Protocol

WASABI: Wiring Adolescents with Social Anxiety Via Behavioral Interventions

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TITLE: Wiring Adolescents With Social Anxiety via Behavioral Interventions (WASABI): a closed-loop mobile intervention to reduce social anxiety and improve social skills

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Title

Wiring Adolescents with Social Anxiety via Behavioral Interventions (WASABI): a closed-loop mobile intervention to reduce social anxiety and improve social skills

Principal Investigator and Key Staff

The trial is sponsored by Posit Science Corporation (PSC) and is funded exclusively by the National Institute on Mental Health (NIMH). Posit Science will serve as the coordinating and data monitoring and management center for this study. Key staff and site information may be found below:

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Site Investigators and Study Locations

The University of Minnesota Child and Adolescent Anxiety Clinic and associated clinics will serve as the primary recruitment site for this study. The Site Principal Investigator, listed below, will oversee participant recruitment and enrollment for this clinical trial.

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Overview

This is a validation study to evaluate the acceptability, feasibility and impact of WASABI (Wiring Adolescents with Social Anxiety via Behavioral Interventions), a clinician-assisted, adjunct to treatment, mobile application employing a closed-loop technology, designed to augment the efficacy of digitally delivered Cognitive Behavioral Group Therapy (dCBGT). The goal of this study is to evaluate WASABI in adolescents with Social Anxiety and to prepare for a large-scale efficacy trial in this population.

Specific Aims

This study will employ an innovative and evidence-based mobile intervention that includes Ecological Momentary Assessments (EMAs) data collected from mobile devices, the WASABI closed-loop algorithm to detect exacerbation of social anxiety, and 1:1 and group-based videoconferencing and Instant Messaging with peers and providers. This study will test WASABI as an adjunct to dCBGT in adolescents with Social Anxiety (SA), in a parallel arm, double-blind, randomized, controlled clinical trial to assess feasibility and initial efficacy, to investigate the generalization of trained cognitive skills in the natural environment and ability to improve anxiety and social functioning, and to prepare for a large-scale efficacy trial in adolescents with Social Anxiety.

Background

Social Anxiety (SA) is characterized by fear of negative evaluation from others in social or performance situations.[1] SA affects up to 9% of adolescents,[2] with 75% of its extreme and persistent forms emerging by mid-adolescence with a median age of onset of 13 years.[3,4] If left untreated, SA can follow a chronic course[2] and lead to consequences such as depression,[5] suicidality,[6] substance and alcohol dependence,[7] academic under-performance, and increased social isolation.[8] In addition, since peer interactions carry learning experiences, avoidance of social exchanges, used to cope with anxiety in social situations, is more disruptive during this time,[9] and often results in an impaired development of social skills.[10] With SA contributing to substantial burden for patients, their families, and to long-term societal costs, it is critical to intervene early.[11,12] Among the psychological Evidence Based Treatments (EBTs) for adolescents with SA, **Cognitive Behavioral Group Therapy** (CBGT) is considered one of the most established, with numerous Randomized Controlled Trials (RCTs) over the last 20 years corroborating its efficacy for both adults and adolescents,[13–17] and with a recent study showing equivalent efficacy after treatment and at one year follow-up between the individual and the group format in youth with anxiety disorders.[18] However, full diagnostic recovery rate is only 20.5% in CBGT,[18] and up to 50% of patients remain symptomatic post-treatment,[19,20] calling for treatment augmenters.[21] Additionally, only 20% of those with SA seek this CBGT, and even fewer ultimately receive it.[4,22–25] Certainly the nature of SA contributes to this delay in seeking

treatment, as in-person social interactions are required to access professional services.[9] For those who do seek treatment, barriers to receiving it include geographic location, availability of trained therapists, long waiting lists, and the requirement to take time off from school for clinic visits.[26,27] Therefore, remotely delivering CBGT through video calls (***d*CBGT**) offers advantages, including ready accessibility, time flexibility, and convenience. While research shows that remotely delivering CBGT to adolescents with SA via digital platforms is adaptable, feasible, efficient, cost-effective, and equally efficacious,[28–33] we believe that recent advances in mobile and communication technology can be harnessed to further improve *d*CBGT delivery for SA:

1) Existing dCBGT is not informed by patient ecologically valid data on social role performance and generalization of trained cognitive skills in real-world settings. Although developmentally informed adaptations to dCBGT for adolescents were shown to reduce lab-based measures of SA symptoms in this population,[34] to date no improvements in social functioning have been reported. This is problematic, as the inability to behave as desired in social situations is the primary reason why most individuals seek treatment, and are of critical importance in the clinical presentation of SA, and in diagnostically determining its presence/absence.[35] Although some authors argue that a patient's perceived lack of social skills is a cognitive distortion that may seriously undermine confidence in social situations,[36] this lack of effect could be due to the fact that dCBGT does not take place within an ecologically valid social context, despite exposure (i.e., repeated confrontation of anxiety-provoking social situations without escape/avoidance in order to facilitate extinction)[37] being one of its founding principles. If integrating cognitive and exposure treatment components is critical to enhance social functioning in SA,[28,29,38] then the first necessary step would be to collect real-time data from social situations at an individual level. Although Ecological Momentary Assessments (**EMAs**) have been shown to increase accuracy, minimize retrospective bias and highlight context-specific relationships of symptoms or behaviors,[39] only a few studies to date have used these experience sampling methods in adolescents to capture manifestations of SA, and/or to measure the actual generalization of trained skills in real-world settings.[40–42]

2) Existing dCBGT does not provide real-time support to adolescents with SA during stressful social situations.

Importantly, these EMA data can be viewed in real time by CBGT clinicians via digital dashboards, and used not only to monitor symptoms and social functioning during the intervention, but also to guide the delivery of personalized care. In particular, communication methods such as 1:1 Instant Messaging (**IM**) can be embedded in the intervention to facilitate real-time remote communication, and extend the reach of the clinician within the environment of adolescents with SA. This was recently demonstrated to be an effective means to provide patients with opportunities, encouragement, and reinforcement for using the behaviors and skills learned and for receiving the appropriate rewards.[43,44] Additionally, these methods help

consolidate therapeutic alliance and maintain inter-session continuity, with important implications for treatment engagement.[45–47] Finally, the reach of peer-support can be extended beyond the clinical setting, by means of direct peer-to-peer 1:1 or group IM.[43,44] This becomes an important source of nonprofessional to practice and improves skills in the everyday lives of patients.[48]

Based on our expertise in the development of digital platforms that provide individualized monitoring and treatments,[44,49] we designed **WASABI** (Wiring Adolescents With Social Anxiety via Behavioral Interventions)–a clinician-assisted, adjunct to treatment, mobile application. WASABI enriches *d*CBGT with a mobile solution that provides multi-modal monitoring through EMAs, detects via a **closed-loop algorithm** patterns of symptom exacerbation, and cues peers and providers to connect in via IM. WASABI is posited to augment the efficacy of *d*CBGT by promoting the generalization of trained skills in the environment of adolescents with SA, thus reducing anxiety and improving real-world social functioning.

