IMPROVING COGNITIVE HEALTH IN COVID-19 SURVIVORS THROUGH DIGITAL THERAPEUTICS

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Statement of Compliance

The trial will be conducted in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR), and the Akili Interactive Terms and Conditions of Award. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Investigational New Drug (IND) or Investigational Device Exemption (IDE) sponsor, funding agency and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the 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. 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.

Confidentiality Statement

This document is confidential and is to be distributed for review only to investigators, potential investigators, consultants, study staff, and applicable independent ethics committees or institutional review boards. The contents of this document shall not be disclosed to others without written authorization from WCM, unless disclosure on ClinicalTrials.gov is federally required.

Department of Psychiatry, Weill Cornell Medicine

Institution Name

Faith Gunning, PhD		12/31/2020
Principal Investigator's Name	**Principal Investigator's Signature**	**Date**

List of Abbreviations

AE	Adverse Event
CFR	Code of Federal Regulations
CRF	Case Report Form
CTSC	Clinical Translational Science Center
DSMB	Data Safety Monitoring Board
DSMP	Data Safety Monitoring Plan
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
HRBFA	Human Research Billing Analysis Form
HUD	Humanitarian Use Device
ICF	Informed Consent Form
IDE	Investigational Device Exemption
IND	Investigational New Drug
IRB	Institutional Review Board
PHI	Protected Health Information
PI	Principal Investigator
REDCap	Research Electronic Data Capture
SAE	Serious Adverse Event
SUSAR	Suspected Unexpected Serious Adverse Reaction
UIRTSO	Unanticipated Problem Involving Risks to Subjects or Others
WCM	Weill Cornell Medicine

1. Protocol Summary

Full Title:	*Improving Cognitive Health in COVID-19 Survivors through Digital Therapeutics*
Short Title:	*Cognitive Health in COVID-19*
Clinical Phase:	*II*
Principal Investigator:	Faith Gunning, PhD
Study Description:	Emerging evidence suggests a subgroup of survivors of COVID-19 have residual difficulties with cognition and daily functioning. These deficits are pronounced in cognitive domains including attention, learning and executive skills, and may continue to impact quality of life after recovery from other COVID-19 symptoms. This study aims to investigate the efficacy of AKL-T01 (Akili Interactive), a remotely-delivered digital cognitive intervention, in targeting and improving cognition and functional outcomes in individuals recovering from COVID-19. The efficacy of the AKL-T01 intervention will be measured relative to a waitlist control group.
Sample Size:	Our target sample size will be 100 COVID-19 survivors, of which 50 participants will be randomized to the AKL-T01 intervention arm and 50 participants will be randomized to a waitlist control arm.
Enrollment:	Our total enrollment will be 125, requiring that we screen up to 500 individuals. We anticipate approximately 75% of individuals will not be eligible based on screening criteria. Further we anticipate approximately 20% of participants who are eligible will elect not to continue participation prior to initiation of intervention.
Study Population:	The study population will be individuals who were diagnosed with COVID-19 and have a deficit in cognition (i.e., attention and/or executive skills > 1 SD below the normal range). The target age range will be adults 18-89 years of age.
Enrollment Period:	We expect the enrollment period to last 12 months.
Study Design:	This study is a randomized clinical trial designed to compare efficacy of the AKL-T01 intervention relative to a waitlist control in patients who were infected with COVID-19. Participants will be selected for the presence of cognitive dysfunction prior to enrollment in the trial and will be randomized to the intervention arm or the waitlist control arm. They will complete an assessment battery designed to assess cognition, functional outcomes, and

	mood symptoms at pre-intervention (at study entry) and post-intervention (following 6 weeks of AKL-T01 or waitlist). The assessment battery will also be administered bi-weekly during the intervention period (i.e., at weeks 2 and 4), and 4 weeks after the end of the intervention period for longitudinal follow-up. We will use a waitlist design; at the end of the intervention period, participants in the control group will have the option to receive the 6-week AKL-T01 intervention. Note that study visits will take place remotely and devices for intervention administration will be mailed to participants.
Description of Sites/ Facilities Enrolling Participants:	Participants will be enrolled through facilities of the Manhattan Campuses of NewYork-Presbyterian Hospital (NYP)/Weill Cornell Medicine (WCM), as well as the NewYork-Presbyterian Westchester Behavioral Health Center.
Study Duration:	The study duration will be two years, including 12 months to recruit, collect data, and conduct data analysis and one additional year to publish results of the study.
Participant Duration:	Participants in the AKL-T01 intervention group will be enrolled in this study for approximately 10 weeks, comprised of the 6-week intervention period and week 10 longitudinal follow-up (4 weeks after completing the intervention). Participants in the waitlist control group who choose to begin the intervention after the initial 6-week period will be enrolled for 16 weeks, comprised of the 6-week waitlist period, the 6-week intervention, and week 16 longitudinal follow-up (4 weeks after completing the intervention).
Study Agent/Device Name Intervention Description:	AKL-T01 will be administered as a 6-week intervention. It is an algorithmically delivered iPad-based video game designed to improve cognitive health by targeting attention and attentional control processes. Participants enrolled in the intervention arm will play the game via an iPad application for 20-25 minutes daily for at least 5 days a week (but up to 7 days a week). Participants will also have weekly check-in visits via phone or a secure HIPAA-compliant videoconferencing platform (Zoom) with a care manager, who will monitor mood symptoms and gameplay adherence.
Primary Objective:	The primary objective of this study is to investigate the efficacy of the AKL-T01 intervention relative to a waitlist control in improving

cognitive functioning in COVID-19 survivors. Our primary measure of cognition is performance on a Digit Symbol Matching Task.

Secondary Objectives:

1) Our main secondary objective is to investigate the efficacy of the AKL-T01 intervention relative to a waitlist control in improving functional outcomes. The main measure of daily functioning is the NeuroQOL Cognitive Function scale.

Additional Secondary Objectives:

2) To examine the effect of cognition across a range of domains, including sustained attention, cognitive control, working memory, and processing speed. We will assess these cognitive functions with a remotely-delivered task battery that includes the following tasks:

- Multiple Object Tracking
- Digit Span Backwards
- Simple Reaction Time
- Choice Reaction Time
- Letter-Number Switching
- Gradual Onset Continuous Performance Test

3) To investigate the efficacy of the AKL-T01 intervention relative to a waitlist control in improving daily functioning and quality of life, as measured by the World Health Organization Disability Assessment Schedule Version 2 (WHODAS 2.0). The WHODAS 2.0 assesses the following domains of functioning that are relevant to our post-COVID sample:

- Cognition – understanding & communicating
- Mobility – moving & getting around
- Self-care – hygiene, dressing, eating & staying alone
- Getting along – interacting with other people
- Life activities – domestic responsibilities, leisure, work & school
- Participation – joining in community activities

Exploratory Objectives:

1) We will explore long-term change in cognition and daily functioning 4 weeks following the end of the intervention.

2) To investigate improvement in learning and episodic memory, as measured by a Visual Paired Associates Task, in the AKL-T01 intervention relative to a waitlist control. This measure is a cognitive domain that is not captured in the primary and secondary tasks listed above and will allow for the measurement of far transfer to less-related cognitive domains.

3) To investigate improvement in fatigue, as measured by the Modified Fatigue Impact Scale, in the AKL-T01 intervention relative to a waitlist control.

4) Explore improvement in mood symptoms from pre- to post-intervention in the AKL-T01 intervention relative to a waitlist control. Symptoms of depression will be measured with the Patient Health Questionnaire (PHQ-9) and symptoms of anxiety will be measured with the Generalized Anxiety Disorder Scale (GADS-7).

Primary Endpoints:

The primary endpoints for our measure of cognitive function is mean change from pre-intervention (baseline) to post-intervention (week 6) on Digit Symbol Matching Task performance.

To assess efficacy of the intervention relative to the wait list control, change scores from baseline to week 6 will be calculated separately and compared for the AKL-T01 intervention arm and the waitlist control arm for the Digit Symbol Matching Task.

Secondary Endpoints:

1) The main secondary endpoint for our measure of functional outcomes is mean change from pre-intervention (baseline) to post-intervention (week 6) on the NeuroQOL Cognitive Function Scale.

