Cognitive Training Video Game to Target Subclinical Depressive Symptoms in Youth

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CONFIDENTIALITY STATEMENT

This document is confidential communication. Acceptance of this document constitutes agreement by the recipient that no unpublished information contained herein will be published or disclosed without prior approval of the Principal Investigator or other participating study leadership and as consistent with the award terms.

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STATEMENT OF COMPLIANCE

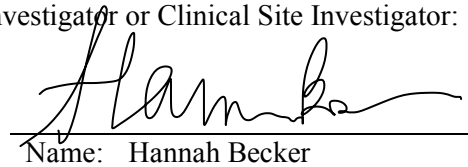
This trial will be carried out in accordance with the United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812) and research best practices. The PIs and all study team members who are responsible for study conduct, management, or oversight will complete Human Subjects Protection and best practices training.

The protocol, and informed consent and recruitment materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent materials will be obtained before any participant is consented. Any amendment to the protocol will be submitted for review and approval by IRBMED before the changes are implemented to the study. All changes to the consent form(s) 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.

INVESTIGATOR'S SIGNATURE

The signature below constitutes the approval of this protocol and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and research best practices, as described in the *Statement of Compliance* above.

Principal Investigator or Clinical Site Investigator:

Signed:  Date: 12/1/2022

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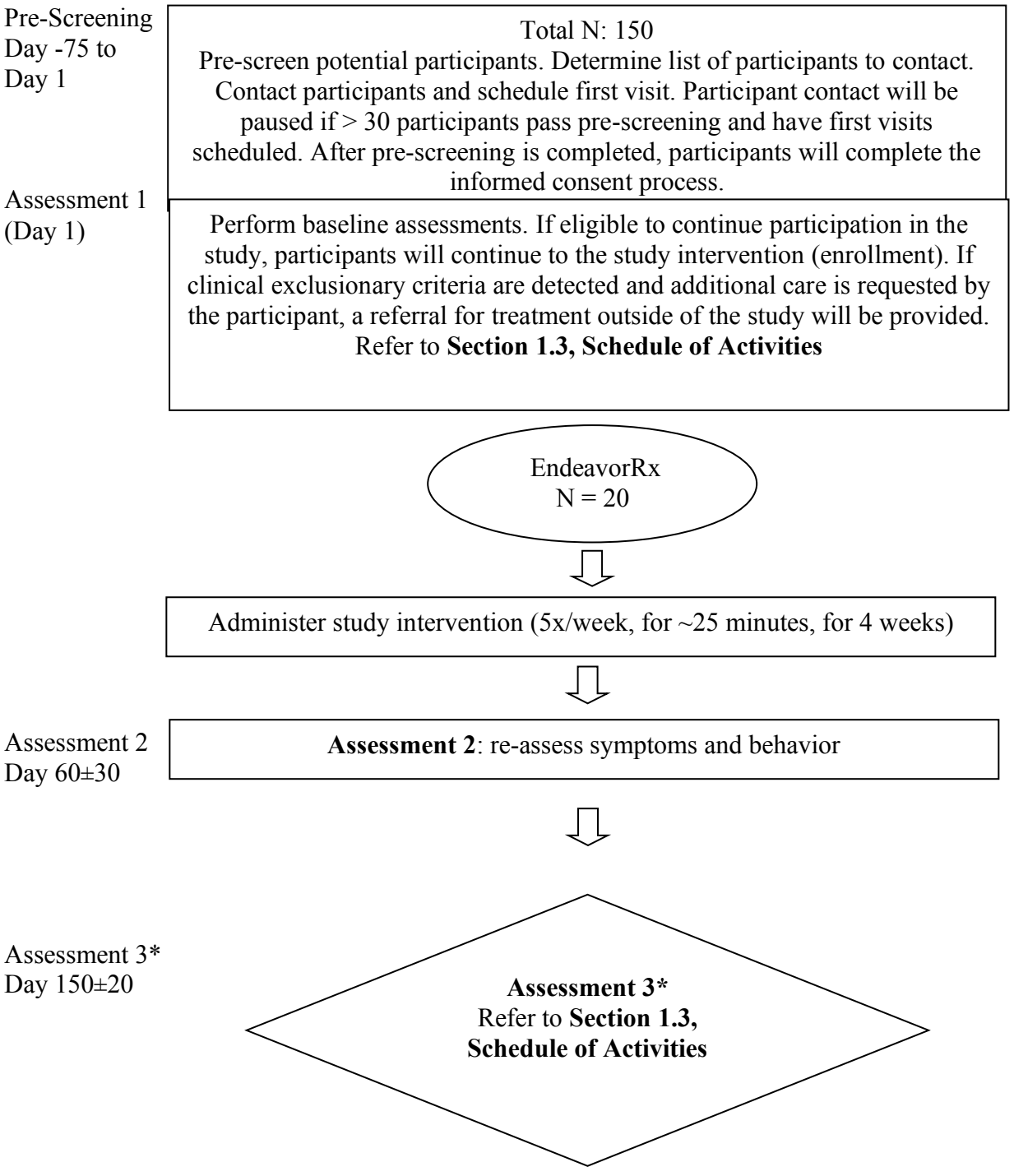
1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Cognitive Training Video Game to Target Subclinical Depressive Symptoms in Youth
Grant Number:	G028070
Study Description:	Youth with subclinical depressive symptoms (9-17) will be recruited to complete a cognitive training, video game-based, preventative intervention (CCT). Multilevel data (clinical measures of depression and anxiety symptoms and behavioral indexes of cognitive control capacity) will be collected before and after the intervention, to examine the extent to which CCT may reduce symptoms of depression and/or enhance cognitive control related behaviors.
Objectives:	Primary Objective: To examine the efficacy of CCT in reducing depressive symptoms and improve cognitive control. Secondary Objectives: To examine the durability *of change in depressive* symptoms *and* (if applicable) cognitive control 3-months after the CCT intervention. Feasibility Objectives: 1) To assess whether participants engage in the intervention as instructed. 2) To assess whether participants enjoy engaging in the intervention. 3) To examine whether the effects of CBT in the Parent study have been maintained at a 2-year follow-up.
Endpoints:	Primary Endpoints: Depressive symptoms and cognitive control behavioral performance after the intervention. Secondary Endpoints: Depressive symptoms and cognitive control behavioral performance 3-months after the intervention. The secondary endpoint was discontinued as of protocol version 2.1 (02 April 2024). Feasibility Endpoints: 1) Game-play metrics provided by Akili software; 2) ESS scores from each assessment; 3) Depressive symptoms at Assessment #1 of current study.
Study Population:	Anxious youth (AY) with subclinical depressive symptoms between the ages of 9 to 17.99
Phase or Stage:	N/A
Description of Sites/Facilities Enrolling Participants:	University of Michigan
Description of Study Intervention/Experimental Manipulation:	Participants will be recruited to complete the CCT intervention. Participants will be offered a 4-week, web-based cognitive control intervention (CCT), which is ~25 minutes a day x 5 days per week.
Study Duration:	24 months
Participant Duration:	Up to 6 months

1.2 SCHEMA



*Assessment 3 was optional to participants and then discontinued in protocol version 2.1 (02 April 2024).

1.3 SCHEDULE OF ACTIVITIES

	Pre-screening (Pre-consent)	Assessment 1 Day 1	Assessment 2 Day 60±30	Assessment 3** 150±20
Review eligibility with phone screen	X			
Informed Consent		X		
Demographics		X		
Clinical assessment				
CBCL		X		
MASC		X	X	X
CDI		X*	X	X
K-SADS (Clinical report)		X		
SCARED-P		X		X
CDSRS		X*	X	X
C-SSRS		X		
ERQ-CA		X	X	X
Behavioral assessment				
Millisecond Inquisit Web Cognitive Battery		X	X	X***
Other assessments				
ESS			X	X
Adherence Metrics from Akili			X	X
Debrief				X
Adverse Events Reporting		X	X	X

*These assessments may be administered more than once if >14 days pass before the cognitive battery and cognitive training can be administered. See Section 6.4 for additional details.