Pilot Trial Design and Procedures

Participants will be recruited to join a pilot trial prior to the implementation of the parallel arm, double-blind, randomized, controlled clinical trial to assess feasibility and initial efficacy of WASABI as an adjunct to dCBGT in adolescents with Social Anxiety (SA). During the pilot trial, three focus groups will be organized with a group of three adolescents with SA and at least one clinician to refine WASABI and qualitatively evaluate its manageability, clinical utility, and acceptability. After the focus groups are completed, participants will be granted access to WASABI for two weeks to test its features and evaluate its usability. At the end of the 2-week trial period, participants will offer feedback on the app through a 1:1 user interview with a member of the research team. It is expected that participants will be enrolled in the pilot trial for approximately 4 weeks.

Participants must be between the age of 14 to 18 (inclusive) and have clinically significant Social Anxiety, as defined by a score of 25 or greater on the Social Phobia and Anxiety Inventory-Brief (SPAI-B) for Adolescents. Participants must have access to reliable Internet connection and must be willing to engage in remote and/or in-person activities to qualify for enrollment.

Prior to initiating any pilot trial procedures, Site Study personnel will screen potential participants (either over the phone or in-person) using an IRB-approved screening questionnaire that assesses for inclusion and exclusion criteria. If the potential participant appears eligible, they and their parents/legal guardian(s), when appropriate, will be invited to a consent/assent discussion with a designated team member prior to enrollment

Consenting/assenting to research activities will take place remotely or in a private room at the Study Site. During the consent/assent discussion, the qualified Site Study personnel authorized by the Site Principal Investigator and the potential participant and their parent/legal guardian will discuss the nature, purpose, and procedures of the pilot trial, the possible risks and benefits of participation, confidentiality, and the voluntary nature of participation in the pilot trial (emphasizing the participant's right to withdraw from the focus group at any time). Participants will also be informed of the compensation procedures; specifically, participants will be paid $10 for completing the consent and screening procedures, $25 for participating in each focus group session, $25 for completing 2-weeks of WASABI app activities, and $15 for completing a 1:1 user interview. Participants that complete all activities will earn a total of $125. Compensation will be provided through CashPass, a reloadable debit card through a third-party vendor, CT Payer. Payment will be provided upon exiting from the pilot trial, following the completion of the 1:1 user interview. If a participant leaves early, for any reason, and does not complete all focus group activities, they will be paid only for activities they have completed. Upon agreeing to participate in the pilot trial and signing consent/assent documents, participants will be asked to complete the SPAI-B to confirm their eligibility for the study (a score of 25 or greater).

Once three participants are deemed eligible and enrolled in the pilot trial, they will be scheduled for three focus group sessions that could occur in-person or remotely, to be completed over the course of approximately 2-weeks. Each session will last approximately 1 hour and will be facilitated by the study clinician(s). After feedback from the focus group sessions is implemented into the app and dashboard design, the three adolescents will be granted access to the WASABI app and engage in a 2-week trial period, during which the predictive ability of the algorithm will be validated by the WASABI clinician, who will verify via 1:1 remote videocalls the actual presence of clinically-significant social anxiety whenever the WASABI clinician receives an alert. Additionally, this trial period will ensure that WASABI EMA data are timely evaluated by the clinician on the dashboard and meaningfully orient the delivery of individualized IM and weekly dCBGT content. At the end of the 2-week trial period of WASABI, participants will be asked to rate their enjoyment, ease of use, product quality, and perceived usefulness in a 1:1 user interview. Finally, we will submit these data from the trial period to our consultant to confirm that WASABI is suitable for the feasibility trial.

General Study Design

We will employ a standard prospective, parallel arm, double-blind, randomized, controlled clinical trial to assess the safety and efficacy of WASABI in adolescents with Social Anxiety (SA), and evaluate its potential in augmenting the efficacy of dCBGT in improving social

anxiety, social skills and social functioning. We will randomize adolescents with SA (ages 14-18) to receive either 12 weeks of dCBGT+WASABI or dCBGT only.

Approximately 32 participants will be consented to ensure the successful completion of 24 participants (12 participants per treatment arm). A diagnostic interview will be performed to determine eligibility. Following inclusion and enrollment, participants will complete a set of assessments prior to the intervention to establish their baseline performance. Participants will then be randomized to dCBGT+WASABI or dCBGT only and spend up to 12 weeks engaged in their assigned intervention.

Participants assigned to receive WASABI will complete at least 3 EMA sessions per week, 1 hour of digitally delivered Cognitive Behavioral Group Therapy (dCBGT) per week, and weekly cognitive biases assessments and self-reports for 12 weeks. During the intervention, these participants will also have daily access to 1:1 and group chat Instant Messaging (IM) and may have weekly electronic check-ins with Site Study personnel (as needed). Participants in the control condition will be asked to attend 1 hour of digitally delivered Cognitive Behavioral Group Therapy (dCBGT) per week for 12 weeks and may have weekly electronic check-ins with Site Study personnel (as needed).

For each arm, as soon as 3-6 participants have completed the baseline assessments and randomization, a cohort will be assembled. The Study Coordinator will meet with the participants to orient them to the study platforms and the WASABI Clinician will meet with each participant individually for a brief introduction and orientation prior to the 12-week intervention and will review of the *Procedures and Guidelines to Group Therapy*. The WASABI Coordinator and/or Clinician will create a virtual support group open only to cohort participants. The WASABI Clinician will explain her role, make group introductions, and will invite participants to attend weekly 1-hour group sessions (dCBGT+ WASABI or dCBGT only, depending on the treatment arm). For the treatment group (dCBGT + WASABI), between group sessions, the WASABI Clinician will spend approximately 30 min/day keeping the chat active during work hours, checking it approximately 3 times a day and may respond to messages participants leave, as appropriate. The WASABI Coordinator will be included in the support group chat and may monitor the chat content, and may be active in the chat in the absence of the WASABI Clinician.

Participants will be re-evaluated again at the expected time of completion, immediately following the 12-week intervention, to evaluate changes in performance. Finally, participants will be asked to fill out an online exit survey to rate enjoyment, usability, perceived benefits, and ease of fit into schedule.

The protocol will be conducted in accordance with the protocol submitted to and approved by the reviewing Institutional Review Board and approval will be obtained prior to implementation.

Study Population

The study population is comprised of adolescents diagnosed with Anxiety Disorder, specifically those with clinically significant social anxiety. The study is open to all races, ethnicities, and genders.

Inclusion/Exclusion Criteria

We will use standard diagnostic criteria and classifications for Social Anxiety. Following informed consent, participants will be screened for the following inclusion/exclusion criteria.