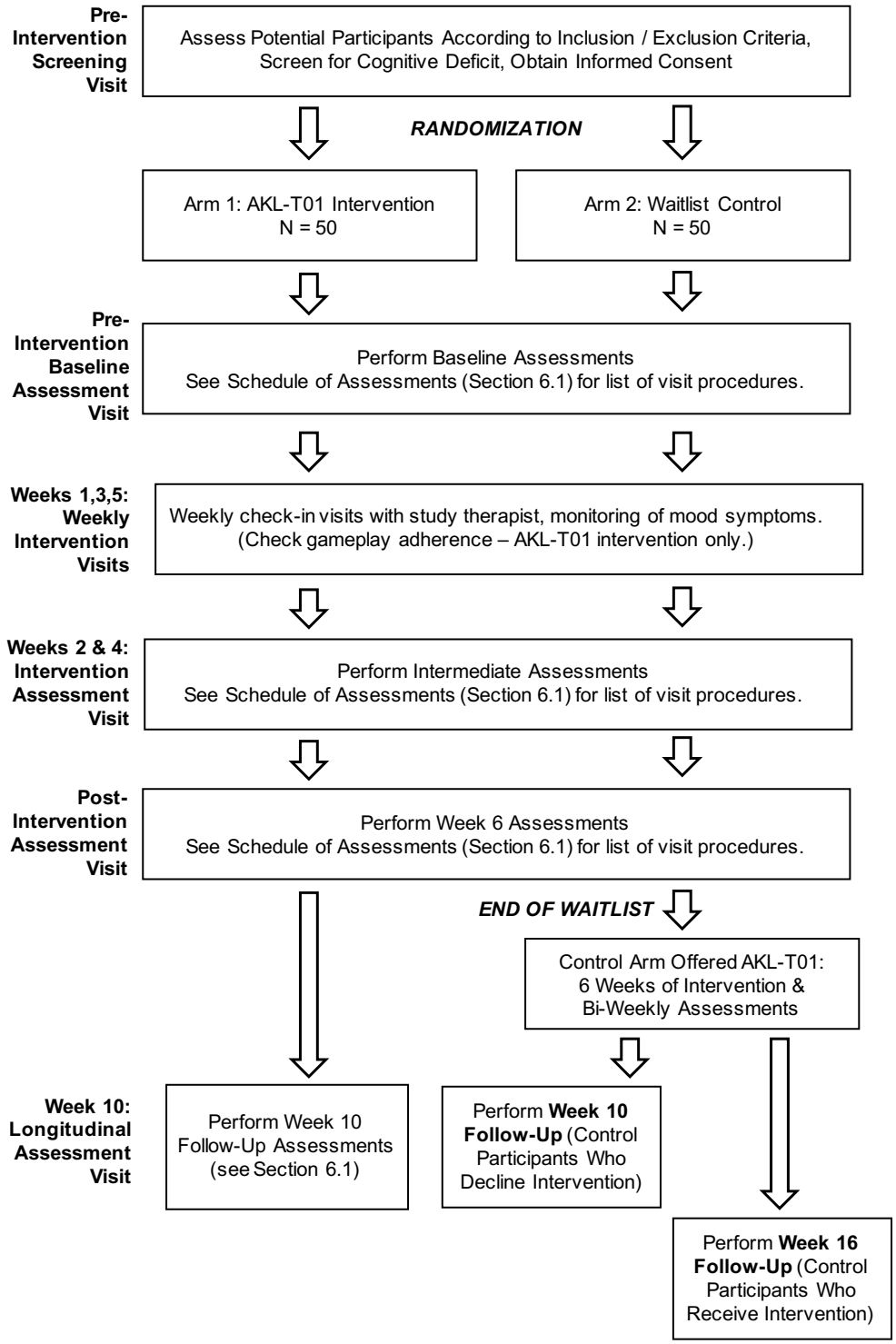
To assess efficacy of the intervention relative to the control, change scores from baseline to week 6 will be calculated separately and compared for the AKL-T01 intervention arm and the waitlist control for the NeuroQOL scale score.

Additional Secondary Endpoints:

2) Secondary endpoints for our measures of cognition is mean change in performance from pre-intervention (baseline) to post-intervention (week 6) on the following tasks: Multiple Object Tracking, Digit Span Backwards, Simple Reaction Time, Choice Reaction Time, Letter-Number Switching, and Gradual Onset Continuous Performance Test, and Visual Paired Associated Task.

3) Additional secondary endpoints for our measure of daily functioning is mean change in WHODAS 2.0 score from pre-intervention (baseline) to post-intervention (week 6).

1.1 Schema


Pre-Intervention Screening Visit
Assess Potential Participants According to Inclusion / Exclusion Criteria, Screen for Cognitive Deficit, Obtain Informed Consent
RANDOMIZATION
Arm 1: AKL-T01 Intervention N = 50
Arm 2: Waitlist Control N = 50
Pre-Intervention Baseline Assessment Visit
Perform Baseline Assessments See Schedule of Assessments (Section 6.1) for list of visit procedures.
Weeks 1,3,5: Weekly Intervention Visits
Weekly check-in visits with study therapist, monitoring of mood symptoms. (Check gameplay adherence – AKL-T01 intervention only.)
Weeks 2 & 4: Intervention Assessment Visit
Perform Intermediate Assessments See Schedule of Assessments (Section 6.1) for list of visit procedures.
Post-Intervention Assessment Visit
Perform Week 6 Assessments See Schedule of Assessments (Section 6.1) for list of visit procedures.
END OF WAITLIST
Control Arm Offered AKL-T01: 6 Weeks of Intervention & Bi-Weekly Assessments
Week 10: Longitudinal Assessment Visit
Perform Week 10 Follow-Up Assessments (see Section 6.1)
Perform Week 10 Follow-Up (Control Participants Who Decline Intervention)
Perform Week 16 Follow-Up (Control Participants Who Receive Intervention)

1.2 Study Objectives and Endpoints

1.2.1 Primary Objectives

The primary objective of this study is to investigate the efficacy of the AKL-T01 intervention relative to a waitlist control in improving cognitive functioning in COVID-19 survivors. Our primary measure of cognition is performance on a Digit Symbol Matching Task.

1.2.2 Secondary Objectives

1) Our main secondary objective is to investigate the efficacy of the AKL-T01 intervention relative to a waitlist control in improving functional outcomes. The main measure of daily functioning is the NeuroQOL Cognitive Function scale.

Additional Secondary Objectives:

2) A secondary objective of the study is to investigate the efficacy of the AKL-T01 intervention relative to a waitlist control in improving cognition across a range of domains, including sustained attention, cognitive control, working memory, and processing speed. We will assess these cognitive functions with a remotely-delivered task battery that, in addition to our primary Digit Symbol Matching Task, also includes the following tasks:

- Multiple Object Tracking
- Digit Span Backwards
- Simple Reaction Time
- Choice Reaction Time
- Letter-Number Switching
- Gradual Onset Continuous Performance Test

3) Another secondary objective of the study is to investigate the efficacy of the AKL-T01 intervention relative to a waitlist control in improving daily functioning and quality of life, as measured by the World Health Organization Disability Assessment Schedule (WHODAS). The WHODAS assesses the following domains of functioning that are relevant to our post-COVID sample:

- Cognition – understanding & communicating
- Mobility – moving & getting around
- Self-care – hygiene, dressing, eating & staying alone
- Getting along – interacting with other people
- Life activities – domestic responsibilities, leisure, work & school
- Participation – joining in community activities

1.2.3 Exploratory Objectives

1) We will explore long-term change in cognition and daily functioning 4 weeks following the end of the intervention.

2) An exploratory objective related to cognition is to investigate improvement in learning and episodic memory, as measured by a Visual Paired Associates Task, in the AKL-T01 intervention relative to a waitlist control, in order to evaluate far transfer to untrained tasks.

3) An exploratory objective related to functional outcomes is to investigate improvement in fatigue, as measured by the Modified Fatigue Impact Scale, in the AKL-T01 intervention relative to a waitlist control.

4) We will also explore improvement in mood symptoms from pre- to post-intervention in the AKL-T01 intervention relative to a waitlist control. Symptoms of depression will be measured with the Patient Health Questionnaire (PHQ-9) and symptoms of anxiety will be measured with the Generalized Anxiety Disorder Scale (GADS-7).