**Assessment 3 was optional to participants and then discontinued in protocol version 2.1 (02 April 2024).

***Provided iPads will be re-collected after Assessment 2. If participants do not have access to a personal tablet from which they can complete the tasks from, then they will not complete the Cognitive Battery at Assessment 3 (if applicable).

2 INTRODUCTION

2.1 STUDY RATIONALE

Rates of depression in children and adolescents are substantial (Basta et al., 2022), and prevalence is steadily increasing (Hawes et al., 2021). Challenges to the treatment of depressive disorders in youth include a dearth of trained providers, treatment cost, and imperfect treatment response with ~30%-60% failing to respond to gold standard treatments (TADS, 2004). These daunting challenges necessitate the development of preventative interventions to reduce subclinical depressive symptoms in children and adolescents *before* full-blown, clinical depression develops. Given links between depressive symptoms and low levels of cognitive control, video-game-based cognitive control training may serve as a low-cost, accessible, and suitable strategy for improving emotion regulation, lessening subclinical symptoms, and thereby reducing risk for developing clinical depression. The video-game intervention assessed in the current study is called *EndeavorRx*. Cognitive control training through *EndeavorRx* will target cognitive and affective domains, with the goal of improving cognitive control/emotion regulation and thus reducing depressive symptoms.

2.2 BACKGROUND

2.2.1 SUBCLINICAL DEPRESSION IS PREVALENT IN YOUTH, INCREASES RISK FOR FULL DEPRESSIVE DISORDER AND LONG-TERM IMPAIRMENT; BETTER INTERVENTIONS ARE NEEDED.

Depressive disorders are extremely common, beginning at peripuberty, with youth who experienced anxiety disorders at younger ages at especially high risk for depression in adolescence (Kessler et al., 2001; Basta et al., 2022). Despite the large number of youth experiencing these disorders a decade ago (~10% for depression and ~30% for anxiety; Merikangas et al., 2010), rates of depression and anxiety have continued to rise during the course of the COVID-19 pandemic (Hawes et al., 2021). Depression symptoms are often evident at young ages, and if left untreated, can lead to significant impairment in social, educational, and familial domains (e.g., school dropout, unemployment, social isolation, and suicide; Rapaport et al., 2005). Further, having symptoms of these disorders increases risk for developing additional psychopathology later in life. Despite treatments that exist to reduce symptoms of depression in youth, such as CBT, many children are left without care. Hospitals and clinics are overwhelmed with demand, and treatments like CBT are resource-intensive, putting a significant time-burden on patients, their families, and the clinicians (Rasing et al., 2017). There are not enough providers or resources to reach all the children and adolescents with depression and/or anxiety, even when considering that many youth and their families will not to seek treatment in the first place (Planey et al., 2019; Reinert et al., 2021). Moreover, once a depressive disorder sets in, full remission following treatment is difficult to achieve, and as many as ~30-60% continue to experience clinically significant symptoms even after receiving treatment (TADS, 2004).

Prior research on youth depression has focused mostly on patients with diagnosed, clinical depression. However, depressive symptoms also exist at the subclinical level. For instance, estimates indicate that more than 20% of adolescents experience subclinical depressive symptoms (Wickrama et al., 2009); these youth have symptoms of depression but do not meet the diagnostic criteria that would indicate a full clinical diagnosis. Although youth who are suffering from subclinical symptoms are often absent from published prevalence estimates of depression, their impact on society and the healthcare system is hardly invisible. A recent study in Dutch youth found that the associated costs of *subclinical* depressive symptoms in adolescents in the Netherlands was equivalent to about $235 million annually (Bodden et al., 2022). In

addition to the impairment associated with subclinical depressive symptoms on their own, research has noted that subclinical depressive symptoms predict the onset of *clinical* depression (Cuijpers et al., 2014; Garber & Weersing, 2010). Having an anxiety disorder diagnosis is also a risk factor for developing clinical depression; these disorders are highly comorbid, though anxiety typically occurs prior to the development of depression (Kalin, 2021). To prevent the development of clinical depression in children and adolescents, depressive symptoms should be intervened upon at the subclinical level. However, in order to be effective, the preventative intervention needs to be accessible, low-cost, and feasible without the use of clinician resources.

2.2.2 SYMPTOMS OF DEPRESISON AND ANXIETY ARE ASSOCIATED WITH DEFICITS IN COGNITIVE CONTROL.

Cognitive control involves the ability to direct attention towards regulating emotions and behaviors, and can be measured by tasks with a high cognitive demand (Joorman & Vanderlind, 2014; Muris et al., 2008). Accumulating evidence indicates that are there cognitive control behavioral deficits in youth with depression and anxiety (Han et al., 2016; Keller et al., 2019; Kertz et al., 2016), a dysfunction that is observed at the neurobiological level as well. For example, cognitive control is facilitated by a network of regions across superior parietal, lateral, and medial prefrontal cortex, sometimes referred to as the frontoparietal network (FPN; Zanto & Gazzaley, 2013). In youth with anxiety, as compared to healthy youth, there is hypo-*activity* of the FPN during cognitive control demanding tasks (Fitzgerald et al., 2013). Additionally, a meta-analysis of studies assessing major depressive disorder identified hypo-connectivity of the FPN as compared to healthy individuals (Kaiser et al., 2015). One model of depression in youth postulates that lower cognitive control capacity confers risk for developing depression; when challenging life events occur, those with lower cognitive control capacity are less able to implement effective emotional regulation, leading to worse symptoms (Joorman & Vanderlind, 2014; Tajik-Parvinchi et al., 2020). Despite evidence that targeting cognitive control might improve outcomes for youth with depression (Han et al., 2016), no preventative interventions for subclinical depression have been developed that specifically target cognitive control. The current project will assess a novel, low-cost and accessible preventative intervention that trains cognitive control, with the goal of reducing subclinical depression symptoms.

2.2.3 A VIDEO GAME (ENDEAVORRX) MIGHT IMPROVE COGNITIVE CONTROL AND THEREFORE REDUCE DEPRESSIVE SYMPTOMS

The intervention used in the current study is *EndeavorRx*, a video game that has been demonstrated to improve cognitive control in youth (Kollins et al., 2020). *EndeavorRx* is designed specifically to improve attention and cognitive control and is FDA approved to support the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD; Davis et al., 2018; Kollins et al., 2020). In studies of ADHD-affected youth, the benefits of *EndeavorRx* on cognitive control appear to be maintained over time. Specifically, following *EndeavorRx* training, ADHD symptom reduction is maintained over a three year span (Jurigova et al., 2021). Though untested in youth with subclinical depressive symptoms, a recent study found that *EndeavorRx* led to improvements in cognitive control in adults with clinical depression (Keefe et al., 2022). Based on this convergence of evidence, we hypothesize that *EndeavorRx* will increase cognitive control and thereby reduce depressive symptoms in subclinically-affected youth. This hypothesis is further supported by preliminary work from our research group which demonstrated that an interactive-play cognitive training intervention in anxious preschoolers improved cognitive control and reduced anxiety symptoms (Schroder et al., 2022), which commonly precede depressive symptoms at later ages.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

1) Risk of boredom or fatigue (likely). Participants may become tired or bored during the intervention, assessments, and computerized cognitive testing.

   To minimize risk: Participants will be allowed breaks in between testing sections and game-play is completed for no more than 25 minutes/day.

2) Loss of confidentiality around sensitive information (rare).

   To minimize risk: All subjects are assigned research numbers, and all research information collected is linked to the subject only by this number. Great care is taken to remove all identifying information from research records. A single tracking file contains links to the research records and subject codes. Recruitment tracking files are kept only for the duration of recruitment. Any paper records are kept in locked file drawers in a locked room, to which only authorized research personnel have access. Any paper records with identifying information (consent form, payment records) are kept in locked file cabinets, physically separate from the research records. Computer records with identifying information are kept on secure, password protected servers. Staff members are trained to scrupulously protect the confidentiality of sensitive information, and take care to limit the printing of documents with identifying information and to avoid unnecessary discussion of subject names. Screening forms for subjects who do not qualify for the study will be destroyed, except for anonymous information unlinkable to the subjects (such as age, gender, and education).