Inclusion Criteria

1) Potential participant is between the age of 14 and 18 (inclusive) at the time of consent
2) Potential participant has a clinical diagnosis of Anxiety Disorder, as confirmed using the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID), a brief structured diagnostic interview using DSM-IV criteria
3) Potential participant has clinically significant Social Anxiety, as defined by a score of 25 or greater on the Social Phobia and Anxiety Inventory-Brief version.
4) Potential participant is clinically stable at time of screening as determined by the screening clinician/study team and the following criteria:
    - Potential participant has not experienced a psychiatric hospitalization within the 4 weeks prior to screening
    - Potential participant on a medication for anxiety and psychiatric disorders must be on a stable medication regimen for ≥ 4 weeks prior to screening, based on self-report.
5) Potential participant has an IQ Score > 80 as determined by performance on the Wechsler Abbreviated Scale of Intelligence (WASI-II)
6) Potential participant is a fluent English speaker, based on participant and/or parent/legal guardian self-report and as determined by the screening clinician, to ensure reasonable neuropsychological results on key assessments
7) Potential participant has adequate sensorimotor capacity to perform the intervention and study activities, including visual capacity adequate to read from a computer screen or mobile device at a normal viewing distance, auditory capacity adequate to understand normal speech, and motor capacity adequate to control and use a mobile device and/or computer, based on participant and/or parent/legal guardian self-report and as determined by the screening clinician and/or study team

8) Potential participant has reliable access to wireless Internet connectivity
9) Potential participant can use iOS mobile applications

Exclusion criteria:

1) Potential participant has a diagnosis of autism spectrum disorders, history of seizure disorder or seizure episodes within the last 2 years
2) Potential participant is receiving psychotherapy at the time of randomization
3) Potential participant has a history of mental retardation, pervasive developmental disorder, head trauma, traumatic brain injury, or other neurological disorder that impairs cognition
4) Potential participant has medical illnesses deemed to interfere with participation in study activities and/or unstable and/or untreated conditions that may affect cognition, including substance abuse/dependence disorders, ongoing chemotherapy or other cancer treatment.
5) Potential participant has history or current DSM-IV diagnosis of organic mental disorder, schizophrenia, schizoaffective disorder, delusion disorder, psychotic disorder NOS, bipolar disorder, substance dependence (<1 year), and/or mood congruent or mood incongruent psychotic features or disorders
6) Potential participants had significant medication changes, including changes to anxiety medications or other psychiatric medications, in the 4 weeks prior to screening
7) Potential adult participant scores less than a 14 (75%) on the University of California, San Diego Brief Assessment of Capacity to Consent (UBACC). Please note, this criteria applies only to adult participants, age 18, at the time of screening.
8) Potential participants who have answered 'yes' to:
    a. Question 5 (Active Suicidal Ideation with Specific Plan and Intent) on the Columbia-Suicide Severity Rating Scale (C-SSRS), or,
    b. Any of the suicide-related behaviors (actual attempt, interrupted attempt, aborted attempt, preparatory act or behavior) on the C-SSRS "Suicidal Behavior" portion

   will be excluded from the study *if the ideation or behavior occurred within 2 months from Participant's date of consent* (as recommended by the FDA for treatment trials.) Participants excluded for this reason will be referred for appropriate treatment. Further, the C-SSRS form will also be administered to all participants at the follow-up visit. Participants meeting these criteria at any time throughout the study will be asked to complete a final assessment, if appropriate, then withdrawn from the study and referred for appropriate treatment.
9) Potential participants that show signs of intoxication or are under the influence due to current substance abuse (including alcohol and/or illegal drugs) during any in person visit or dCBGT session will be evaluated on a case-by-case basis. Such participants may have that visit re-scheduled or may be asked to exit the dCBGT session, as appropriate.

Participants with this problem occurring more than once may be excluded and dropped at the discretion of the PI(s).

10) Potential participant has problems performing assessments or comprehending or following spoken instructions, or participant displays behaviors during assessments visits or dCBGT sessions that, in the judgment of the clinician and study team, are likely to present significant problems for the Site Study personnel or other participants.
11) Potential participant is enrolled in a concurrent clinical trial involving an investigational pharmaceutical, medical device, behavioral treatment, or any other clinical trial that could affect the outcome of this study. However, participation in standard treatments (e.g., occupational therapy) or use of prescribed medications is allowable.

Recruitment

Study participants will be recruited through several recruitment mechanisms in an effort to examine engagement and acceptability in a representative sample of patients with Social Anxiety. Following IRB approval, IRB-approved recruitment materials and information about the study aims and procedures may be posted on Youtube, Facebook, Craigslist, Reddit, Instagram, Tik Tok, newsletters, the study website, as well as other web-based recruitment and social media sites. In addition, efforts will be made to recruit participants through several community mental health and primary care clinics and/or referrals, school-based settings and/or referrals, community organizations, and publicly hosted information sessions and webinars. Following IRB approval, a WASABI recruitment video, which includes a brief description of the study and may include members of the study team, may be shared with potential participants, with identified recruitment sources, and the community for recruitment purposes and engagement. Patients may also contact the Site Study team directly via the phone or the internet (email, website, social media, etc.).

The PI has extensive professional contacts and community clinician referrals. Thus, study participants may also be recruited through the patient network of the University of Minnesota Department of Psychiatry Child and Adolescent Anxiety Clinic and the University of Minnesota Physicians (UMP) Psychiatry Clinics. Potential participants may be identified by clinicians within the UMP Psychiatry Outpatient Clinics. Clinicians treating eligible patients in clinic may briefly introduce the study to their patients and/or the patient's parents/legal guardians. To prevent perceived therapeutic benefit or other coercion for participation in this trial, principal investigators will not be involved in consent discussions and will be minimally involved in study procedures that involve direct participant contact. If the individual is interested, they will be introduced to a member of the Site Study personnel or the Psychiatry Research Recruitment Specialist to explain the study in greater detail.

The Department of Psychiatry & Behavioral Sciences at the University of Minnesota provides patients with the opportunity to indicate whether they are interested in being contacted to learn about research studies through enrollment into a recruitment registry. This is accomplished through provision of a secure electronic REDCap consent form. Access to the voluntary contact information is managed by the Department of Psychiatry & Behavioral Sciences and securely stored and accessed by the Institute for Health Informatics Data Warehouse (BPIC) at CTSI (UL1TR002494). The department's Research Recruitment Specialist partners with BPIC to request a registry database for specific, IRB approved research. The Study Site intends to request permission to receive this contact information to recruit participants for the study.

Additionally, this study may be advertised on the Psychiatry Department website and recruitment areas in the lobbies of the Child and Adolescent Anxiety Clinic and/or other University of Minnesota Physicians (UMP) Outpatient Clinics. Potential participants and/or their parents/legal guardians may self-identify to advertisements online or to advertisements (e.g. flyers, recruitment contact cards) posted in the recruitment areas in the lobbies of the UMP Psychiatry Clinics.

The Site study team may host various information sessions and/or webinars within the Minnesota community in an effort to recruit participants. The Site Study team may also contact schools and school personnel (e.g., teachers, nurses, counselors, etc.) and/or school-related organizations within Minnesota to host a webinar or information session about the WASABI Study. These sessions may include discussions regarding approaches to identify students who may be experiencing social anxiety or have related concerns. The Site Study team may provide the school staff with resources to refer students of concern (e.g. flyers, the recruitment video and other recruitment materials).

As the Sponsor, Posit Science will strictly serve as a coordinating and data monitoring and management site. The Posit Science study team will directly manage this study using standard and established methods. Site Study personnel will be invited to complete virtual training sessions conducted by Posit Science study team and/or the PI will visit the Study Site to engage in a hands-on orientation of the mobile application and clinician's portal. Eligible patients undergoing treatment for Social Anxiety, with the exception of psychotherapy, that participate in the study will be able to continue with their treatment regime as planned. Potential participants receiving psychotherapy at the time of randomization will not be eligible for the study and will not be randomized and enrolled, per exclusion criteria. The intervention is designed to serve as adjunct to conventional care to remotely capture and document changes in anxiety, social anxiety, real-world social functioning and cognitive biases.