1.2.4 Primary Endpoints

The primary endpoints for our measure of cognitive function and is mean change from pre-intervention (baseline) to post-intervention (week 6) on Digit Symbol Matching Task performance.

To assess efficacy of the intervention relative to the control, change scores from baseline to week 6 will be calculated separately and compared for the AKL-T01 intervention arm and the waitlist control arm for the Digit Symbol Matching Task.

1.2.5 Secondary Endpoints

1) The main secondary endpoint for our measure of functional outcomes is mean change from pre-intervention (baseline) to post-intervention (week 6) on the NeuroQOL Cognitive Function Scale.

To assess efficacy of the intervention relative to the control, change scores from baseline to week 6 will be calculated separately and compared for the AKL-T01 intervention arm and the waitlist control for the NeuroQOL scale score.

Additional Secondary Endpoints:

2) Secondary endpoints for our measures of cognition is mean change in performance from pre-intervention (baseline) to post-intervention (week 6) on the following tasks: Multiple Object Tracking, Digit Span Backwards, Simple Reaction Time, Choice Reaction Time, Letter-Number Switching, and Gradual Onset Continuous Performance Test, and Visual Paired Associated Task.

3) The secondary endpoint for our measure of daily functioning is mean change in WHODAS 2.0 score from pre-intervention (baseline) to post-intervention (week 6).

1.2.6 Exploratory Endpoints

1) Long-term change in cognition and daily functioning 4 weeks following the end of the intervention will be assessed by calculating change scores from baseline to week 10 and from week 6 to week 10 in our primary and secondary measures of cognitive and daily function.

2) To explore improvement in far transfer to an untrained cognitive domain, we will calculate mean change in score on the Visual Paired Associates task from pre-intervention (baseline) to post-intervention (week 6).

3) The exploratory endpoint for our measure of fatigue is mean change in Modified Fatigue Impact Scale score from pre-intervention (baseline) to post-intervention (week 6).

4) The exploratory endpoints for our measure of moody symptoms is mean change in PHQ-9 and GADS-7 scores from pre-intervention (baseline) to post-intervention (week 6).

2. Background

2.1 Disease

Cognitive deficits are frequent, persistent, and disabling following critical illness. They are increasingly recognized as a common complication of COVID-19. Multiple factors associated with the illness and its treatment may contribute to cognitive sequelae. These include hypoxia, ventilation, sedation, delirium, cerebrovascular events, and inflammation. 81% of patients had cognitive impairment, ranging from mild to severe. In our preliminary study of cognitive impairment in 57 hospitalized patients recovering from COVID-19, deficits were most common in working memory (55% of patients impaired), multitasking (47%), divided attention (46%), and processing speed (40%) (Jaywant et al., under review); these deficits were more common than deficits in memory. An additional study of 29 community-dwelling adults in China recovered from COVID-19 found a deficit in sustained attention relative to a control group, Thus, the emerging research suggests that aspects of attention and executive functions are commonly affected after COVID-19. The time-sensitive need to understand and address cognitive deficits early in the disease course is underscored by the surging incidence of COVID-19 coupled with the long-term cognitive complications that were associated with the coronaviruses that caused the first Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS). Further, cognitive dysfunction is a known predictor of long-term functional disability.

2.2 Investigational Agent/Device, or Surgical Treatment/Method

The study intervention, AKL-T01 (Akili Interactive) is a digital intervention. The intervention was designed to target and improve cognition through a fun and engaging video game played on an iPad. Its efficacy has been demonstrated in individuals across the lifespan with mental health disorders that commonly have symptoms of cognitive dysfunction, such as depression and ADHD. AKL-T01 recently received FDA clearance for the improvement of attention in children with ADHD (Kollins et al., 2020). Further, our group has shown that this video game intervention is non-inferior to gold standard psychotherapy in improving cognition and symptoms of depression (Anguera et al., 2017) and improves cognitive control at the neural, behavioral, and self-report levels (Gunning et al., under review).

The AKL-T01 intervention specifically targets attention and attentional control, two key executive skills that we expect to demonstrate deficits in our sample of individuals previously diagnosed with COVID-19 (Jaywant et al., under review). The video game combines aspects of navigation and target identification. It uses an innovative algorithmic design that adjusts to individuals' ability levels, such that the complexity and cognitive load increases as the game progresses in an optimized and personalized fashion.

2.3 Rationale

Emerging evidence suggests a subgroup of survivors of COVID-19 have residual difficulties with cognition and daily functioning. These deficits are pronounced in cognitive domains including attention, learning and executive skills, and may continue to impact quality of life after recovery from other COVID-19 symptoms (Jaywant et al., under review). Thus, there is an urgent need to investigate the efficacy of potentially beneficial cognitive interventions such as AKL-T01 (primary objective of the study) that can be widely disseminated. The telehealth, iPad-based nature of AKL-T01 is critical in mitigating the spread of infection during the ongoing COVID-19 pandemic and in the potential for eventually scaling and disseminating the intervention broadly.

Whether or not the potential benefit of AKL-T01 can persist post-intervention and generalize to related cognitive functions (secondary objectives) is also important in determining the transfer of gains to broader cognitive skills and to their endurance once the intervention is concluded.

Anxiety, depression, and fatigue have been reported after COVID-19 (Garrigues et al., 2020), are related to attention and executive functions (Zhou et al., 2020),and are known to be associated with daily function. Our previous work has demonstrated that the AKL-T01 intervention can improve mood symptoms in adults with major depression. Thus, an exploratory objective is to determine whether the AKL-T01 intervention improves symptoms of depression, anxiety, and fatigue, which is important in determining additional impacts of the intervention that have ramifications for COVID-19 survivors' daily function and quality of life.

We anticipate that the results of this study will inform refinement and improvement of AKL-T01 for COVID-19 and provide valuable data for future study of the intervention.

2.4 Risk/Benefit Assessment

2.4.1 Known Potential Risks

This study presents no greater than minimal risk. The potential risks of participation are frustration, feeling anxious and/or fatigued during intervention gameplay and assessment administration. There is also a risk that participants may develop headaches during gameplay, due to the fast-paced nature of the game and the need to focus on the screen during the intervention. To mitigate risk, we will emphasize that participants can take breaks as frequently as they would like when completing the intervention exercises. The computerized exercises are graded in difficulty (i.e., start relatively easy and becoming more challenging over time) and adapt to the participant's cognitive skill level, which will mitigate the risk of frustration and feelings of anxiety.

2.4.2 Known Potential Benefits

This study has the potential to improve participants' cognitive and daily function. The AKL-T01 intervention has been shown to improve mood symptoms, as well as executive skills and cognitive control through measures of neural activation and connectivity, performance on tasks measuring working memory and sustained attention, and self-reported symptoms of cognitive control function in adults diagnosed with depression (Anguera et al, 2017; Bove et al., 2019; Gunning et al., under review). The control group also has the potential to improve their cognitive and daily function as they will be given the opportunity to begin the intervention after the waitlist period.

2.4.3 Assessment of Potential Risks and Benefits

We will use study procedures designed to maximize the benefit and minimize the risk of participation in this study. Participants in the intervention arm will receive adequate training in gameplay (~45 minute training session with a member of the study team) and have weekly check-ins with trained care managers to troubleshoot issues with the game and monitor gameplay adherence. Participants in the waitlist control arm will also have weekly check-in visits with a care manager.

Assessment sessions will be conducted by PhD-level investigators of this study protocol or Research Assistants who have received extensive training in assessment administration. The assessment battery for this study was optimized to provide measures across a range of cognitive and functional domains that we expect to be impacted in COVID-19 survivors, use well-validated tasks that can be administered remotely, and be as brief as possible to minimize participant burden.

This study will also use a waitlist design to ensure that all participants have the opportunity to receive the benefits provided by the AKL-T01 intervention. At the completion of the 6-week intervention period, participants in the waitlist control group will be given the option to begin 6 weeks of the intervention, which will include the same schedule of weekly check-in and assessment visits.

We expect that the potential benefits of participation outweigh the minimal risks. Participants may experience an improvement in multiple aspects of cognition and daily functioning in COVID-19 survivors. The knowledge gained would inform future clinical trials.