   However, if a subject may become eligible in the near future, e.g. they need to wait 1 month after a recent medication change, we will retain certain records so as not to repeat the assessments, with the assent of the potential participant.

3) Worsening of depressive symptoms, including suicidal thoughts plans, intentions or behaviors.

   Depressive symptoms may worsen during the course of the participation in the study, including the emergence of suicidality. During the screening period in Assessment 1, suicidal thoughts, plans, intentions and behaviors will be assessed with the Columbia-Suicide Severity Rating Scale – Screen Version (C-SSRS). If assessment uncovers suicidal plans or intentions or recent behaviors, emergency evaluation will occur, and an appropriate plan of action will be followed, e.g. safety plan will be created and referral to psychiatric emergency room. Subjects will not continue to be enrolled in the study if any items on the C-SSRS are endorsed during the screening period of Assessment 1. Therefore, any potential participant with suicidal thoughts or behaviors will be excluded from the study. Suicidal thoughts will also be assessed after the 4-week intervention and (if applicable) at a 3-month follow up through items on the CDI and CDSRS. If these items are endorsed, then evaluation will occur, followed by an appropriate plan of action (as stated above). If symptoms worsen during the course of participation, but not to the level of suicidal thoughts, plans, intentions or behaviors, the participant may be withdrawn (see 7.1 below).

2.3.2 KNOWN POTENTIAL BENEFITS

For all participants, there is a potential benefit from the CCT intervention. For those who may have previously received CBT, there is an added potential benefit from the effect of combined therapy and cognitive control training (CCT). It is also possible that participants may not derive any direct benefit from participating in the study. Please refer to *section 2.2.3* for additional information about potential benefit from the CCT intervention.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The risks associated with this study are no greater than those associated with usual clinical management of subclinical depression and anxiety in children and adolescents. The proposed experiment could reveal important information about the nature of mental processes involved in the pathophysiology of subclinical depression and anxiety. It is expected that this information may indirectly lead to the development of better forms of preventative intervention for depression and for treatment for anxiety and/or depression. There is no other, safer or less-invasive means of answering the questions posed by the experiment described above. Strategy has been made to minimize each risk, respectively.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS	PUTATIVE MECHANISMS OF ACTION
Primary			
To examine the efficacy of CCT in reducing depressive and anxiety symptoms and improve cognitive control.	Depressive symptoms and cognitive control behavioral performance after the intervention.	We anticipate that CCT will result in increased cognitive control capacity, which will also relate to reductions in depressive symptoms.	Enhanced cognitive control ability (as trained with CCT) will improve the ability to regulate symptoms, thus lowering symptoms and reducing risk of developing full disorder.
Secondary*			
To examine the durability of change in depressive symptoms and cognitive control 3-months after the CCT intervention. *Secondary endpoint was optional to participants and then discontinued after protocol version 2.1 (02 April 2024).	Depressive symptoms and cognitive control capacity 3-months post-intervention.	We anticipate that depressive symptoms will be reduced, and cognitive control enhanced, to a greater extent 3-months post-intervention as compared to immediately post-intervention.	Changes in cognitive control that may also support a reduction in depressive symptoms may have solidified over 3-months and therefore become detectible in self-report and clinician-administered assessments.
Feasibility/Acceptability and Experimental Outcomes			
1) To assess whether participants engage in the intervention as instructed.	1) Game-play metrics provided by Akili software; 2) ESS scores from	1) We anticipate that participants will play the game as instructed, 2) that they will have	Prior studies of *EndeavorRx* have demonstrated the feasibility and

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS	PUTATIVE MECHANISMS OF ACTION
2) To assess whether participants enjoy engaging in the intervention. 3) To examine whether the effects of CBT in the Parent study have been maintained at a 2-year follow-up.	each post-intervention assessment; 3) Depressive symptoms at Assessment #1 of current study	favorable emotions associated with game play and, 3) that depressive symptoms will still be reduced from the original baseline assessment, but that they will be greater than they were immediately after intervention in the Parent study.	acceptability of the intervention. Also, that treatment for anxiety disorders in the Parent study should also reduce co-morbid depressive symptoms, and that this reduction should be maintained over time.

4 STUDY DESIGN

4.1 OVERALL DESIGN

We hypothesized that cognitive training *EndeavorRx* may augment cognitive control and reduce depressive symptoms. In this study, youth with subclinical depressive symptoms (ages 9 to 17) will be recruited to complete the CCT intervention for 4-weeks. Before and after the intervention, all participants will complete semi-structured clinical assessment of depressive symptoms and a computerized evaluation of cognitive control capacity (e.g., Millisecond Inquisit Web Cognitive Battery; Zelazo, Anderson, Richler, Wallner-Allen, and Beaumont, 2013)

Recruitment will leverage a well-characterized sample from a recently completed study ("Parent study"; HUM00118950) of clinically significant anxiety, a known risk factor for emergence of later depressive symptoms in the subclinical-to-clinical range. In the Parent study, 148 youths (7-17 years) with impairing anxiety were recruited and randomized 2:1 to receive 12-week CBT or a non-active control therapy, "relaxation and mentorship therapy" (RMT); behavioral, neurobiological (fMRI), and clinical measures were collected before and after treatment. Additional participants may need to be recruited beyond the "Parent study" sample (for reasons such as: slow recruitment from "Parent study" or not enough participants from "Parent study" meeting enrollment criteria).

Up to thirty subjects from the Parent study will be recruited to complete the *EndeavorRx* intervention. The intervention will be played at home for ~25 min/day), 5x per week, for 4 weeks. Designed as an exciting, youth-friendly computer game, EndeavorRx engages and trains cognitive control across component processes of attention, response inhibition, shifting and working memory. Of note, EndeavorRx game difficulty is titrated to individual performance, and thus age; the increasing difficulty helps to reduce participant boredom and progressively train cognitive control. Adherence to prescribed training will be monitored using an Akili-provided dashboard, available to the research study team, that interfaces real-time as participants access EndeavorRx via their iPads. If there is no game play for ≥48 hours, a parent will be contacted in order to ensure compliance with the intervention.

If the Parent study does not yield sufficient participation, then we will recruit through the community using the social media campaign strategies that have proven effective in our past work, including UMHealthResearch. The proposed study will add up to three additional timepoints of assessment (pre-intervention, post-intervention, and (if applicable) 3-months post-intervention. All study activities will be completely remotely via an encrypted HIPAA-compliant video conferencing platform (e.g., Zoom), phone

call, and/or Qualtrics links. Depressive symptoms, anxiety symptoms, general psychopathology, and cognitive control behavior as indexed by a *Millisecond Inquisit Web* Cognitive Battery will be assessed pre-intervention. After the intervention, the same symptoms and cognitive control behavioral will be assessed. These variables will optionally be assessed again 3-months post intervention.

Data analyses will compare pre- and post-CCT data. Additionally, multilevel models will assess change in depressive symptoms and cognitive control over time and comparing between those who received CBT as compared to those who received RMT in the Parent study. These data will include *Millisecond* measures of behavioral capacity for cognitive control and detailed assessment of depressive and anxiety symptoms using both clinician-interview and self-report. Pre- to post-CCT change in depressive symptom severity (clinician-measured) will serve as the primary outcome variable.

At protocol version 2.1 (02 April 2024), Assessment #3 (3-month follow-up) was removed to increase feasibility so that resources could focused on increased recruitment.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

We hypothesize that CCT will improve cognitive control capacity and thereby reduce depressive symptoms post-intervention and (if applicable) after a 3-month period post intervention. Therefore, we will enroll youth with subclinical depressive symptoms to complete the CCT intervention and measuring their cognitive control capacity and clinical symptomology after the intervention.