Enrollment and assessments will be performed by authorized Site Study personnel remotely and/or at the Study Site, the University of Minnesota. Participants will perform the intervention activities, either dCBGT+WASABI or dCBGT only, remotely in their place of residence. This project will employ established Sponsor- and Site-procedures for compliance, treatment delivery and communication to ensure standardization of all study procedures.

The emphasis of the benefit will be on advancing science to assist others with Social Anxiety. Compensation will be described in appropriate terms that are not overemphasized relative to the remainder of the text. No indication of "free medical treatment" will be communicated. All materials used for advertising or recruitment will have received IRB approval prior to implementation. The Site Study Coordinator will manage these efforts and contact individuals that express interest. The aim of this discussion is to describe the study, answer any questions, and if the potential participant agrees, conduct a preliminary screening. Site Study personnel will conduct an interview with a screening questionnaire, over the phone or in person, in which potential participants will be asked about the presence of inclusion and exclusion criteria. If the participant appears eligible, they and their parents/legal guardians, when appropriate, will be invited to a consent discussion.

All study team members are required to follow Good Clinical Practices and institutional best practices in the identification and recruitment of research participants. Volunteer selection will be equitable: all participants meeting Inclusion/Exclusion criteria will be offered the opportunity to participate in this study regardless of gender, race and/or ethnic origin. Basic demographic data will be collected from participants screened for participation but not meeting study eligibility requirements to ensure that the opportunity to participate in this research study has been extended to all potential participants in an equitable manner.

Description of Informed Consent Process

For participants that move forward following the initial screening, every effort will be made to send a copy of the consent form and HIPAA waiver via email ahead of their scheduled appointment. Assent/Consent forms for adults, minors (youth), and parents/legal guardians of minors will be written using appropriate vocabulary and language and will be accessible (non-technical). As minors cannot give legal consent to participate in research, a parent or legal guardian must sign a consent form on their behalf. However, we will still obtain the minor's written or electronic assent to ensure their voluntary participation in the research study. As with consent, the research study will be explained to them in language they will understand.

To ensure that the potential adult participants have the capacity to provide informed consent, a modified version of the UCSD Brief Assessment of Capacity to Consent (UBACC) will be

administered. In the modified version of the UBACC, Question 10 was not included as the risk of hospitalization due to research is unlikely, and there is no corresponding information in the consent document. If the participant scores less than a 14 (75%) on the UBACC, the study staff obtaining consent may review the study details and re-administer the UBACC. If the participant is still unable to pass during the second administration, they will not be offered participation at this time. Participants may return for a consent visit in the future if, in the opinion of the clinical care provider and/or the PI, their status has improved and they may have regained capacity to consent to research. In addition, if at any point during the study the staff has reason to suspect that the individual's capacity to provide consent has diminished (e.g., the participant has increased symptoms), the study staff may choose to conduct another consent discussion and/or re-administer the UBACC to confirm that the participant has capacity to provide ongoing consent. If the participant does not show capacity to consent, the PI will review their case and determine whether it would be best to withdraw the participant from the study or place their participation on a temporary hold until the participant is capable of providing informed consent. If the participant is placed on hold, they must successfully complete the UBACC prior to continuing with study procedures.

Potential participants will meet with the designated team member for assent/consent and potential enrollment. Consenting to research activities will take place in a private room at the Study Site or electronic consent may be conducted remotely, by phone or videocall. During this visit, the qualified Site Study personnel authorized by the Site Principal Investigator and the potential participant and their parent/legal guardian will discuss the nature of the trial, the purpose of the research, the trial procedures, the possible risks and benefits of participation, confidentiality and the voluntary nature of participation in the trial (emphasizing the participant's right to withdraw from the study at any time). Site Study personnel obtaining consent will emphasize that the study will not influence that participant's clinical care or their relationship to the University of Minnesota and/or Posit Science.

Following this discussion, potential participants and their parents/legal guardians will be offered the opportunity and encouraged to ask any study-related questions and enroll by providing written assent/consent on the IRB-approved form. For remote consent discussions, participants and/or their parent/legal guardian will navigate to the electronic consent/assent form shared through REDCap. The electronic consent/assent form has been designed so that the participant and their parent/legal guardian are unable to complete the consenting process without completing the consenting process with a member of the research team. Participants and/or their parent/legal guardian will first receive a "Read Only" version of the consent. Only after the research coordinator has completed the informed consent discussion and determined the parent/legal guardian and/or participant fully understand all procedures and are capable

of informed consent will he/she sign the electronic consent form and deliver an "editable" version of the electronic consent form which the participants and/or their parent/legal guardian will be able to sign. For the electronic consent process to be considered complete, the consenting team member will access REDCap in real-time to confirm the parent/legal guardian and/or participant have signed the consent/assent form correctly.

Participants will be allowed as much time as needed, with Site Study personnel or in private, to review the HIPPA waiver and consenting documents before making the decision to participate. Potential participants may invite a friend or family member to be present during the visit, to further discuss their decision to enroll and/or contact (e.g., phone call) a friend or family member that is not physically present for discussion before deciding to enroll. At the potential participant's request, Site Study personnel may be asked to 'step-out' of the room or end/mute the call during remote discussions, to provide privacy for such discussions. In addition, potential participants will be provided the option to defer their decision to allow them to review the consent form and other study information forms at their convenience, and later reconnect with the Site Study team remotely or return to the Study Site to enroll (i.e., complete the informed consent procedures). No study activities will take place prior to completion of the consenting process.

Participants will not be invited for consent discussions during periods of greater impairment. Participants must have been in outpatient status and on stable medications for 4 weeks prior to signing assent/consent. If a participant is hospitalized for psychiatric reasons during the study, they will be withdrawn from study activities. Additionally, consent to continue in the study will be addressed as needed throughout the study and the participant will be reminded that their participation in this study is completely voluntary and they do not have to continue unless they choose to.

The consenting Site Study team member will inform participants about compensation for their participation in the study. Specifically, participants will be compensated $20 for completing the *Screening* assessment visit (V0), $25 for completing the *Baseline* (pre-intervention) assessment visit (V1), $15 for completing the *Program Set-up* visit (V2), $10/week during the 12-week intervention period, given participants complete their weekly dCBGT session, and $75 for completing the *End of Study* (post-intervention) assessment visit (V3). Participants that complete the study in its entirety will earn $255. Compensation will be provided through CashPass, a reloadable debit card through a third-party vendor, CT Payer. For remote assessments, the CashPass card will be mailed to participants to a mailing address of their choice after the completion of the *Screening* assessment visit (V0). Compensation will not be provided to participants that complete the informed consent process but do not complete the

Screening assessment visit (V0). In the unlikely event that a participant must repeat an assessment visit due to administrative assessment or Site Study personnel errors, participants may be provided additional compensated for that session. Compensation during the intervention period will occur on a weekly basis and participants will be paid for attending their dCBGT treatment session that week.

Visit	Compensation
Screening	$20
Baseline	$25
Program Set-up	$15
Intervention Period ($10/week for 12-weeks, up to $120)	$120
Post-Intervention	$75
Total Participant Compensation	$255

If, for any reason, e.g. technical or CT Payer vendor issues prevent the Site Study personnel from issuing the reloadable debit card, adding funds to the reloadable debit card, or making any other changes to the debit card, participants may be compensated through a gift card (e.g. Amazon eGift Card, Visa Gift Card, or similar vendor). In such cases, participants are expected to read the associated terms and conditions for the respective gift card. For Amazon eGift Cards, the participant must accept the eGift Card through their email; participants will be notified of this requirement prior to sending the payment, and will be asked to provide verbal consent to receiving payment in this method.