<u>Plan to Address Subjects with Suicidal Ideation and/or Other Mental Health Needs</u>
Suicidal ideation may be identified by the PHQ-9. Identification of suicidal ideation will trigger a suicide risk assessment following an established protocol and algorithm developed by investigators in the Department of Psychiatry (see attached form). The suicide risk assessment will be completed under the supervision of a licensed clinician or by the licensed clinician themselves. Depending on the level of risk, study staff may provide referrals for further care, which may include outpatient or inpatient treatment according to clinical indication. Involuntary admission may become necessary in patients at acute and imminent risk for harming themselves. In the unlikely event that a licensed clinician is not available for immediate clinical evaluation of a subject reporting suicidal intent or plan, the research staff member will contact emergency medical services.

The suicide risk assessment classifies subjects who endorse suicidal ideation as having Mild Risk, Intermediate Risk, or High Risk. For subjects classified as having Mild or Intermediate Risk, referrals for outpatient mental health services will be provided and study staff will discuss a plan of action should the subject's frequency or intensity of ideation increase (call 911, go to ER). If the subject is classified as having High Risk with imminent danger of self-harm, then the study staff member will contact emergency medical services.
Risk assessment and safety monitoring will be conducted under the supervision of study staff who are licensed clinical psychologists

2.5 Correlative Studies Background

In a preliminary study (Jaywant et al., under review), we evaluated the frequency, severity, and profile of cognitive dysfunction in hospitalized patients recovering from COVID-19. We obtained and analyzed cross-sectional neuropsychological data from a cohort of N=57 patients participating in inpatient rehabilitation. 81% of patients had cognitive impairment, ranging from mild to severe. Deficits were most common in working memory (55% of patients impaired), set-shifting (47%), divided attention (46%), and processing speed (40%). Executive dysfunction was not significantly associated with intubation length or the time from extubation to assessment, nor was it associated with the presence of a psychiatric diagnosis. The results highlight the importance of studying interventions that target attention and executive functioning after COVID-19. Given the prevalence of COVID-19, targeting these deficits through scalable cognitive interventions that have been demonstrated to improve similar deficits and can be widely disseminated in patients' homes through reliance on technology may support optimal cognitive and functional outcomes.

3. Study Design

3.1 Overall Design

The primary objective of this study is to investigate the efficacy of AKL-T01 (Akili Interactive), a remotely-delivered digital cognitive intervention, in targeting and improving cognition and functional outcomes in individuals recovering from COVID-19. The efficacy of the AKL-T01 intervention will be measured relative to a waitlist control group. We hypothesize that the AKL-T01 intervention will show greater efficacy relative to the waitlist control at improving cognitive and daily function in COVID-19 survivors.

To test this hypothesis, adults who were previously infected with a diagnosis of COVID-19 and confirmed history of SARS-CoV-2 infection will be recruited for our study sample. This is a single site study, and all participants will be recruited through Weill Cornell Medicine and the NewYork-Presbyterian Hospital system. We will screen the electronic medical record (Epic) for NYP, Weill Cornell Medicine. Potential participants can also be referred by their doctor. We will also contact potential participants who were previously enrolled in COVID-19 research studies at NYP/WCM and agreed to be contacted for future research opportunities. We will also post flyers at NYP/Weill Cornell Medical Center and other relevant locations in the greater New York City area.

Due to the ongoing threat of COVID-19 and the remote nature of this trial, informed consent will also be obtained remotely. For participants with access to technology that will allow them to consent electronically, the participant and the member of the research team (co-

investigator or trained research assistant) obtaining informed consent will meet over a HIPAA-compliant video conference platform (i.e., Zoom). At the start of this video meeting, the researcher will share their screen and highlight each section of the consent form while discussing it with the participant. After discussing the consent form with the participant, they can then re-read it and sign it via REDCap. These participants will be provided with a PDF of their signed consent form for their records.

For participants without access to technology that would allow them to consent electronically, the participant and researcher will review to consent form over the phone. A copy of the consent form will be mailed or emailed to the participant in advance so that it can be viewed by the participant during the phone call. They will return the signed consent form in a stamped, self-addressed envelope provided by the researcher. These participants will then be mailed a copy of their signed consent form for their records.

To screen prospective participants, we will conduct an initial screening via a secure HIPAA-compliant videoconferencing platform (Zoom). Participants will be queried for inclusion and exclusion criteria. Participants will be administered via Zoom the Oral Trail Making Test, Stroop Test, and the Frontal Systems Behavior Rating Scale (FrSBe). Participants will be eligible for enrollment if they score <1 standard deviation below their age-normed peers on at least one of these three screening tests.

Participants will be randomized into the intervention arm or a waitlist control arm, with an option for the control participants to receive the AKL-T01 intervention at the conclusion of the initial 6-week waitlist period.

All participants (intervention & waitlist control arm): Full assessment visits will take place pre-intervention (baseline) and post-intervention (week 6). During the 6-week intervention period, shorter intermediate assessment visits will take place at weeks 2 and 4. Participants in the waitlist control arm will continue any ongoing self- or provider-based cognitive intervention (or no intervention) during the initial 6-week waitlist period.

Participants in the intervention arm & participants in the control arm who decline the intervention: A full assessment session at will take place at week 10 (4 weeks post-intervention) for longitudinal follow-up.

Participants in the control arm who begin the intervention at the conclusion of the waitlist period: The week 6 assessment visit will also serve as the baseline for the beginning of the intervention. Intermediate assessment visits will take place at weeks 8 and 10, a full post-intervention assessment visit will take place at week 12, and a follow-up assessment visit will take place at week 16 (4 weeks post-intervention).

See Section 6.1 for the complete Schedule of Assessments.

Participants will be aware of their assignment to study arm because it is not possible to blind them. The research team members conducting the study assessments will be blind to assignments. The care managers will not be blinded because it is not possible to blind them and it is necessary for them to know of a participant's assignment to assist in troubleshooting.

Our primary cognitive outcome will be measured by performance on a Digit Symbol Matching Task and our primary functional outcome will be measured by assessment score on the NeuroQOL scale. Additional cognitive tasks will be administered during the assessment visits to measure additional domains of cognition and daily functioning for our secondary and exploratory endpoint analyses. See Schedule of Assessments (Section 6.1) for list of assessments included in battery.

3.2 Scientific Rationale for Study Design

In order to evaluate the efficacy of AKL-T01 for COVID-19, we require comparison to a control group. Because of the potential negative impact of COVID-19 on cognition and functional outcomes, the control arm will be offered the intervention at the end of 6 weeks to ensure all participants ultimately have access to the intervention. Because the control group will not be engaging in any active control condition, there is potential for dropout; however, we will mitigate this dropout via weekly check-ins from the care managers and by providing compensation for those check-in visits to encourage retention.

3.3 Justification for Dose

Participants will complete 6 weeks of the AKL-T01 intervention. Previous research supports improvement of cognition following 4 weeks of the intervention, however continued improvement in a 4 week period after the intervention was observed. However, we are proposing a 6 week intervention to maximize the potential for cognitive change in COVID-19 survivors and because the overall gameplay dose is small (20-25 minutes daily for 5 days a week), and the additional time and remote delivery will not present additional burden to the participants.

3.4 End of Study Definition

A participant is considered to have completed the study for the primary objective of the study if he or she has completed the 6 weeks of the intervention and the post-intervention assessment. For the secondary and exploratory objectives, the end of the study is defined as completion of the week longitudinal follow-up visit.

4. Subject Selection

4.1 Study Population

The study population will be individuals who were diagnosed with COVID-19 (determined by a documented previous positive test results for SARS-CoV-2 infection) and have a deficit in cognition (i.e., attention and/or executive skills > 1 SD below the normal range).

4.2 Inclusion Criteria

1. Male or female 18-89 years of age.
2. Documentation of a deficit in cognitive function (score > 1 standard deviation below normal range) compared to age-adjusted normative data) on at least one screening measure of attention and executive function (Oral Trail Making Test, Stroop Test, or FrSBe).