The aims of this project are to:

1. Examine whether CCT will reduce depressive and anxiety symptoms and improve cognitive control after the 4-week intervention.
2. If applicable, examine whether the effects of CCT change in a 3-month period after the CCT intervention.
3. Examine the feasibility and accessibility of the CCT intervention.
4. If applicable, examine whether the effects of cognitive behavioral therapy (CBT) in a previous intervention and protocol have been maintained at a 2-year follow-up.

4.3 JUSTIFICATION FOR INTERVENTION

The CCT intervention will consist 4-weeks of video game play (for 25 minutes/day, 5 days/week).The *EndeavorRx* video game is designed to target focused attention, response inhibition, working memory and multiple simultaneous attention to constitute a general executive function training, and activate neural systems associated with executive function/cognitive control. All video game play will be done remotely, at-home, via iPad. iPads will have EndeavorRx preloaded or downloaded onto a personal iPad, which participants will access through a unique username and password. Difficulty of the games will be titrated individually and by session to avoid boredom and progressively activate the functional systems underlying cognitive control, which we hypothesize will subsequently reduce depressive symptoms. Prior clinical trials have administered *EndeavorRx* for this duration and frequency (4 weeks, 25 minutes/day, 5 days/week) in youth (Kollins et al., 2020).

4.4 END-OF-STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed the baseline assessment, at least 4 weeks of CCT intervention, *Millisecond* battery, post-intervention assessment, and

the final assessment. If a participant completes all these activities but not the final, optional (3-month post-intervention) assessment, then they will, at PI discretion, still be considered to have completed the study. In other words, if a participant does not to participate in Assessment #3, they will still be considered to have completed the study. At protocol version 2.1 (02 April 2024), Assessment #3 (3-month follow-up) was removed altogether.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

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

1. Parent or guardian willing to give informed consent, and children willing to give informed assent to participate in the study.
2. Males and females (age 9 – 17.99)
3. Participant is willing to engage in a technology-based intervention (technology will be provided to participants who live in the state of Michigan, if not already accessible to participant).
4. Self-reported depressive symptoms (CDI score between 3-19 at Assessment 1)
5. Participants will be required to maintain a stable dose of medications for 4 weeks prior to the first assessment and stable medication throughout the intervention period. Participants may change medication after completion of the post-intervention assessment (i.e. in between the post-intervention assessment and follow-up assessment).

5.2 EXCLUSION CRITERIA

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

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

1. Color blindness
2. Unable to play the video game for any reason
3. K-SADS diagnosis of clinical depression, psychosis, or Autism Spectrum Disorder
4. Has enrolled in new psychotherapy (for the treatment of a mood or anxiety disorder) or had changes to their psychotherapy in the 4-weeks prior to study enrollment
5. Endorses items #1, #2, #3, #4, #5. #6 on the C-SSRS Screener (Past-Month); i.e., has present suicidal intention/behavior.
6. Has had any changes to their medication in the 4-weeks prior to study enrollment

5.3 LIFESTYLE CONSIDERATIONS

Participants must maintain stable doses of any medication throughout participation in this study. Initiation of new medications, or substantial changes in dosage of current medications, prior to the end of the study, may be requested by the patient. In this event, the patient will be withdrawn from the study and referred to clinical care.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in this study but are not subsequently assigned to the study intervention or entered in the study. Individuals who do not meet the criteria for participation in this trial (screen failure) because of meeting one or more exclusion criteria that are likely to change over time may be rescreened. Rescreened participants will be assigned the same participant number as for the initial screening.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Recruitment will be mostly from participants who had already enrolled in the Parent study and who, at the time of enrollment in the parent study, had consented to be re-contacted for research purposes. All participants will be contacted via phone call or email and asked if they are interested in hearing about another research study involving a preventative intervention. If they are, we will conduct our phone screen to determine initial eligibility and whether they should be scheduled for a consent visit. After the original contact, we may also reach out to parents via text message (using a prepared and approved message template) to direct their attention to their voicemail or email, and request to schedule a phone screen. Parents of potential participants will be contacted from the sample of eligible participants of the Parent study until target enrollment of the current protocol is reached. If it is decided to recruit from outside of the Parent study, those new participants will be not be contacted via text message to complete the phone screen, as we will not have access to their contact information at that time. Only participants from the Parent study (who had consented to be re-contacted originally) will be contacted via text message).

Participants from the Parent study were initially recruited to the Parent study from outpatient psychiatry programs at the University of Michigan Health System, from multi-media advertisements (UMClinicalStudies.org, passive advertisements on social media sites and Craigslist Ann Arbor, Google Adword campaigns, print and electronic media, radio ads and flyers) and by referral from community clinicians. Participants from the Parent study can be enrolled in the current protocol if they previously endorsed elevated depressive symptoms during the Parent study and do not possess any of the exclusionary criteria. Initial screening will occur in a telephone interview. Participants can enroll in the study from anywhere in the United States, as all aspects of the study protocol will be completed remotely. Based on the demographic characteristics of the sample with elevated depressive symptoms (CDI T-scores > 50) from in the Parent study, we anticipate that the sample of the current protocol will be primarily composed of youth that identify as female (90%) and are Caucasian (75%).

If needed to reach recruitment goals, new participants may be recruited through multi-media advertisements (UMHealthResearch.org, passive advertisements on social media sites, print and electronic media, and flyers). If additional recruitment is conducted, recruitment of male youth and youth from unrepresented racial and ethnic groups will be prioritized. Additionally, recruitment outside of the Parent study will be restricted to potential participants who live in the state of Michigan, in order to ensure that an iPad can be provided to participants (via drop-off, pickup, or mail delivery) if they do not already have access to one. Interested participants (i.e., as indicated on UMHealthResearch) will fill out several pre-screen eligibility questions on UMHealthResearch. If eligible based on these pre-screening questions, participants will be contacted via phone or email to complete the phone screen.

Minimizing the potential for coercion of patients to participate: Because members of the research team are involved in clinical care and research, there is the potential that some patients of the study team may be recruited. It will be made clear to all potential subjects that participation is entirely optional and not a part of regular treatment. The bulk of the recruitment process will occur with the study coordinator, who does not treat patients in any of the clinical venues where recruitment will occur. Overall, the research team is experienced in clinical research and very mindful of the conflict between the dual roles of clinician and researcher. They firmly believe that the safety and desires of the patient take precedence over any research protocol, and work hard to assure their patients that research participation is not required for treatment. In

the case where a patient of a study team member is recruited, the consent process and signature on the informed consent document and will be obtained by the study coordinator**.**

Payment of participants

In the current protocol, participants will receive the following payments:

1. After completing Assessment #1 (including semi-structured interview, *Millisecond* battery, and self-report clinical measures), participants will *earn* $50. If participants screen out during Assessment 1, participants will receive up to $50 for their participation (according to the time spent completing the assessment; up to 2 hrs ($25), up to 4 hours (the full $50).
2. After completing one half of the CCT training (2 weeks), participants will *earn* an additional $25.
3. Once the full training has been completed (4 weeks of at least 80% compliance), participants will *earn* another $25.
4. *After completing Assessment #2, participants will *earn* another $25.
5. **For those who have completed Assessment #3 3-months post-intervention, participants earn an additional $25.

Therefore, if all three assessments are completed in addition to the full EndeavorRx intervention, each participant will receive a total of $150. All participants will have the opportunity to earn the same amount of compensation (if completed Assessment #3). Incentives are structured to promote retention of participants throughout the full intervention period, as well as for Assessment #3 (if applicable). Payment for all enrolled participants will be made in up to two payments: at payment step #4* and again at payment step #5**, if all activities completed. If participants screen out during Assessment 1, they will be provided payment after screening out. The participant will receive the incentive directly. If a participant withdraws from the study or does not complete certain parts of the study, payment will be distributed for the amount earned at the point of study discontinuation. If a participant does not complete at least 2 weeks of the CCT intervention, they will not complete the post-intervention assessments.