If the participant does not complete the study or withdraws early for any reason, the participant will only be compensated for the study visits and/or treatment sessions they have completed.

All participants will receive compensation for the *Screening* assessment visit (V0) after the end of the visit, regardless of eligibility. For participants who are loaned a mobile device for the duration of the intervention period, compensation for all study activities completed from V1 through V3, including the intervention period, will occur after the participant returns the loaned device to the Site Study personnel. If participants are unable to meet with Site Study personnel in person to return the device, the participant will be sent a pre-paid label and box (if necessary) to return the mobile device at no cost to them. Participants who withdraw from the study will be compensated for all study visits they have completed once the loaned device has been returned to the Site Study personnel. For participants who do not return the device,

all forms of appropriate means and communication (e.g. phone contact, email, mailed letters) will be used in an effort to retrieve the study device. The mobile device that is loaned out may have GPS enabled as part of the Find My Device feature that will allow the Site Study personnel to ping the device if the participant needs assistance with locating it. This feature will also be used to remotely deactivate a device so that the device is unusable, and/or erase the contents of the iPad, when necessary and if a loaned study device is not returned to the Site Study personnel at the end of the study.

Participants who do not return the study device will receive their compensation after Site Study personnel have exhausted all means of contact in an attempt to return the device (a maximum of three months after the end of study participation). Participants will not face any legal or financial retribution for failure to return the study mobile device.

During the consenting process, participants will also be requested to fill out an emergency contact form. This form will detail primary and secondary emergency contact information. If the participant agrees to fill this form out, the participant authorizes the Site Study personnel to contact the primary or secondary emergency contact in case of a study-related emergency. Participants will also be asked to sign a Site-specific Release of Information authorizing Site Study personnel to communicate with the participant's clinical care provider to confirm and discuss their diagnosis, symptoms, treatment status, study participation, and to discuss any safety concerns that are discovered during the course of the study. Site Study personnel may request relevant records from the participant's care team if there is a relevant health concern (e.g., hospitalization for psychiatric reasons). Participants will be notified before Site Study personnel contacts their care team for any reason.

A copy of the informed assent/consent will be provided directly to the participant and/or parent/legal guardian, a fully-executed copy will be retained in a secure manner at the recruitment site and be available for inspection at the site upon the request of representatives of the reviewing Institutional Review Board or other relevant regulatory agencies. No study activities will take place prior to completion of the assent/consent process. The copy of the consent form provided to the participant will include telephone and email contact information for the Site Study Coordinator and the Site PI. At any point during or after completion of the study, the participant may contact the Site Study Coordinator, Site PI or the reviewing Institutional Review Board to obtain additional information regarding his/her rights as a participant. No participant will be under legal commitment at the time of their consent or during their participation in the study.

Screening Procedures

Following informed consent, potential participants will go through a set of structured interviews and short neuropsychological assessments and provide basic demographic information to evaluate their suitability for the study given the inclusion/exclusion criteria. The screening procedures include:

- Clinical Evaluation: Clinical diagnosis of Anxiety Disorder will be assessed using the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID), a brief structured diagnostic interview using DSM-IV criteria. Clinically significant Social Anxiety will be assessed using the Social Phobia and Anxiety Inventory-Brief version, as defined by a score of 25 or greater.
- Cognitive Status: the Wechsler Abbreviated Scale of Intelligence (WASI-II), specifically the Vocabulary and Reasoning subscales, will be used to assess participant IQ. Participants' IQ score must be great than 80 to be eligible for enrollment. For adult participants, the UBACC will serve as an additional measure to assess cognitive status. Participants scoring less than a 14 (75%), may be indicative of compromised cognitive status. Those that cannot pass the UBACC will not be eligible for enrollment
- Participants will be asked to complete the Columbia-Suicide Severity Rating Scale (C-SSRS); potential participants that answer 'yes' to:
    - Question 5 (Active Suicidal Ideation with Specific Plan and Intent) or,
    - Any of the suicide-related behaviors (actual attempt, interrupted attempt, aborted attempt, preparatory act or behavior) on the "Suicidal Behavior" portion

  will be excluded from the study *if the ideation or behavior occurred within two months from Participant's date of consent* (as recommended by the FDA for treatment trials.) Participants excluded for this reason will be referred for appropriate treatment. Further, participants meeting these criteria at any time throughout the study will be asked to complete a final assessment, if appropriate, then withdrawn from the study and referred for appropriate treatment
- Demographics and Medical History: A structured clinical interview will be used to collect key demographic and medical history information, including medical diagnoses or conditions that may be grounds for exclusion (e.g., schizophrenia, ongoing or recent chemotherapy), current therapies (including enrollment in other clinical trials that may be grounds for exclusion), medications, as well as age. Those taking medications for anxiety and psychiatric disorders will not be excluded; instead, their treatment will be evaluated and entered as covariates in all statistical analyses.

Participants expressing interest in the study that do not meet certain eligibility criteria, e.g. have experienced a change in medication or have been hospitalized within the last 4 weeks, have an upcoming medical procedure, surgery or treatment that would interrupt their participation, have experienced suicidal ideation or behavior within two months or those with known future end dates to psychotherapy treatment, will be placed on hold and re-screened for appropriate eligibility criteria.

Study Procedures/Research

Study Procedures: Participants at the recruitment Site will flow through the study in the following manner:

1. *Informed Consent Discussion*: Site Study personnel will discuss study goals, activities, and requirements with the parent/legal guardian and/or potential participant; complete the informed consent discussion, and if/when appropriate the potential participant will complete assent/consent to join study.
   Duration: ~30-60 minutes remotely or in-person at the Study Site.

2. *Initial Screening Visit (V0)*: Following assent/consent, Site Study personnel will perform diagnostic assessments and interviews and assess inclusion/exclusion to determine if the participant is eligible for enrollment.
   Duration: ~2-3 hours remotely or in-person at the Study Site. The *Informed Consent Discussion* and the *Initial Screening Visit (V0)* may occur independently or may be combined in a single session.

3. *Baseline Assessment (V1):* Following enrollment, the participant will perform all social/cognitive baseline characterization assessments and questionnaires prior to the intervention period. Duration: ~2 hours remotely or in-person at the Study Site.

4. *Randomization*: Participants will be randomized into one of two treatment groups.

5. *Mobile device Set-Up and Proctored Application Use (V2)*: The participant will be oriented to the intervention activities and program application(s). Participants assigned to both WASABI and the active control arm will complete a series of mobile assessments during this visit (embedded baseline assessments via BrainHQ) .

   Participants with a compatible personal device that are willing to download the necessary application(s) for program use will have their device set-up at this visit. Participants in assigned to WASBAI will be guided to schedule reminders for

completing their study activities. Participants that do not have a compatible personal device, do not wish to use their personal device, or do not agree to configure their settings and download the necessary application(s) for program use will be loaned a mobile device for the duration of the *Intervention and Program Use* period. Participants will be asked to sign a form acknowledging they have been loaned a study device. The research team may attempt to complete this visit on the same day as *Baseline Assessment (V1)*, but a separate visit may be scheduled, if necessary.
Duration: ~30-60 minutes remotely or in-person at the Study Site.