3. Previous diagnosis of COVID-19 confirmed via SARS-CoV-2 polymerase chain reaction (PCR) test (or reported experience of COVID-19 symptoms with a documented positive antibody test or clinical diagnosis based on symptoms and accompanying physician's note) documented in the electronic medical record or in other existing medical records.
4. Access to and self-report of ability to connect wireless devices to a functional wireless network.
5. Ability to follow written and verbal instructions (English) as assessed by the PI and/or co-investigator.
6. Able to comply with all testing and study requirements and willingness to participate in the full study duration.

4.3 Exclusion Criteria

1. History of neurologic disorder prior to COVID-19 diagnosis, such as Parkinson's disease, multiple sclerosis, Alzheimer's disease, stroke, brain tumor, or dementia.
2. History of severe mental illness (e.g., schizophrenia, psychosis, history of suicide attempt in the last year) or substance use disorder, recent history (in the past year) of alcohol/substance use disorder or symptoms of psychosis.
3. Participant is currently considered at risk for attempting suicide by the Investigator, has made a suicide attempt within the past year, or is currently demonstrating active suicidal ideation or self-injurious behavior.
4. Motor condition (e.g., physical deformity of the hands/arms) that prevents game playing as reported by the participant or observed by the Investigator.
5. Recent history (within 6 months prior to screening/baseline) of substance use disorder.
6. History of seizures (excluding febrile seizures), a tic disorder, significant tics, a current diagnosis of Tourette's Disorder.
7. Color blindness as determined by self-report.
8. Regular use of psychoactive drugs other than antidepressants or benzodiazepines, including stimulants that in the opinion of the Investigator may confound study data/assessments.
9. Any other acute medical condition that may interfere with participation or interpretation of the results.
10. Previous exposure to AKL-T01.

4.4 Lifestyle Considerations

Not applicable.

4.5 Screen Failures

Screen failures are defined as participants who consent to be screened to participate in the clinical trial but are not subsequently randomly assigned to the study because they do not meet inclusion/exclusion criteria. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, 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, eligibility criteria, and any serious adverse event (SAE).

4.6 Strategies for Recruitment and Retention

We will recruit subjects from the Weill Cornell/NYP system. We anticipate that we will have to screen up to 500 subjects to meet our target enrolment. We will recruit by retrospective review of the electronic medical record, via social media, study flyers and posters, and via referral from providers throughout NYP and WCM. We will attempt to recruit an equal number of males and females; however, anticipate that our sample will reflect current demographic estimates of prevalence of COVID-19, i.e., increased prevalence of severe illness in men. We anticipate that a significant percentage of our sample may be of African American race and/or Hispanic ethnicity due to known racial/ethnic disparities in COVID-19. We will contact patients via contact information listed in the electronic medical record.

We will be recruiting individuals with cognitive impairment because we hypothesize that our intervention has the potential to improve cognitive deficits in this population. We will determine whether participants can sign consent by using teach-back methods to verify comprehension of risks and benefits. We will also use a capacity to consent form (see attachment) to verify comprehension of risks and benefits for subjects deemed to have more than mild impairment based on clinician interview.

Compensation for participation will be provided as follows:

Week	**Visit**	**Compensation * Arm**		
		AKL-T01 Intervention	***Waitlist Control (No Intervention)***	***Waitlist Control (Intervention)***
0	*Pre-Intervention Assessment*	$50	$50	$50
2	*Intermediate Assessment*	$25	$25	$25
4	*Intermediate Assessment*	$25	$25	$25
6	*Post-Intervention Assessment*	$50	$50	$50
10	*Follow-Up Assessment **	$75	$75	
		End of Waitlist		
8	*Intermediate Assessment*			$25
10	*Intermediate Assessment*			$25
12	*Post-Intervention Assessment*			$50
16	*Follow-Up Assessment*			$75
Total Per Participant		***$225***	***$225***	***$325***

* Also serves as pre-intervention assessment for waitlist control participants.

5. Registration Procedures

5.1 Subject Registration (WCM only)

Subjects will be registered within the WRG-CT as per the standard operating procedure for Subject Registration.

5.2 Subject Registration (Sub-sites)

Not applicable.

6. Study Procedures

6.1 Schedule of Assessments

Table 1. Schedule of trial events

	WEEK														
Measure	**Sc**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**16**
Consent	❖														
Demographics	❖														
Medical History	❖														
Cognitive Screen	❖														
Randomization	❖														
Intervention / Check-In		❖	❖	❖	❖	❖	❖	❖	★	★	★	★	★	★	★
Digit Symbol Match		❖		❖		❖		❖		★		❖		★	★
Multiple Object Tracking		❖		❖		❖		❖		★		❖		★	★
Digit Span Backwards		❖		❖		❖		❖		★		❖		★	★
Simple RT		❖		❖		❖		❖		★		❖		★	★
Choice RT		❖		❖		❖		❖		★		❖		★	★
Letter/Number Switch		❖		❖		❖		❖		★		❖		★	★
Gradual CPT		❖		❖		❖		❖		★		❖		★	★
Visual Paired Associates		❖						❖				o		★	★
NeuroQOL		❖		❖		❖		❖		★		❖		★	★
WHODAS (36-item)		❖						❖				o		★	★
WHODAS (12-item)				❖		❖				★		★			

Modified Fatigue Impact		❖						❖				⭘		★	★
PHQ-9		❖	❖	❖	❖	❖	❖	❖	★	★	★	⭘	★	★	★
GADS-7		❖						❖				⭘		★	★
Adverse Event Monitoring	❖	----------													❖

❖ All Participants (Intervention & Control Arm)
★ Intervention Arm & No Waitlist Controls ONLY
⭘ Waitlist Controls ONLY

6.1.1 Screening Visit (< *1 week before enrollment and randomization*)

Participants will be screened and assessed for eligibility before enrollment and randomization to the intervention and waitlist control arms. During the screening visit, participants will meet via HIPAA-compliant video conferencing platform with a PhD-level member of the study team. During this visit, potential participants will be screened for the cognitive deficit required for participation in the study. Eligible participants will be randomized to the intervention arm or the waitlist control arm in a 1:1 using a computer-generated randomization scheme developed by the data manager at the conclusion of the screening visit. A block randomization approach will be used based on a block of 6.

The screening visit will include the following study procedures:

- Informed consent
- Demographics (in EMR or collected at screening visit)
- Medical / medication history (in EMR or collected at screening visit)
- Additional Medical/Psychiatric symptom screening (completed by member of the research team)
- Cognitive screening (Oral Trail Making Test, Stroop Test, FrSBe)

6.1.2 Treatment Phase

6.1.2.1 Week 0 (Baseline/Pre-Intervention), Week 6 (Post-Intervention), Week 12 (Post-Intervention; waitlist control participants only)

The pre- and post-intervention visits will take place at the beginning and the end of the intervention period. Participants in both arms will meet remotely with a member of the research team via a HIPAA-compliant video conferencing platform (Zoom). The full battery of cognitive tasks (~35 minutes), functional assessments (~30 minutes), and mood symptom scales (~10 minutes) will be conducted at the baseline visit. Participants in the AKL-T01 intervention arm will be trained in procedures for gameplay during this visit. (Note that the week 6 assessment session will also serve as the baseline assessment for control participants who begin the intervention following the waitlist period.)

The pre- and post-intervention assessment visits will include the following study procedures:

- ***Cognitive Tasks:***
- Digit Symbol Matching

- Multiple Object Tracking
- Digit Span Backwards
- Simple RT
- Choice RT
- Letter/Number Switch
- Gradual CPT
- Visual Paired Associates
- ***Functional Assessments:***
- NeuroQOL
- WHODAS (36-item)
- Modified Fatigue Impact Scale
- ***Mood Symptom Scales:***
- PHQ-9
- GADS-7

6.1.2.2 Weeks 2 & 4 (± 2 days; *all participants*) & Weeks 8 & 10 (± 2 days; *waitlist control participants only*)

The intermediate assessment visits at weeks 2 & 4 (and weeks 8 & 10 for waitlist control participants) will include a shorter battery of cognitive tasks (~25 minutes) and functional assessments (~10 minutes) measuring the primary and secondary endpoints, as well as the PHQ-9 (~5 minutes) for monitoring of mood symptoms.