6 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S)

6.1 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION OR EXPERIMENTAL MANIPULATION DESCRIPTION

The *EndeavorRx* video game is a digital therapeutic designed to improve attention and related cognitive control processes by training interference management. The video game design displays two tasks that are to be completed in parallel, which requires multitasking and thus cognitive control. Task performance is assessed during single and interference (multitask) conditions. Difficulty of the game is titrated, in real time, to adapt to the individual's performance. The game-player makes progress by earning rewards and thus unlocking new environments. Periodic recalibration occurs throughout gameplay to maintain an optimal difficulty level. This feature of the game helps to avoid participant boredom and progressively activate the functional systems underlying cognitive control. EndeavorRx is similar to other cognitive training intervention games used in prior research and are well-tolerated by participants of varying ages (Keefe et al., 2022).

6.1.2 ADMINISTRATION AND/OR DOSING

Computerized cognitive training: The CCT intervention will consist of ~25 minutes of EndeavorRx video gameplay per day (at any time of the day), for 5 days/week, for 4 weeks. This is the duration of gameplay used in prior studies of the *EndeavorRx* game (Kollins et al., 2020) and the dose suggested by *Akili Interactive*. Participants will be instructed to try not to play the game for more than 30 minutes a day, though time of gameplay will be monitored directly by the research team using Akili software. If participants are playing the video game too much, or for not enough time, parents will be contacted via email. The video game is designed to improve attention and engage cognitive control. Gameplay sessions will be completed at home. Participants will complete CCT on an iPad provided by the research team, or they may complete CCT by downloading the *Akili Interactive* application onto their own Akili-compatible personal device.

6.2 FIDELITY

6.2.1 INTERVENTIONIST TRAINING AND TRACKING

An evaluator will assess the patients with the scales described below. The assessments will be completed via Zoom.

To ensure that there is consistency across participants in understanding of gameplay instructions, participants will be instructed to play the CCT intervention for about 5 minutes while the coordinator monitors the session over Zoom. The research coordinator will then be able to answer any questions that the participant might have about game instructions. All participants will also be provided with the same instruction manual.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

There is no randomization in this pilot study.

6.4 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION ADHERENCE

Tolerability and compliance with the intervention will also be assessed. The CCT application will measure the amount of time each day that the child spends playing the video game. Additionally, completion of self-report questionnaires and *Millisecond* assessments will be tracked to ensure that these assessments are completed within the specified time period. If the cognitive task battery and start of the cognitive training intervention are not completed within sufficient time of the baseline clinical and self-report assessment (i.e., within 14 days of completing the CDI; due to scheduling and/or equipment constraints), then the CDI and CDRS-R will be re-administered prior to initiating the cognitive task battery and cognitive training.

Assessments will include (refer to 1.3 Schedule of Activities for a list of which measures are completed at each assessment):

Assessments by Clinician

a) C-SRSS
b) CDRS-R
c) K-SADS

Assessments Completed by Subjects

a) MASC
b) CDI
c) SCARED (parent)
d) CBCL (parent)
e) ERQ-CA

Other Assessments

a) ESS (parent and child)

6.5 CONCOMITANT THERAPY

Participants can remain on medication throughout the duration of the study, so long as a stable dose was maintained at least 4 weeks prior to study enrollment, and that this dose in maintained throughout the study's duration. Participants will be excused from the study if they decide to seek new therapy or medication during the course of the study.

6.5.1 RESCUE THERAPY

If a participant's depression symptoms worsen over the duration of the study (as measured at Assessment #2 or spontaneously reported), the participant will be referred to receive therapy. Please refer to section 2.1.3 for additional details on the safety procedure if depressive symptoms worsen.

7 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

When a subject discontinues from CCT but not from the study, remaining study procedures will be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed.

Discontinuation of study for a given participant will occur in the event of any of the following:

- Suicidal thoughts with specific plans and intentions (Endorse item 9 the CDI)
- The participant is hospitalized for any psychiatric symptoms
- A participant reports symptom worsening: > 25% increased CDI score (referenced to baseline)

Reasons for discontinuation will be documented, and all outcome assessments will proceed as scheduled, if possible.

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 a participant from the study for the following reasons:

- Significant study intervention non-compliance, such as not engaging in the video game intervention at all (compliance will be monitored in real-time using Akili software).
- Lost-to-follow up; unable to contact subject (see **Section 7.3, Lost to Follow-Up**)
- Any event or medical condition or situation occurs such that continued collection of follow-up study data would not be in the best interest of the participant or might require an additional treatment that would confound the interpretation of the study
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- The study is suspended or canceled

The reason for participant discontinuation or withdrawal from the study will be recorded. Subjects who sign the informed consent form but do not receive the study intervention, may be replaced. Subjects who sign the informed consent form and receive the study intervention, and subsequently withdraw, or are discontinued from the study, will 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 a scheduled visit and study staff are unable to contact the participant after at least 3 attempts for each visit.

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

- The site will attempt to contact the participant via email to the parent and/or phone call to parent, reschedule the missed visit within two weeks, 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 or emails). These contact attempts will be documented in the participant's 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 ENDPOINT AND OTHER NON-SAFETY ASSESSMENTS

Participants will complete questionnaires in order to collect basic health and demographics information. The initial assessment is completed as part of the parent study and will occur during Visit 1 (or the day prior for the Qualtrics questionnaires). Data collected from this assessment will be used for analysis for this protocol. The following evaluations and assessment tools (or subsets of questions from these measures) may be used to determine eligibility for the study and gather baseline information:

1) Demographics and medical history form. An in-house form for basic demographic information, medical and family history completed by study team or as self-report.

2) Child Behavior Checklist (CBCL; Achenbach and Rescorla 2001). A 126-item parent-completed checklist which provides DSM-IV oriented subscales for Depressive Problems, Anxiety Problems and Attention Deficit/Hyperactivity Problems (Inattention and Hyperactivity/Impulsivity subscales). Approximately 10 minutes.
3) Screen for Child Anxiety Related Disorders (SCARED Parent Version): Developed by Boris Birmaher, M.D., Suneeta Khetarpal, M.D., Marlane Cully, M.Ed., David Brent, M.D., and Sandra McKenzie, Ph.D., Western Psychiatric Institute and Clinic, University of Pittsburgh (October, 1995). The SCARED consists of 41 items and 5 factors that parallel the DSM-IV classification of anxiety disorders.
4) Multidimensional Anxiety Scale for Children (MASC); (March, Parker et al. 1997). Self-report assessing anxiety. Approximately 10-15 minutes.
5) Children's Depression Inventory (CDI); (Kovacs, 1992). Self-report, 27 item scale on depressive symptoms. Approximately 5 minutes.
6) Columbia Suicide Severity Rating Scale, Screen Version - Recent (Posner, Oquendo et al. 2007). A clinician-rated scale assessing suicidal ideation and behavior. Approximately 5 min.
7) Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS); (Kaufman, Birmaher et al., 1997). Standard assessment tool to obtain a diagnosis, may include parent interview. Approximately 3-4 hours.
8) Children's Depression Rating Scale, Revised (CDRS-R); (Poznanski & Mokros, 1996). A clinician-administered semistructured interview to assess depression symptoms in children and adolescents. Can be used to monitor intervention response as it captures slight changes in symptoms. Approximately 15-20 minutes.
9) Endeavor Satisfaction Survey (ESS; Subject, may be completed before and after CCT intervention) – A 5-item scale rating the participant's and participant guardian's feelings of satisfaction with the video game and its effect on participant's symptoms – approximately 1 minute.
10) Emotion Regulation Questionnaire for Children and Adolescents (ERQ-CA) – (Gullone & Taffe, 2012). A 10-item self-report questionnaire to assess emotion regulation (subcomponents of reappraisal and suppression) in children and adolescents. Approximately 5 minutes.