6. *Intervention and Program Use:* Participants will have a 1:1 orientation with the WASABI Clinician prior to engaging in their assigned group intervention activities. Site Study personnel will review the *Procedures and Guidelines to Group Therapy* and will ask the parent/legal guardian and/or participant to review and sign this form. After which, participants will remotely engage in the intervention for 12 weeks, completing approximately 12 hours of dCBGT in addition to other assigned study activities.

7. *Post-Intervention Assessment (End of Study Visit; V3):* After the *Intervention and Program Use* period is completed, the participant will be asked to complete their final assessment visit, where they'll repeat all assessments performed at baseline to assess changes in performance.
Duration: ~2 hours remotely or in-person at the Study Site.

   Participants expressing interest in returning their device to its original settings will be instructed by Site Study personnel on how to delete study application(s) during this visit or at the time of study exit. Participants loaned a study device will be asked to return the loaned device at this visit.

   If participants were loaned a mobile device to complete study activities at home and no longer wish to participate in study activities, including their post-intervention interview, Site Study personnel will attempt to coordinate with the participant to return the device at a time that is convenient for the participant. If participants are patients at the Child and Adolescent Anxiety Clinic or associated UMP Psychiatry Clinics, Site Study personnel may attempt to meet them before or after a regularly scheduled clinic appointment to return the loaned device. If the participant cannot be reached, Site Study personnel will send them a letter asking them to return the device along with a box with a return label. Participants will be invited to come back for a follow up visit in this letter, but also reminded that they are free to no longer participate in the study. Site Study personnel may also send this letter to participants who completed all study

activities but forgot to return the device and are unable to coordinate with Site Study personnel to return it.

8. *Exit Survey* (~10 minutes): Participants will be asked to fill out an online exit survey to rate enjoyment, usability, perceived benefits, and ease of fit into schedule.

Assessments.
The complete assessment battery will be performed at the pre-intervention assessment (*Baseline Assessment*, V1) visit and at the post-intervention assessment (*End of Study*, V3) visit. For a full list of all assessments and administration times, please direct your attention to the *Description of Assessments* or *Appendix I*. We will use assessments of functional abilities to determine the degree of transfer of benefit to real-world experience (e.g., symptoms, social functioning, quality of life).

All assessments will be administered to all participants; alternate forms of the assessments will be used when available to mitigate test-retest effects. Performance on all measures will be scored, submitted into the study database, and monitored for accuracy and integrity. Any discrepancies in scoring will be resolved by referring to the raw data collected during the assessment visit(s).

Description of Assessments

Diagnostic Assessment
Standard diagnostic criteria and classifications for Anxiety Disorder as defined by the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID), a brief structured diagnostic interview using DSM-IV criteria and standard diagnostic criteria and classifications for Social Anxiety, as defined by the Social Phobia and Anxiety Inventory-Brief version, as defined by a score of 25 or greater, will be used to assess eligibility. If information is gathered from self-report questionnaires, emergency contacts, the participant's psychiatrist, therapist, and/or primary care physician, this may be used to corroborate and supplement the participant interview to assess eligibility.

Clinical and Neuropsychological assessments and characterization
The study will employ empirically validated assessment measures specific to anxiety and depression, and also adhere to recent *NIH Toolbox* recommendations. Collectively, we have chosen a battery based on five key criteria (when possible), including 1) existing standardization, to ensure reliable data collection procedures, 2) sensitivity to the impairment typical of this study population, 3) normative data availability, 4) reasonable test-retest

stability (i.e., to control for potential participant improvement through strategy learning over repeated measures) for use in a treatment trial with two repeated measures, and 5) good sensitivity to change following remediation. Several measures will be used to provide gross clinical characterization.

Cognitive Assessments

Screening. Cognitive status will be assessed using WASI-II, specifically the Vocabulary and Reasoning subscales. Participants must score IQ > 80 to enroll in the study. Adult participants will undergo an additional cognitive assessment, the UBACC. Participants must score within the normal range; participants who cannot pass the UBACC will not be eligible for enrollment.

Anxiety and Social Anxiety

Clinician ratings of anxiety and social anxiety symptoms will be assessed through the Liebowitz Social Anxiety Scale for Children and Adolescents (LSAS-CA).[50] Self-report inventories of social anxiety symptoms through the Social Phobia and Anxiety Inventory (SPAI)[51] will be completed at the *Baseline* (V1) and *End of Study* (V3). Broad measure anxiety and potential generalization of treatment to other anxiety domains will be captured through the Multidimensional Anxiety Scale for Children 2nd Edition (MASC-2).

Social Functioning

We will assess social skills by administering the Social Skills Questionnaire (SSQ);[52] and social functioning using the Adolescent Social Self-Efficacy Scale (ASSES).[53]

Suicidality Assessment

The Columbia Suicide Severity Rating Scale (C-SSRS) will be used to screen for and assess suicidal ideation. Those that do not meet inclusion criteria for this assessment will not be enrolled in the study. Participants who do not meet this criteria but express interest in the study may be reengaged and reassessed following a 2-month period. The C-SSRS will be repeated at the *End of Study* (V3) Visit to screen for any changes in suicidal ideation over the course of the study. The C-SSRS may be re-administered during the intervention period, as needed, should there be any concerns for safety or increasing symptoms.

Intervention Embedded Assessments

Cognitive Biases. Participants in both the WASABI and active control arm will complete embedded assessments immediately before and after the 12-week intervention. Additionally, for participants assigned to WASABI, during the intervention and program use period, WASABI weekly collects performance data on two cognitive assessments that capture attention bias assessment, and an interpretation bias assessment. Participants assigned to

receive WASABI will also complete a weekly SPAI-B assessment. Performance on these assessments will be modeled longitudinally to examine if these measures can serve as potential moderators and mediators of treatment efficacy.

The primary outcome measures, including assessment adherence, dCBGT and IM engagement, EMA, SPAI-B and overall program completion rates, reported adverse effects, usability ratings and clinician burden, will be used to assess feasibility, acceptability and usability of WASABI.

Secondary outcomes include clinical ratings of anxiety and social anxiety symptoms (LSAS-CA), self-report inventories of social anxiety symptoms (SPAI), broad measures of anxiety (MASC-2), as well as measures that capture social skills (SSQ), and social functioning (ASSES).