The intermediate assessment visits will include the following study procedures:

- ***Cognitive Tasks:***
- Digit Symbol Matching
- Multiple Object Tracking
- Digit Span Backwards
- Simple RT
- Choice RT
- Letter/Number Switch
- Gradual CPT
- ***Functional Assessments:***
- NeuroQOL
- WHODAS (12-item)
- ***Mood Symptom Scales:***
- PHQ-9

6.1.3 Follow-up Phase

Longitudinal follow-up assessment visits will take place 4 weeks after the end of the intervention period. For participants in the AKL-T01 intervention arm this visit will take place at week 10. For participants in the control arm who do begin the intervention at the end of the waitlist period, this visit will take place at week 16. This visit will include the full battery of cognitive tasks, functional assessments, and mood symptom scales collected at the pre- and post-intervention visits.

7. Study Intervention

7.1 Study Intervention/Device Description

The AKL-T01 intervention and the study assessments will be administered on an Apple iPad. The intervention video game is an iPad application that will be pre-installed on the iPads provided to participants. The iPad will also include shortcuts to the cognitive tasks and the RedCap database through which they will complete the self-report scales. All other applications and web pages will be locked on the intervention iPads. Participants in both the intervention arm and the waitlist control arm will be provided with iPads to ensure consistency in the data collection device.

The iPads will be shipped to participants' homes with a self-addressed return envelope for the iPad to be mailed back to the research team at the conclusion of participation in the study.

7.2 Availability

An Apple iPad will be provided to the participants for the duration of their participation by Akili Interactive.

7.3 Acquisition and Accountability

iPad Device Logs – The investigator, or a responsible party designated by the investigator, will maintain a careful record of the inventory and disposition of all iPads received from Akili Interactive in the study's Device Log.

7.4 Formulation, Appearance, Packaging, and Labeling

The devices provided to the participants will be Apple iPads. Participants will only be able to access the AKL-T01 video game interface (intervention arm only), the cognitive task battery, and the RedCap database for assessment administration. Participants will review instructions for using the iPads with a member of the research team during their first weekly check-in visit.

7.5 Product Storage and Stability

Not applicable.

7.6 Preparation

Not applicable.

7.7 Dosing and Administration

Participants in the AKL-T01 intervention arm are required to play the game for 25 minutes per day for at least five days (but up to 7 days) per week. The game will automatically "lock" after 25 minutes to prevent participants for playing longer than specified.

7.7.1 Dosing Delays/Dose Modifications

Not applicable.

7.8 General Concomitant Medication and Supportive Care Guidelines

Not applicable.

7.9 Duration of Therapy and Criteria for Removal from Study

In the absence of intervention delays due to adverse event(s), intervention may continue until one of the following criteria applies:

- Intercurrent illness that prevents further administration of the intervention,
- Unacceptable adverse event(s),
- Subject decides to withdraw from the study, or
- General or specific changes in the subject's condition render the subject unacceptable for further intervention in the judgment of the investigator.
- The investigators of this study may stop the study or remove participants from the study at any time should they judge that it is in the participants' best interest to do so or if they do not comply with the study plan.

For device/interventional studies -
Study Termination Guidelines: A subject's follow-up in the study will end after one of the follow applies:

- Subject's voluntary withdrawal
- Subject lost to follow-up
- Completion of all scheduled study follow-up appointments

7.10 Duration of Follow Up

Subjects removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

7.11 Measures to Minimize Bias: Randomization and Blinding

A WCM data manager not involved in any other aspects of the study will use a computer-generated randomization table to determine whether the patient will be assigned to the AKL-T01 intervention arm or the waitlist control arm.

Participants will be aware of their assignment to study arm because it is not possible to blind them. The researchers conducting the study assessments will be blind to assignments. The care managers will not be blinded because it is not possible to blind them and it is necessary for them to know of a participant's assignment to assist in troubleshooting.

Participants and care managers will be instructed not to reveal the group assignment to the member of the research team conducting assessments. Following the completion of recruitment, data analysts will be provided with the data for the arms simply labelled as "Group A" and "Group B" to avoid bias. These generic labels will be unmasked only after completion of all the planned statistical analyses described below. Participants in the waitlist control arm who begin the intervention at the end of the waitlist period will have different

assessors for the initial 6-week control procedures and the subsequent 6-week intervention period so as to maintain the blind.

7.12 Study Intervention/Follow-up Compliance

Adherence to video game play for the participants in the AKL-T01 intervention arm will be monitored by a member of the research team using the intervention dashboard, which provides the researchers with information about duration and frequency of gameplay, progression through game levels, etc. Participants who are not playing for the required duration of 25 minutes a day for at least 5 days a week will work with their care manager during a weekly check-in visit to make a plan for game play (e.g., playing at a specific time each day, setting reminders to play).

Participants will be considered lost to follow up and no longer participating in the study when they do not respond to attempts at communication with the researcher for two weeks and miss an assessment visit during that window.

8. Study Intervention Discontinuation and Participant Discontinuation/Withdrawal

8.1 Discontinuation of Study Intervention

Discontinuation from the AKL-T01 intervention does not mean discontinuation from the study, and we will attempt to complete remaining study procedures 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.

The data to be collected at the time of study intervention discontinuation will include the collection of the post-intervention assessment data, including all cognitive tasks, functional assessments, and mood symptom scales.

8.2 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 intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant.
- Participant lost to follow-up after several attempts to contact subject to schedule study visit.

The reason for participant discontinuation or withdrawal from the study will be recorded in the case report form (CRF). Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

8.3 Lost to Follow Up

A participant will be considered lost to follow-up if they do not complete a scheduled visit within two weeks of the assessment window and is unable to be contacted by the study site staff.

The following actions must be taken if a participant does not complete a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit for two weeks 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.

9. Correlative/Special Studies

Not applicable.

9.1 Laboratory Correlative Studies
Not applicable.

9.1.1 Title – Laboratory Correlative Study #1
9.1.1.1 Collection of Specimen(s)
9.1.1.2 Handling of Specimen(s)
9.1.1.3 Shipping of Specimen(s) (if multicenter)
9.1.1.4 Site(s) Performing Correlative Study (if multicenter)

9.2 Special Studies
Not applicable.

9.2.1 Title – Special Correlative Study #1
9.2.1.1 Assessment
9.2.1.2 Method of Assessment
9.2.1.3 Timing of Assessment

10. Measurement of Effect

Calculated for primary and secondary outcome measures, comparing the active intervention (AKL-T01; week 0 to week 6 for intervention arm) to the waitlist control (week 0 to week 6) using standard inferential statistical techniques and calculation of effect sizes. Formally, for primary and secondary outcomes, we will apply linear mixed effects models with fixed effects for treatment group as the between-subjects factor, time (week number) as the within-subjects factor, and group-by-time interaction. A random intercept will be included. Effect size will be reported in terms of group-by-time interaction (i.e., difference in slope of change between

groups). Despite the protection afforded by randomization, should potential confounding variables be identified from among baseline sociodemographic and clinical features, secondary analyses will incorporate fixed terms for those putative confounders in linear models.

10.1 Response Criteria

Primary Outcome:
1) Improvement in cognitive function on the Digit Symbol Matching Test from pre-intervention to post-intervention.

Secondary Outcomes:
1) Improvement in daily function on the NeuroQOL Cognitive Function Scale from pre-intervention to post-intervention.
2) Improvement in cognitive function (improved accuracy and/or decreased response time) on Multiple Object Tracking, Digit Span Backwards, Simple RT, Choice RT, Letter/Number Switch, Gradual CPT from pre-intervention to post-intervention.
3) Improvement in daily function on the WHODAS 2.0 from pre-intervention to post-intervention.

Exploratory Outcomes:
1) Long-term improvement in cognition and daily function 4 weeks following completion of the intervention.
2) Improvement in cognitive function on the Visual Paired Associates Task.
3) Improvement in fatigue on the Modified Fatigue Impact Scale.
4) Improvement in mood symptoms on the PHQ-9 and GADS 7.

10.2 Duration of Response

Not applicable.

10.3 Progression-Free Survival

Not applicable.

10.4 Other Response Parameters

Not applicable.