Electronic data capture:

Subjects will complete the self-report forms described above using Qualtrics. Qualtrics is an Application Service Provider (ASP) with a Software-as-a-Service (SaaS) platform for creating and distributing online surveys and related research services. The platform records response data, performs analysis, and reports on the data. All services are online and require no download software; only modern JavaScript-enabled browsers are required (no Java/JVM or Flash). Surveys are usually taken online within a web browser, with optional SMS surveys and offline methods available for smartphones/tablets. Qualtrics has been approved for the University of Michigan research community, and individual investigators access the web interface through a University of Michigan Qualtrics portal. Subjects will receive a coded link via email which will take them to the required surveys. The emailed link contains no identifiable information about the subjects, and once activated, establishes an https encrypted link with the Qualtrics server. Once completed, each survey is locked so that re-access is not permitted. We can also adapt the process for each subject, e.g. provide access on computers or tablets in the Department of Psychiatry for subjects who do wish or cannot use email. Some subjects may request paper, and, if so, paper forms will be provided.

Subjects will be asked to complete the consent form online (provided through a secure web-link sent via email) via SignNow prior to their initial evaluation. A copy of the consent will be emailed to the subject. Data will be downloaded from Qualtrics and stored on protected computers to be used for analysis.

Responses entered by subjects will be available to the clinicians working with the subjects in the study. Please note that the suicide assessment rating (C-SSRS) is administered at the screening evaluation in Assessment 1. Thus, any potentially dangerous clinical condition will be identified prior to further enrollment in the study and the participant will not continue with the current protocol or start the intervention. If suicidal ideation is endorsed at any point on self-report measure of CDI, this will be flagged in Qualtrics and a member of the study team will act accordingly on this information and in a timely fashion. Additionally, language is provided at the top of every Qualtrics page assessing clinical symptomology (from parent- or child-report) in which the child or parent is notified that survey responses may not be read immediately by study staff and that the child or parent should contact emergency services (with numbers provided) if the parent or child is worried about the current safety of the child.

EXPERIMENTAL NEUROCOGNITIVE TASKS

During the first, second, and third visit, participants may be asked to complete a Millisecond Inquisit Web Cognitive Battery.

- Millisecond Inquisit Web cognitive battery **of assessments** will be administered electronically using an iPad, and will be completed before and after the CCT intervention, and (if applicable) again 3-months after the intervention. Tasks may include Flanker inhibitory control and attention task, Game of Dice task, Little Man Test (mental rotation), Emotional Stroop task, BIRD task (distress tolerance), and Delay Discounting task; these tasks are not specifically trained in CCT to ensure that we measure transfer of training to general cognitive control capacity, rather than practice effect on specific tasks. Composite scores may be used to index cognitive control capacity. All cognitive tasks were developed by the Adolescent Brain Cognitive Development (ABCD) Research Consortium will be completed using the Inquisit Web platform (https://www.millisecond.com/).

8.2 SAFETY ASSESSMENTS

Safety assessments include the following:

- **Columbia Suicide Severity Rating Scale** (C-SSRS), Screen Version - Recent (Posner, Oquendo et al. 2007). A clinician-rated scale assessing suicidal ideation and behavior.
- **Child Depression Inventory** (CDI). A self-report assessment to rate the severity of depression symptoms in children. Total scores on this measure range from 0 to 54. Symptom worsening: > 25% increased CDI score (referenced to baseline).

Any safety-related assessments (C-SSRS administered at Assessment #1) or primary outcome measure (CDI at Assessments #1 or #2) that are missed will be reported to the IRB as a protocol deviation. We will accept a window of ± 1 week. However, for the other assessments, missing or late assessments will not be reported as protocol deviations unless they constitute > 50% of the total assessments. These allowances should affect neither the scientific integrity nor the safety monitoring provisions of the protocol.

All SAEs will be:

- recorded on the appropriate SAE Report Form
- followed through resolution by a study clinician
- reviewed and evaluated by a study clinician.

The study will comply with IRB reporting requirements and guidelines for SAEs.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS

This protocol uses the definition of adverse event from 21 CFR 312.32 (a): any untoward medical occurrence associated with the use of an intervention in humans, ***whether or not considered intervention-related***.

Any unfavorable or unintended symptom, sign, or disease associated with a medical treatment or procedure that may or may not be related to the treatment or procedure. Adverse events can be related to the intervention or to the symptoms that the intervention is intended to act on (e.g. subclinical depressive symptoms), or to another disorder (e.g. Anxiety), or they could be entirely unrelated to any of these (e.g., motor vehicle accident).

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS

An SAE is defined as an AE that meets one of the following conditions:

- Death during the period of protocol-defined surveillance
- Life-threatening event (defined as a subject at immediate risk of death at the time of the event)
- An event requiring inpatient hospitalization or prolongation of existing hospitalization during the period of protocol defined surveillance
- Results in congenital anomaly or birth defect
- Results in a persistent or significant disability/incapacity

Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse/overdose or cancer.

All SAEs will be:

- recorded on the appropriate SAE Report Form
- followed through resolution by a study clinician
- reviewed and evaluated by a study clinician

The study will comply with IRB reporting requirements and guidelines for SAEs.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

All adverse events (AEs) will have their relationship to study procedures, including the intervention, assessed by an appropriately-trained clinician based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Definitely/Probably Related** – There is evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study procedures administration and is unlikely to be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study procedures should be clinically plausible. The event must be pharmacologically or phenomenologically definitive.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of study procedures). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related/Not related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study procedures administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study procedures) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments). Or, the AE is completely independent of study procedures administration.

8.3.3.3 EXPECTEDNESS

A clinician with appropriate expertise in treating youth anxiety and depression will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE 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 procedures, as outlined in this document, the consent materials and documents related to the video game and its use.

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

The occurrence of an adverse event (AE) or serious adverse event (SAE) 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 AEs, not otherwise precluded per the protocol, will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study procedures (assessed only by those with the training and authority to make a decision), and time of resolution/stabilization of the event. All AEs occurring while on study will be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution, such that the participant has been offered or received necessary care.

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

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. Documentation of onset and duration of each episode will be maintained for AEs characterized as intermittent.

A study team member will record events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Participants and/or their parent can spontaneously notify the investigator of an AE or health status change via phone call or email, if necessary, in between scheduled visits. Events will be followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

The occurrence of an AE may come to the attention of study personnel during study visits. At each visit, subjects will be questioned about putative AEs. Information to be collected includes event description, time of onset, clinician's assessment of severity (mild, moderate, or severe), relationship to study (assessed by the study PI and clinical team), expected versus unexpected, local versus systemic, and time of resolution/stabilization of the event. All AEs occurring while in the study will be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution. Adverse event reporting will occur on the standard IRBMED timetable.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

N/A

8.3.7 REPORTING EVENTS TO PARTICIPANTS

N/A

8.3.8 EVENTS OF SPECIAL INTEREST

N/A

8.3.9 REPORTING OF PREGNANCY

N/A

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS

This protocol uses the definition of Unanticipated Problems as defined by the Office for Human Research Protections (OHRP). 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 Institutional Review Board (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); and
- 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.

8.4.2 UNANTICIPATED PROBLEMS REPORTING

The investigator will report an other reportable incident or occurrence (ORIO) to the reviewing Institutional Review Board (IRB). The ORIO report will include the following information:

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

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

- ORIOs that are serious adverse events (SAEs) will be reported to the IRB and to the study sponsor/funding agency within 7 calendar days of the investigator becoming aware of the event
- Any other ORIO will be reported to the IRB within 7 calendar days of the investigator becoming aware of the problem

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

N/A

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Primary Endpoint:

We hypothesize that CCT will increase cognitive control capacity (Millisecond battery composite score and individual cognitive test scores) and reduce depressive symptoms (CDI and CDRS-R scores) over the 4 week period of the intervention. Specifically, we hypothesize that CCT will improve cognitive control which will in turn improve depressive symptoms as a consequence of enhanced emotional regulation. Alternatively, our null hypothesis is that there will be no difference in cognitive control capacity or depressive symptoms immediately post-intervention as compared to pre-intervention.

Secondary Endpoint*:

We hypothesize that CCT will further increase cognitive control capacity (measured by Millisecond battery composite score and individual cognitive test scores) and reduce depressive symptoms (as measured by CDI and CDRS-R) further 3-months post-intervention than immediately after the intervention. The null hypothesis is that there is no difference in cognitive control capacity or depressive symptoms from immediately post-intervention to 3-months after the intervention.