Description of Protocol Devices (Software Program)

This study employs two mobile-device delivered interventions: the treatment intervention (dCBGT+WASABI) and an active control (dCBGT). Participants will be asked to use their assigned program activities over the course of the 12-week *Intervention and Program Use* period. Participants will be asked to complete 12 weekly 1-hour group sessions (dCBGT) led by a Site Study Clinician (WASABI Clinician). Participants assigned to the treatment intervention (WASABI) will be asked to complete at least 3 EMA sessions per week and weekly cognitive assessments, in addition to dCBGT. Several elements of flexibility are allowed in the schedule to accommodate the challenges that adolescents with Social Anxiety may face:

- *Location of Use:* Some participants may experience barriers to receiving treatment, including geographic location, availability of trained therapists, long waiting lists, and the requirement to take time off from school for clinic visits. This intervention is a remote intervention that allows participants to access the intervention and program activities remotely. Every effort will be made to schedule the weekly group therapy sessions at a time that is most convenient for the participant. EMAs and weekly cognitive assessments are mobile-accessible, allowing participants to complete them at different locations, as convenient.
- *Variable Number of Total Sessions:* Given fatigue (common in this population), commitments to non-study activities, health issues and/or re-integration into school, work and home life, we expect that some participants will not be able to complete the weekly dCBGT sessions for 12 weeks. To accommodate this, we will be understanding of their circumstances, recommend that participants complete as many sessions as their schedule permits, and explain that the results of the trial may benefit from frequent and consistent involvement in group sessions. Similarly, participants granted access to daily EMAs and weekly cognitive assessments will be encouraged to complete at least 3

sessions per week and the weekly cognitive assessments. Participants will be informed that the study will work if the participant is unable to commit to recommended minimum EMA sessions per week and weekly cognitive assessments. The Site Study Coordinator may offer their support to work with the participant on a schedule that is feasible, given participant's current life circumstances, as appropriate. To ensure a time-bounded study commitment, after 12 weeks such participants will perform their post-intervention assessment (*End of Study, V3*) visit, given that they have met the minimum number of sessions required to complete this visit.

- *Extra Time: :* Under special circumstances, dCBGT session(s) may be paused for 1 or more weeks. This may occur if the WASABI Clinician is unable to conduct the session and no alternate WASABI Clinician is available to conduct the session. In such cases, the intervention will be extended by the number of weeks it has been placed on hold. Participants will resume the assigned dCBGT session such that all 12 sessions intended for the 12-week intervention are delivered to participants. Similarly, participant access to BrainHQ app will be extended by the same number of weeks. While the intervention is on hold, access to BranHQ may be revoked and participants will not be asked to completed BrainHQ study activities until dCBGT sessions resume. Access to other study applications, such as Google Apps, Google Meet and Chat, may be available until the final dCBGT session is completed, but participants will not need to engage with these activities while the intervention is on hold and participants will be informed the WASABI Clinician will not be monitoring or engaging in the group chat.
- *Cessation of Program Use While Continuing Participation in the Study:* In some cases, a participant may wish to stop or minimize use of the program, while remaining in the study. Potential reasons for this decision might include changes in school or work circumstances, changes in residence, health issues, family/personal issues, or a lack of interest in program activities. While the participant will be encouraged to meet their weekly goals, in such cases, after discussion with the Site Study Coordinator, the participant will be permitted to cease using the program and undergo the post-intervention assessment (*End of Study*, V3) visit, given they have met the minimum number of sessions required to complete this assessment.
- *Emergency:* All participants will be told how to contact the appropriate Site Study personnel in the case of an emergency.

Several of these options in aggregate are likely to lead to variation within a group and between groups with regard to the total number of sessions completed, and may cause an imbalance between the number of sessions completed within and between groups. Although this is not ideal, we believe that this is the correct approach given that such flexibility will allow more participants to join the study (compared to no program use flexibility), and may produce less

drop-out. In addition, this approach has the value of more closely mimicking real-world use of the program, increasing the prospective validity of the study. We will continuously monitor the distribution of completed sessions and will consider modifications to the protocol (see Modifications to the Protocol) if it appears that this flexibility is causing meaningful differences to emerge. The data analysis plan is generally robust to variations in number of sessions completed (see Data Analysis Plan).

Each study participant will be remotely supervised by a Site Study Coordinator. The Site Study Coordinator will inform participants of designated office hours that the Site Study Coordinator will be available in real-time. Participants will be able to contact Site Study Coordinator by email or by phone and may leave a message outside of designated office hours. Participants may be contacted once per week by a member of the Site Study team to discuss lack of engagement with the study apps or intervention activities, and contact may be adjusted depending on each participant's needs. Based on our previous experiences with in-residence trials, we have developed protocols and training that will allow the Site Study Coordinator and WASABI Clinicians to establish rapport with participants, identify and tend to any barriers to program use or compliance (such as establishing reminders to complete assessments or reducing distracters in the environment), and to provide feedback and support around performance. The Site Study Coordinator and WASABI Clinician will also be specifically trained to deal with specific issues that might arise with individuals with Social Anxiety.

Experimental Treatment Intervention (dCBGT+WASABI): The Experimental Treatment Intervention is a mobile-delivered and clinically-supervised adjunct to treatment composed of three primary treatment tools. Participants will be asked to 1) attend 12 weekly, 1-hour, group dCBGT sessions and complete "homework" associated with traditional dCBGT; 2) complete 3 EMA sessions per week, weekly standardized SA self-report, and weekly cognitive assessments; 3) use IM for 1:1 and group conversations. At the beginning of each treatment cohort, the WASABI Clinician will create a group text open only to cohort participants, explain their role, and make introductions. Between group sessions, the WASABI Clinician will spend approximately 30 min/day keeping the chat active during work hours, checking it approximately 3 times a day and responding to any messages participants leave, as appropriate. The WASABI Clinician will also receive notifications whenever the WASABI algorithm detects SA symptom exacerbation, and engage participants in synchronous or asynchronous IM. In absence of alerts, the WASABI Clinician will monitor the WASABI dashboard the day before each dCBGT session to customize the delivery of targeted content during the videocall.

- *Digitally delivered Cognitive Behavioral Group Therapy (dCBGT).* Participants are expected to join weekly, hour-long, group-video calls to complete dCBGT sessions using the Google Meet application. The WASABI Clinician uses EMAs and weekly assessment and self-report data completed by participants to calibrate and personalize the delivery of weekly dCBGT structured sessions through videoconferencing**.** Sessions replicate the protocol described in "Cognitive-behavioral group therapy for social phobia in adolescents,"[54] with 12 weekly sessions that center CBT content around the young person's developmental context, needs, and capacities, and adapt it to the unique developmental issues characteristic of adolescence (e.g. ascendancy of the peer group, identify formation, propensity towards limit testing). Sessions 1-4 focus on psychoeducation on recognizing and understanding social anxiety symptoms (e.g., avoidance cycle that maintains anxiety over time; rationale for exposure to overcome avoidance cycle). Sessions 5-6 implement cognitive restructuring (focusing on the identification/modification of dysfunctional thoughts) and social skills training. Session 7-8 include instruction in exposure principles and role-play/modeling of exposure exercises. Sessions 9-11 focus on in vivo exposure to anxiety provoking situations. In vivo exposure during these sessions focuses on anxiety provoking situations that can be created within the social setting of the video chat, such as a person giving a speech or singing a song, members engaging in "small talk" with each other, or people altering their appearance in a socially conspicuous way (e.g., messy hair, wearing silly attire). Session 12 focuses on how to avoid personal pitfalls and relapse. Adjustments may be made to the dCBGT treatment protocol described in "Cognitive-behavioral group therapy for social phobia in adolescents" during COVID-19 to allow for a more appropriate treatment given current shelter-in-place and distance-learning procedures that may not allow for replication of the traditional protocol. Participants are assigned "homework" focused on practicing specific skills in anxiogenic, in vivo situations to promote skills generalization and anxiety/fear extinction learning. Finally, content of the group-therapy sessions and "homework" assignments are personalized on the basis of the EMAs data each user has provided during the week.
- *EMAs*. Participants will be asked to complete at least three sessions of mobile-based self-report questionnaires of social anxiety and social role performance (EMAs *Thoughts*, *Feelings*, and *Goals)* per week. EMAs will be available daily for those who wish to complete more than the minimum recommendation. In the EMA *Thoughts* questionnaires, participants are asked to rate 1-7 how closely ten example cognitive distortions relate to their current thoughts. These 10 example

cognitive distortions are related to 10 overarching cognitive distortion categories (emotional reasoning, mental filter, magnification, disqualifying, all or nothing, jumping to conclusions, overgeneralization, personalization, labelling, should statements). In the EMA *Feelings* questionnaires, participants are asked to rate how closely they are feeling certain negative and positive emotions (comfort, relax, excited, serenity, confidence, gratitude, reward, hope, courage, joy, upset, dissatisfaction, annoyance, resentment, pessimism, guilt, powerlessness, disappointment, discouragement, fear, shame). In the *Goals* questionnaires, participants are asked to fill out short-term goals and rate their confidence of goal completion.