11. Data Reporting / Regulatory Considerations

11.1 Data Collection

The data collection plan for this study is to utilize REDCap to capture all intervention, toxicity, efficacy, and adverse event data for all enrolled subjects. The REDCap database will be maintained by WCM and only members of the WCM research team will have access to the REDCap data.

Akili Interactive will have access to de-identified data related to gameplay during the video game intervention (metrics such as number of sessions played, time spent playing

the game, scores and performance, etc.). Gameplay data will be accessible via a dashboard linked to the iPad study devices; the device data will be connected to a unique ID number and will not be linked to participant PHI or identifiable information. Akili will not have access to participant medical records or identifiable information.

The computerized cognitive task battery is administered by a company called ManyBrains. They will have access to the scores collected during the cognitive tasks. Cognitive task data will be connected to a unique ID number and will not be linked to participant PHI or identifiable information. ManyBrains will not have access to participant medical records or identifiable information. They will store de-identified task scores in a research repository to be analyzed in aggregate form with other task scores to develop more optimized cognitive tasks in the future.

11.1.1 REDCap

REDCap (Research Electronic Data Capture) is a free data management software system that is fully supported by the Weill-Cornell Medical Center CTSC. It is a tool for the creation of customized, secure data management systems that include Web-based data-entry forms, reporting tools, and a full array of security features including user and group based privileges, authentication using institution LDAP system, with a full audit trail of data manipulation and export procedures. REDCap is maintained on CTSC-owned servers that are backed up nightly and support encrypted (SSL-based) connections. Nationally, the software is developed, enhanced and supported through a multi-institutional consortium led by the Vanderbilt University CTSA.

11.2 Regulatory Considerations

11.2.1 Institutional Review Board/Ethics Committee Approval

As required by local regulations, the Investigator will ensure all legal aspects are covered, and approval of the appropriate regulatory bodies obtained, before study initiation.

Before initiation of the study at each study center, the protocol, the ICF, other written material given to the patients, and any other relevant study documentation will be submitted to the appropriate Ethics Committee. Written approval of the study and all relevant study information must be obtained before the study center can be initiated or the IP is released to the Investigator. Any necessary extensions or renewals of IRB approval must be obtained for changes to the study, such as amendments to the protocol, the ICF, or other study documentation. The written approval of the IRB together with the approved ICF must be filed in the study files.

The Investigator will report promptly to the IRB any new information that may adversely affect the safety of the patients or the conduct of the study. The Investigator will submit written summaries of the study status to the IRB as required. On completion of the study, the IRB will be notified that the study has ended.

All agreed protocol amendments will be clearly recorded on a protocol amendment form and will be signed and dated by the original protocol approving signatories. All protocol

amendments will be submitted to the relevant institutional IRB for approval before implementation, as required by local regulations. The only exception will be when the amendment is necessary to eliminate an immediate hazard to the trial participants. In this case, the necessary action will be taken first, with the relevant protocol amendment following shortly thereafter.

Once protocol amendments or consent form modifications are implemented at the lead site, Weill Cornell Medicine, updated documents will be provided to participating sites, as applicable. Weill Cornell Medicine must approve all consent form changes prior to local IRB submission.

Relevant study documentation will be submitted to the regulatory authorities of the participating countries, according to local/national requirements, for review and approval before the beginning of the study. On completion of the study, the regulatory authorities will be notified that the study has ended.

11.2.2 Ethical Conduct of the Study

The Investigators and all parties involved should conduct this study in adherence to the ethical principles based on the Declaration of Helsinki, GCP, ICH guidelines and the applicable national and local laws and regulatory requirements.

This study will be conducted under a protocol reviewed and approved by the applicable ethics committees and investigations will be undertaken by scientifically and medically qualified persons, where the benefits of the study are in proportion to the risks.

11.2.3 Informed Consent

The investigator or qualified designee must obtain documented consent according to ICH-GCP and local regulations, as applicable, from each potential subject or each subject's legally authorized representative prior to participating in the research study. Subjects who agree to participate will sign the approved informed consent form and will be provided a copy of the signed document.

The initial ICF, any subsequent revised written ICF and any written information provided to the subject must approved by IRB prior to use. The ICF will adhere to IRB requirements, applicable laws and regulations.

We will use verbal teach-back methods to verify comprehension of risks and benefits and capacity to consent to participation. For participants who screen as having moderate cognitive impairment (e.g., <2 SD below the normative mean on screening measures), we will use additional safeguards to verify comprehension of risks and benefits and study procedures, and to verify capacity to consent. The research staff member will conduct a formal interview (see attached questionnaire) to ensure that the participant comprehends study procedures, risks, and benefits. This questionnaire will ascertain whether the patient can communicate their choice; can attend to, understand, and recall the information discussed; and can weigh the risks and benefits to participating.

11.2.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor-Investigator of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to http://www.clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

11.2.5 Record Retention

Essential documents are those documents that individually and collectively permit evaluation of the study and quality of the data produced. After completion of the study, all documents and data relating to the study will be kept in an orderly manner by the Investigator in a secure study file. Essential documents will be retained for 2 years after the final marketing approval in an ICH region or for at least 2 years since the discontinuation of clinical development of the IP. In addition, all subjects medical records and other source documentation will be kept for the maximum time permitted by the hospital, institution, or medical practice.

12. Statistical Considerations

12.1 Study Design/Endpoints

We will test the hypothesis that patients receiving the AKL-T01 intervention will have significantly enhanced improvement in cognition and daily functioning, relative to a waitlist control group.

1) Our primary cognitive measure will be change in performance on a Digit Symbol Matching Task from baseline (pre-intervention) to week 6 (post-intervention) in all participants randomized to the AKL-T01 intervention arm or the waitlist control arm.

2) Our primary daily functioning measure will be change in score on the NeuroQOL Cognitive Function scale from baseline (pre-intervention) to week 6 (post-intervention) in all participants randomized to the AKL-T01 intervention arm or the waitlist control arm.

We will use analysis of variance (ANOVA) to test for differences in 1) Digit Symbol Matching and 2) NeuroQOL change scores across the intervention and control arms.

A secondary outcome analyses will use ANOVA to test for group differences in change in performance on the remaining cognitive tasks (Multiple Object Tracking, Digit Span Backwards, Simple RT, Choice RT, Letter Number Switch) and group differences in the WHODAS 2.0, our secondary measure of daily functioning.

We will use the Holm-Bonferroni method to correct for multiple comparisons. An intent-to-treat approach will be used in for all of the analyses above, including outcomes in participants who did not complete the intervention.

12.2 Sample Size/Accrual Rate

Our target sample size will be 100 COVID-19 survivors. 50 participants will be randomized to the AKL-T01 intervention arm and 50 participants will be randomized to a waitlist control arm.

Our total enrollment to meet our target sample size of 100 participants will be 125. Based on previous research conducted at our institution, we anticipate ~20% of individuals will decide not to participate after meeting eligibility criteria.

As primary analysis will utilize linear mixed models (as implemented in lme4) to examine slope of symptom change, we utilized the simr package in R (4.0) to estimate power for the specified model assuming 50 participants per study arm in 100 simulated data sets. For standardized beta coefficient corresponding to Cohen's d of ~0.4, power exceeds 88% (95% confidence interval 80.0-93.6%) for the base case, and exceeds 80% under a range of conservative assumptions, with alpha=0.05 for the primary hypothesis test.

We expect enrollment to last approximately 12 months, yielding an accrual rate of ~10 participants per month.

12.3 Stratification Factors

Not applicable.

12.4 Analysis of Endpoints

12.4.1 Analysis of Primary Endpoints

Our primary cognitive measure will be change in performance on a Digit Symbol Matching Task from baseline (pre-intervention) to week 6 (post-intervention) in all participants randomized to the intervention or control arm. Our primary daily functioning measure will be change in score on the NeuroQOL Cognitive Function scale from baseline (pre-intervention) to week 6 (post-intervention) in all participants randomized to the intervention or control arm. We will use analysis of variance (ANOVA) to test for differences in Digit Symbol Matching and NeuroQOL change scores across the two arms.

12.4.2 Analysis of Secondary Endpoints

Our secondary outcome analyses will use ANOVA to test for group differences in change in performance on the remaining cognitive tasks (Multiple Object Tracking, Digit Span Backwards, Simple RT, Choice RT, Letter Number Switch) and group differences in the WHODAS 2.0, our secondary measure of daily functioning.