*Secondary endpoint was optional to participants and then discontinued after protocol version 2.1 (02 April 2024).

Feasibility/Acceptability and Experimental Endpoints*:*

1. We hypothesize that the majority of participants will complete the intervention with at least 80% compliance.
2. We hypothesize that participants will have favorable emotions associated with game play.
3. We hypothesize that depressive symptoms will be reduced from the baseline assessment of the Parent study but that they will be slightly elevated from the post-intervention assessment in the Parent study.

The statistical tests used to test these hypotheses will be outlined later in this protocol and registered with clinicaltrials.gov.

9.2 SAMPLE SIZE DETERMINATION

Sample size was determined based on results from a power analysis and feasibility of participant recruitment. A sample size of 32 participants would yield 80% power for the planned analyses in the current study, but 30 participants is a more achievable initial target for recruitment. Though there is minimal data

to generate hypothesized effect sizes, the proposed study will allow for generations of effect sizes to be used in future, larger studies.

9.3 POPULATIONS FOR ANALYSES

Complete-Case Analysis Population: This population will consist of enrolled participants without missing data on variables of interest from Assessment #2.

Per-Protocol Analysis Dataset: This population will consist of participants who complete all four weeks of the intervention (with at least 80% compliance to the guidelines of 25 minutes/day for 5 days a week across the 4 weeks. Compliance of 80% can be achieved by completing at least 20 minutes of gameplay on 80% of the days that they could play the game in the 4 week period, if assuming a 5-day week. For instance, assuming that a participant would complete at least 20 minutes of gameplay for 20 days during the 4 week period, a participant with 80% compliance would engage in at least 20 minutes of gameplay for at least 16 days during this period. Compliance will be assessed using gameplay metrics provided by Akili that are automatically measured when the game is played on a participant's device.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Data will be analyzed using statistics software such as SPSS and R software. For descriptive statistics, means with standard deviation and range will be computed for continuous data (all behavioral data and some of the clinical data). In general, statistical significance is reported based on $p < 0.05$ two-tailed. Missing data from Assessment 3 (if applicable) will be handled using pairwise deletion. Missing data from Assessment 1 or 2 will be handled using listwise deletion.

9.4.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

We hypothesize that CCT will increase cognitive control capacity and reduce depressive symptoms. The hypothesis will be tested using paired samples (repeated measures) *t*-tests (pre vs. post) for each dependent variable (CDI score and Millisecond battery composite score). Both of these dependent variables are interval variables.
Standard deviations and effect sizes will be assessed for each of these analyses.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)*

We hypothesize that CCT will further increase cognitive control capacity (measured by Millisecond battery composite scores) and further reduce depressive symptoms (as measured by CDI and CDRS-R) 3-months post-intervention than immediately after the intervention. This hypothesis will be tested using repeated-measures ANOVAs, with three timepoints (pre-intervention, immediately post-intervention, and 3-months post intervention), on behavioral performance (cognitive control capacity) and depressive symptoms.

Standard deviations and effect sizes will be assessed for each of these analyses.

*Secondary endpoint was optional to participants and then discontinued after protocol version 2.1 (02 April 2024).

9.4.4 SAFETY ANALYSES

N/A

9.4.5 BASELINE DESCRIPTIVE STATISTICS

N/A

9.4.6 PLANNED INTERIM ANALYSES

At Time 2, after the completion of the CCT intervention, CDI scores will be evaluated across all participants. If scores are significantly worse at Time 2 than at Time 1 (a significantly higher average CDI score across participants), then the study may be halted. Similarly, if greater than one third of the participants (~7 subjects) withdraw from the study due to symptoms, then the study may be halted. If there is no change, or an improvement in CDI scores (lower CDI scores), then the study will continue as planned. This interim analysis will be conducted with the intention of maintaining safety of participants, rather than for assessing the efficacy of the intervention.

9.4.7 SUB-GROUP ANALYSES

The sample included in this pilot study will not be large enough to conduct subgroup analyses based on sex or race/ethnicity. However, if applicable, in the secondary endpoint models, age and sex may be included as covariates. The current analyses will assess the efficacy of the study intervention in youth only (ages 9-17).

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

All clinical and behavioral measures will be listed by timepoint when applicable.

9.4.9 EXPLORATORY ANALYSES

Linear regression models will be built to test whether change in cognitive control indices (behavioral performance on *Millisecond* battery) will associate with change on clinical outcomes (CDI or CDRS-R scores). The standardized parameter estimates in each model will be examined.

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 intervention, study procedures, and risks will be given to the participant and electronic documentation of informed consent will be completed prior to starting the study intervention. The following consent materials are submitted to IRBMED with this protocol: Assent Form and a Parent-only Consent Form to accompany the child Assent Form.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

The protocol will begin by having the subject (or their parent[s]/guardian[s] for adolescent subjects) provide assent and informed consent. Informed consent will be obtained at the beginning of a remote visit. This remote visit will include a review of an oral assent script, assent from the minor subject, and signed electronic consent from their parent/guardian. Electronic informed consent signatures will be collected using SignNow. All procedures will adhere to the IRBMED Guidance for use of SignNow for Electronic Informed Consent Procedures. Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of this intervention will be provided to the subject/parents. Consent forms (written in non-technical language, understandable by the youngest subject to be enrolled in the study) describing in detail the study interventions/products, study procedures, and risks will be given to the subject/parent. Participants may also be presented with a visual timeline of the tasks that may be involved in participating in this study, during the consenting process or at another time during the study, to aid their understanding of the process. Upon reviewing the document, one of the investigators (or their designee) will explain the research study to the subject/parent and answer any questions that may arise.

All youth subjects will be given an assent form and/or will be read an assent script by study staff. The parent will sign the parental informed consent document prior to any procedures being done specifically for the study, besides the prescreen questions on UMHealthResearch and/or initial phone screen, which is conducted with the parent. Youth subjects will be asked to sign in the assent box on the assent form written in language that is developmentally appropriate for their understanding of study participation, along with parent signature on the parental consent form. Children under age 10 (age 9) will be read an assent script by study staff and will not have to sign the document, but to verbally give assent and study staff will indicate their assent and sign the document. If the child wishes to sign, they may do so. For all subjects, parents will sign a separate parent consent form. All subjects or their parents may withdraw consent at any time throughout the course of the trial. A copy of the parental informed consent and child assent documents will be given to the subjects for their records.

The subjects may withdraw consent at any time throughout the course of the trial. The rights and welfare of the subjects will be protected by emphasizing that the quality of their medical care will not be adversely affected if they decline to participate in this study. NOTE: older teens may become legal adults (i.e., reach the age of 18 years) during the course of the study. If the teen is still actively involved in the study (i.e., data collection ongoing), then a new consent form, signed by the teen, will be obtained. However, if the teen reaches 18 years of age *after* their data collection has been completed, we will *not* re-contact to re-consent. This approach is intended to avoid burdening study participants and their parents.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Reasons for discontinuation will be document, and all outcome assessments will proceed as scheduled, if possible. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly

inform study participants, the Institutional Review Board (IRB), and sponsor/funding agency and will provide the reason(s) 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 of CCT include, but are not limited to:

- Hospitalization required for any psychiatric symptoms
- Suicide behaviors during the study period (assessed by CDI and CDSRS post-intervention)
- Determination of unexpected, significant, or unacceptable risk to participants
- Data that are not sufficiently complete and/or evaluable

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the funding agency and IRB.

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by investigator, research staff, and the sponsor(s) and funding agency. This confidentiality is extended to the data being collected as part of this study. Data that could be used to identify a specific study participant will be held in strict confidence within the research team. No personally-identifiable information from the study will be released to any unauthorized third party without prior written approval of the sponsor/funding agency.

All research activities will be conducted virtually, but in as private a setting as possible, so that participants feel comfortable to share details about their symptoms to the assessing clinician.

Other authorized representatives of the sponsor or funding agency, representatives of the Institutional Review Board (IRB), or 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 research team will permit access to such records.

