701
Tel: (919) 684-0056	Tel: (919) 668-0014	Tel: (919) 684-0056	Tel: (919) 668-7356
Email: danl@neuro.duke.edu	Email: kolli001@mc.duke.edu	Email: danl@neuro.duke.edu	Email: kelly.mundy@duke.edu

A team of Key Opinion Leaders has been formed for the trial, with a purpose of informing Akili Interactive of any considerations that should be reviewed regarding the protocol, study procedures, clinical rater assessments, and other key decisions which are study-related. The Key Opinion Leaders will meet on an ad-hoc basis throughout the course of the trial.

10.1.6 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected; that the reported trial data are accurate, complete, and verifiable; and that the conduct of the trial is in compliance with the currently approved protocol/amendments, with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirements.

Details of clinical site monitoring are documented in a Clinical Monitoring Plan (CMP). The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports. Following written standard operating procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and collected, documented (recorded), and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements.

Independent audits will be conducted by Akili Interactive's Quality Assurance team to ensure monitoring practices are performed consistently across all participating sites and that monitors are following the CMP.

10.1.7 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct and data collection, documentation, and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system, and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the sites for clarification/resolution.

The investigational site will provide direct access to all trial-related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor and inspection by local and regulatory authorities.

10.1.8 DATA HANDLING AND RECORD KEEPING

10.1.8.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All written source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study assessment forms will be provided for use as source documents for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including AEs and concomitant medications) will be entered into IBM Clinical Development, a 21 CFR Part 11-compliant data-capture system provided by the Duke Clinical Research Institute. Clinical data will be entered directly from the source documents.

10.1.8.2 STUDY RECORDS RETENTION

Study documents should be retained for at least 2 years beyond the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor. It is the responsibility of the sponsor to inform the investigator when these documents need no longer be retained.

10.1.9 PROTOCOL DEVIATIONS

The site investigator will use continuous vigilance to identify and report deviations to the sponsor or their representative within five (5) working days of identification of the protocol deviation. Protocol deviations must be reported via entry into the IBM Clinical Development EDC system, within the appropriate eCRF page(s). All deviations must be addressed in study source documents. Protocol deviations must be submitted to the reviewing IRB per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB's requirements.

10.1.10 CONFLICT-OF-INTEREST POLICY

Any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial.

10.2 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
1.0	28Jun2018	Original Protocol	N/A
2.0	27Feb2019	Administrative update	Provide clarification to the protocol

11 REFERENCES

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Zar, J. H. (1984). *Biostatistical Analysis, Second Edition.* Englewood Cliffs, NJ: Prentice-Hall.