12.5 Interim Analysis

Interim analyses will be provided to Akili Interactive as requested.

12.6 Reporting and Exclusions

12.6.1 Evaluation of Toxicity

Not applicable.

12.6.2 Evaluation of Response

All subjects included in the study will be assessed for response to the intervention (if they have received the intervention).

13. Adverse Event Reporting Requirements

The research team is responsible for notifying the WCM IRB of all unexpected adverse events and serious adverse events. After faxing or e-mailing the Cornell IRB reporting forms to Cornell, the Research Assistant should follow-up with an e-mail or phone call to verify that the forms were received. Additionally, copies of these forms should be kept in the patient file as source documentation.

In addition to the WCM IRB, AEs, SAEs, death, protocol violations, non-compliance, suspensions and terminations will be reported to the Akili Interactive (as the industry funding partner). All reports must be made in writing to Akili. These reports should indicate that the monitoring entities (i.e., the PI and IRB) have been notified in accordance with the approved monitoring plan.

13.1 Adverse Event Definition

Adverse event is defined as any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related.

13.1.1 Investigational Agent or Device Risks (Expected Adverse Events)

We do not anticipate significant risks for our behavioral intervention beyond boredom, frustration, fatigue, and/or headaches.

13.1.2 Adverse Event Characteristics and Related Attributions

All AEs must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study device must always be suspect.

- ***Definitely Related*** – There is clear 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 intervention administration and cannot be explained by concurrent disease or other drugs or chemicals.
- ***Probably Related*** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other

drugs or chemicals.

- Potentially Related – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). 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*** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- ***Not Related*** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

13.1.3 Recording of Adverse Events

All adverse events will be recorded on a subject specific AE log. The AE log will be maintained by the research staff and kept in the subject's research chart.

13.1.4 Reporting of AE to WCM IRB

All AEs occurring on this study will be reported to the IRB according to the IRB policy, which can be accessed via the following link: http://researchintegrity.weill.cornell.edu/forms_and_policies/forms/Immediate_Reporting_Policy.pdf.

13.1.5 Reporting Events to Participants

Events leading to substantive changes in the consent form or procedures will be communicated to the current participants enrolled in the study.

13.1.6 Events of Special Interest

Not applicable.

13.1.7 Reporting of Pregnancy

Not applicable.

13.2 Definition of SAE

Serious adverse event or serious suspected adverse reaction. An AE or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse

event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such an event would include a seizure or suicide attempt requiring inpatient hospitalization.

13.2.1 Reporting of SAE to IRB

All SAEs occurring on this study will be reported to the IRB according to the IRB policy, which can be accessed via the following link: http://researchintegrity.weill.cornell.edu/forms_and_policies/forms/Immediate_Reporting_Policy.pdf.

13.2.2 Reporting of SAE to FDA [For Protocols Where WCMC is the Sponsor-Investigator]

Not applicable.

13.2.3 Reporting of SAE to Akili Interactive

Institution will send Akili Interactive copies of any and all serious adverse event reports filed with the IRB, as well as copies of any correspondence with the IRB, regarding any and all serious adverse events, irrespective of association with the AKL-T01 intervention in the course of the Clinical Trial, within 5 business days of such report or correspondence being sent to the IRB. Copies should be sent via secure file transfer directly to Deb Farlow in the Clinical Research and Operations Department at Akili Interactive.

13.3 AE/SAE Follow Up

All SAEs and AEs reported during this study will be followed until resolution or until the investigator confirms that the AE/SAE has stabilized and no more follow-up is required. This requirement indicates that follow-up may be required for some events after the subject discontinues participation from the study.

13.4 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 including local and systemic reactions not meeting the criteria for SAEs 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 product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be

documented appropriately regardless of relationship. All AEs 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 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. AEs characterized as intermittent require documentation of onset and duration of each episode.

The study research assistant will record all reportable 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. Events will be followed for outcome information until resolution or stabilization.

14. Unanticipated Problems Involving Risks to Subjects or Others

14.1 Definition of Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSO)

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 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.

This definition could include an 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 subjects (21 CFR 812.3(s)).

14.1.2 Unanticipated Problem Reporting

The investigator will report unanticipated problems (UPIRTSOs) to the reviewing Institutional Review Board (IRB) and to the Data Coordinating Center (DCC)/lead principal investigator (PI). The UPIRTSO 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 UPIRTSO;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UPIRTSO.

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

- UPIRTSOs that are serious adverse events (SAEs) will be reported to the IRB and to the DCC/study sponsor within <insert timeline in accordance with policy> of the investigator becoming aware of the event.
- Any other UPIRTSO will be reported to the IRB and to the DCC/study sponsor within <insert timeline in accordance with policy> of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), Food and Drug Administration (FDA), and the Office for Human Research Protections (OHRP) within <insert timeline in accordance with policy> of the IRB's receipt of the report of the problem from the investigator.

An investigator will submit to the sponsor and to the reviewing Institutional Review Board (IRB) a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect (21 CFR 812.150(a)(1)), 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 IRB's and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter the sponsor shall submit such additional reports concerning the effect as FDA requests (21 CFR 812.150(b)(1)).

15. Data and Safety Monitoring Plan (DSMP)

Data and safety monitoring will be performed internally by licensed clinical psychologists on the study protocol. This is a minimal risk study. Safety including AE/SAE will be monitored by licensed clinical psychologists (Drs. Gunning, Jaywant, Kanellopoulos) on the study staff. The monitoring clinicians will review the data that will be captured will be from 1) the pre-intervention assessments; 2) mid-intervention assessments; 3) post-intervention assessments; 4) and follow-up assessments. They will also monitor for acute medical illness or change in medical status that requires admission to a hospital and/or prevents participation in the study.

Since this is a minimal risk study, there are no stopping rules as the risks are fatigue, frustration, and boredom. Subjects will continue to have the right to withdraw at any time.

The monitoring entity's comments will be submitted to the IRB at the time of continuing review.

16. References

Anguera JA, Boccanfuso J, Rintoul JL, Al-Hashimi O, Faraji F, Janowich J, Kong E, Larraburo Y, Rolle C, Johnston E, Gazzaley A. Video game training enhances cognitive control in older adults. Nature. 2013 Sep;501(7465):97-101.

Anguera JA, Gunning FM, Areán PA. Improving late life depression and cognitive control through the use of therapeutic video game technology: A proof-of-concept randomized trial. Depression and anxiety. 2017 Jun;34(6):508-17.

Bove RM, Rush G, Zhao C, Rowles W, Garcha P, Morrissey J, Schembri A, Alailima T, Langdon D, Possin K, Gazzaley A. A videogame-based digital therapeutic to improve processing speed in people with multiple sclerosis: a feasibility study. Neurology and therapy. 2019 Jun 1;8(1):135-45.

Garrigues E, Janvier P, Kherabi Y, Le Bot A, Hamon A, Gouze H, Doucet L, Berkani S, Oliosi E, Mallart E, Corre F. Post-discharge persistent symptoms and health-related quality of life after hospitalization for COVID-19. Journal of Infection. 2020 Aug 25.

Gunning FM, Anguera JA, Victoria LW, Arean PA. A Digital Intervention Targeting Cognitive Control Network Dysfunction in Middle Age and Older Adults with Major Depression. Under Review, Translational Psychiatry.

Jaywant A, Vanderlind WM, Alexopoulos GS, Fridman CB, Perlis RH, Gunning FM. Frequency and profile of objective cognitive deficits in hospitalized patients recovering from COVID-19. medRxiv. 2020 Jan 1.

Kollins SH, DeLoss DJ, Cañadas E, Lutz J, Findling RL, Keefe RS, Epstein JN, Cutler AJ, Faraone SV. A novel digital intervention for actively reducing severity of paediatric ADHD (STARS-ADHD): a randomised controlled trial. The Lancet Digital Health. 2020 Feb 24.

Zhou H, Lu S, Chen J, Wei N, Wang D, Lyu H, Shi C, Hu S. The landscape of cognitive function in recovered COVID-19 patients. Journal of Psychiatric Research. 2020 Oct 1;129:98-102.

Appendix A

Not applicable.