The study participant's contact information will be securely stored 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/funding agency requirements.

All paper and computer research records will be identified by subject ID number rather than name or other personally identifying information. Paper records are stored in a double-locked environment to which only authorized study team members have access. The link between subject ID and subject name will be kept within a secure study folder (only primary research team members have access; requires Level-2 Login) that can only be accessed on computers that are password protected. Consent documents and any other forms with identifying information will be maintained separately from research data files (identified by subject ID only).

The assessments in this protocol will ask participants about sensitive topics, such as mental illness and substance use. We will inform the consenting parents of minor participants at the beginning of the process that we will respect the confidentiality of all participants. It is important for us to let participants know that they can be honest about sensitive topics without fear of reprisal from their parents. However, all participants will also be informed about limits to confidentiality. If we learn that a subject has potential to harm him or herself, or another individual, we will break confidentiality and take steps to prevent harm. Similarly, any evidence of potential child abuse will be reported to Child Protective Services. If we become

aware of imminent risk of harm to a parent, steps will be taken to ensure safety (e.g. referral to psychiatric emergency services or contacting appropriate authorities).

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

The value of this research is significantly enhanced by making the data available for the widest possible use, and because of the rapidly changing world of data analysis, it is impossible to predict what future research will do with data collected for any particular project in the present. By keeping the data indefinitely, it will become available for projects, yet to be determined. These include projects run by the investigators, as well as those outside the institution through data sharing plans or central repositories.

When data are transferred to co-investigators, de-identification will be performed, removing all HIPAA identifiers from the files.

Subjects will be informed in the consent document that the data will be stored and that it may be shared with other investigators, both at the University and outside the University. The risk posed to subjects will be very, very small. Storing the data for an indefinite amount of time will follow strict protocols, outlined above, that will ensure the safety of the data and minimize the risk of accidental disclosure. Data that is shared will be de-identified and will be effectively anonymized, since investigators using the shared data will not have access to the keys linking individual subjects to the data. It is extremely unlikely that an investigator would even be able identify subjects from shared data, without already having access to a subject's identifiers.

If subjects object to data sharing, they have the option of not participating in the research. Although our project does provide a potential direct benefit in the form of CCT intervention, this intervention is readily available outside of the research protocol.

In some cases, participants may either be ineligible for the current protocol or be eligible for an additional study protocol. In these cases, if participant has indicated in the consent that they would like to be contacted for future studies, we will share their contact information with other research teams at the University of Michigan for screening purposes, and if eligible, can share some of our data with these investigators to assist in their screening and assessment process (per consent form).

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator
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10.1.6 SAFETY OVERSIGHT

The investigator and members of active study team will meet biweekly (as close to that as permitted by travel and holidays) to monitor the study activities in order to ensure that the human subject protection,

study procedures, administration, and data collection processes are of high quality and meet the appropriate, regulatory guidelines. No regular monitoring by an external monitor is planned.

10.1.7 CLINICAL MONITORING

No additional monitoring is required – the nature and size of this study does not require additional safety monitoring to that provided by the IRB. However, participant well-being will be monitored at both of the assessments (self-report but also clinical assessments with trained clinician). The study team will check for worsening depressive symptoms after the assessment for each participant. Video game play will also be monitored by the study team so that families can be contacted if any concern for well-being is implicated (i.e., not playing enough or playing the video game with extremely high intensity/frequency). The study team will also regularly monitor clinical self-report assessments in Qualtrics (at least 1x/week) to identify whether any safety items have been flagged in Qualtrics (Qualtrics will be set up to flag certain self-report items if endorsed).

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Quality control (QC) procedures will be implemented as follows:

Informed consent --- Study staff will review both the documentation of the consenting process as well as a percentage of the completed consent documents. This review will evaluate compliance with GCP, accuracy, and completeness. Feedback will be provided to the study team to ensure proper consenting procedures are followed.

Source documents and the electronic data --- Data will be initially captured on source documents (see **Section 10.1.9, Data Handling and Record Keeping**) and will ultimately be entered into the study database. To ensure accuracy site staff will compare a representative sample of source data against the database, targeting key data points in that review.

Intervention Fidelity — Consistent delivery of the study interventions will be monitored throughout the intervention phase of the study. Procedures for ensuring fidelity of intervention delivery are described in **Section 6.2.1, Interventionist Training and Tracking**.

Protocol Deviations – The study team will review protocol deviations on an ongoing basis and will implement corrective actions when the quantity or nature of deviations are deemed to be at a level of concern.

Should independent monitoring become necessary, the PI will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor/funding agency, and inspection by local and regulatory authorities.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

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

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

For the assessments, subjects will enter information directly onto a computer or electronic device. This data will be stored within Qualtrics, Data recorded in the electronic case report form (eCRF) derived from source documents will be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into Michigan Medicine servers in Qualtrics and/or statistical datasets. Clinical data will be entered directly from the source documents. Research data will be maintained on password protected computers, on a secure linux cluster maintained in the Psychiatry Affective Neuroimaging Laboratory (PANLab) or on secure UMHS-administered servers.

10.1.9.2 STUDY RECORDS RETENTION

Files will be stored in a double-locked environment and access-limited under the purview of the PI. All research records will be identified by subject ID; pre-screening records will be scrubbed of identifiers and date shifted to preserve confidentiality.

Study database records will be identified by subject ID, and the link between identifiers and subject ID will be maintained by the PI and study coordinator within the protected study folder. The file with this link will be destroyed after publication of the primary outcomes manuscript. When the PI has completed their training locally (by May 2026), all paper files will be destroyed. Electronic database records will be maintained by members of the research study team that remain at the University.

10.1.10 PROTOCOL DEVIATIONS

This protocol defines a protocol deviation as any noncompliance with the clinical trial protocol. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions will be developed by the site and implemented promptly.

These practices are consistent with:

- Section 10.1.1: Informed consent procedures
- Section 10.1.3: Confidentiality and privacy
- Section 10.1.4: Future data use and data storing
- Section 10.1.6: Safety oversight
- Section 10.1.8: Quality control
- Section 10.1.9: Data handling

It will be the responsibility of the site investigator to use continuous vigilance to identify and report deviations. All deviations will be addressed in study source documents and will be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator will be responsible for knowing and adhering to the reviewing IRB requirements.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

This trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Considerations for ensuring confidentiality of these shared data are described in Section 10.1.3.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, 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 ADDITIONAL CONSIDERATIONS

N/A

10.3 ABBREVIATIONS AND SPECIAL TERMS

AE	Adverse Event
CBCL	Child Behavior Checklist
CBT	Cognitive Behavior Therapy
CCT	Cognitive Control Training
CDI	Children's Depression Inventory
CDRS-R	Children's Depression Rating Scale - Revised
CFR	Code of Federal Regulations
COC	Certificate of Confidentiality
CRF	Case Report Form
C-SSRS	Columbia-Suicide Severity Rating Scale
EC	Ethics Committee
eCRF	Electronic Case Report Forms
ERQ-CA	Emotion Regulation Questionnaire for Children and Adolescents
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act

IB	Investigator's Brochure
IRB	Institutional Review Board
ITT	Intention-to-Treat
K-SADS	Kiddie Schedule for Affective Disorders and Schizophrenia
MASC	Multidimensional Anxiety Scale for Children
NCT	National Clinical Trial
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
ORIO	Other Reportable Information or Occurrence
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
ESS	Endeavor Satisfaction Survey
SAP	Statistical Analysis Plan
SCARED-P	Screen for Child Anxiety Related Disorders
SOA	Schedule of Activities
SOP	Standard Operating Procedure
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
1.8	10/16/23	Consent process changes	In response to ORIO
1.9	12/11/23	Additional detail added about recruitment outside of parent-study	Need to recruit outside parent-study; want to make sure processes are outlied
2.0			
2.1	4/02/24	Removed Assessment #3	Feasibility of enrollment and to shorten overall timeframe of study
2.2	10/8/24	Added language to clarify optional nature of Assessment #3	In tandem with ORIO, to provide clarity of safety assessments

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