- *Standardized Self-Report Questionnaires.* WASABI includes standardized self-reports of social anxiety (SPAI-B), and weekly assessments that implicitly evaluate core cognitive operations known to be impaired in social anxiety (e.g., attention bias, interpretation bias). The SPAI-B consists of 16 items using a 5-point Likert scale (1–5). It assesses the cognitive, somatic, and behavioral symptoms (triple-response-system) and captures interactional and performance-provoking socially anxious situations. In the attention bias assessment, neutral and negative faces are presented for a limited time, followed by a letter that is displayed in the region of the screen where the neutral face was. Participants need to identify the letter as quickly as possible. In the interpretation bias assessment, a series of ambiguous images is presented for a limited time (for example, a situation in which one friend walks past another without acknowledgement), followed by a screen where three images with clear emotional valence are concurrently presented. Participants need to choose the image that captures the emotion that best explains the ambiguity of the previous images. The rationale behind the assessment is that participants with interpretation bias may develop expectations that ambiguous situations are more likely to end negatively.
- *WASABI Alerts*. If WASABI detects clinically-significant social anxiety through EMA metrics (EMA Thoughts, EMA Feelings, EMA Goals), cognitive biases assessments, and the Social Phobia and Anxiety Inventory-Brief (SPAI-B), the monitoring clinician will receive an alert that cues them to connect via Instant Messaging with the participant. The algorithm will be used to alert the WASABI clinician when a trial participant reaches clinically significant social anxiety, so that symptom exacerbation can be addressed over Instant Messaging.

EMAs, cognitive biases assessments and self-reports are meant to support standard clinical care by providing additional structured tools for an individual to use to address cognitive biases that often co-occur with anxiety. To complete these activities, a participant opens a

standard application (BrainHQ) on an Internet-connected iOS device and goes to a general log-in screen. The participant then logs into the experimental treatment program platform through the BrainHQ application (using a study provided username that contains no personally identifiable information). Participants are directed to their assigned EMAs, cognitive biases assessments, or self-report questionnaire and perform their assigned activities over the course of a session.

Participant will use Google Meet and Chat, a HIPAA-compliant videoconferencing and instant messaging application on an Internet-connected iOS mobile device and goes to a general log-in screen. The participant then logs in using a study provided account. Participants assigned to the WASABI are expected to join 12, 1 hour-long dCBGT sessions using the Google Meet application. These will be scheduled and facilitated by the WASABI Clinician.

Active Control Program (dCBGT): Given the nature of the augmentation study, it's expected that participants in the control condition may spend less time, overall, on study activities as compared to the *Experimental Treatment Intervention* (dCBGT+WASABI). In an effort to equate time spent in the intervention and control for the effects of mobile device use, contact with personnel, monetary payments, and nonspecific engagement, participants in the control condition will be asked to attend 12 weekly, 1-hour, group dCBGT sessions and complete "homework" associated with traditional dCBGT.

Digitally delivered Cognitive Behavioral Group Therapy (dCBGT). The WASABI Clinician will lead weekly dCBGT structured sessions through videoconferencing**.** Sessions replicate the protocol described in "Cognitive-behavioral group therapy for social phobia in adolescents",[54] with 12 weekly sessions that center CBT content around the young person's developmental context, needs, and capacities, and adapt it to the unique developmental issues characteristic of adolescence (e.g. ascendancy of the peer group, identify formation, propensity towards limit testing). Sessions 1-4 focus on psychoeducation on recognizing and understanding social anxiety symptoms (e.g., avoidance cycle that maintains anxiety over time; rationale for exposure to overcome avoidance cycle). Sessions 5-6 implement cognitive restructuring (focusing on the identification/modification of dysfunctional thoughts) and social skills training. Session 7-8 include instruction in exposure principles and role-play/modeling of exposure exercises. Sessions 9-11 focus on in vivo exposure to anxiety provoking situations. In vivo exposure during these sessions focuses on anxiety provoking situations that can be created within the social setting of the video chat, such as a person giving a speech or singing a song, members engaging in "small talk" with each other, or people altering their appearance in a socially conspicuous way (e.g., messy hair, wearing silly attire). Session 12 focuses on how to avoid personal pitfalls and relapse. Adjustments may be made to the dCBGT treatment

described in "Cognitive-behavioral group therapy for social phobia in adolescents" during COVID-19 to allow for a more appropriate treatment given current shelter-in-place and distance-learning procedures that may not allow for replication of the traditional protocol. Participants are assigned "homework" focused on practicing specific skills in anxiogenic, in vivo situations to promote skills generalization and anxiety/fear extinction learning.

Participants in the active control will complete two sessions of embedded assessments, one immediately before and one after the 12-week intervention. The embedded assessments include two cognitive assessments—an attention bias assessment and interpretation bias assessment—and the SPAI-B assessment.

The active control program is designed to: 1) be a face-valid approach to remediation in anxiety disorders, to ensure that participants remain blind to group affiliation, and match the experimental treatment program in halo or expectation-based influence on performance in outcome measures; 2) match the experimental treatment program in overall dCBGT session intensity, time-spent attending, and overall engagement; and 3) provide a comparison group that matches the experimental treatment group on the aforementioned attributes, but without the adjunct to treatment component, WASABI.

To use the active control, a participant opens Google Meet, a HIPAA-compliant videoconferencing and instant messaging application on an Internet-connected iOS mobile device and goes to a general log-in screen. The participant then logs in using a study provided account). Participants assigned to the active control are expected to join 12, 1 hour-long dCBGT sessions using the Google Meet application. These will be scheduled and facilitated by the WASABI Clinician. To complete the BrainHQ embedded assessments, a participant opens a standard application (BrainHQ) on an Internet-connected iOS device and goes to a general log-in screen. The participant then logs into the experimental treatment program platform through the BrainHQ application (using a study provided username that contains no personally identifiable information).

Application Security

BrainHQ: All usage and progress data collected through the BrainHQ application is encrypted then transmitted to a central server. Data is encrypted in transit and at rest, and access is limited and audited. Data collected through the BrainHQ platform will not include geographic information. IP address data is stored only in memory and in request logs, and is used for technical support and troubleshooting, but not persisted with the participant's data. However, data as it relates to dates that assessments are completed is collected and stored. The EMA

questionnaires include open text boxes for participants to include their goals, thoughts, and feelings. Participants will be aware that research team members at the University of Minnesota and Posit Science will have access to the questionnaires and that any personally identifying information voluntarily shared on this platform will be viewed by staff at both the University of Minnesota and Posit Science. On the server, the data are available for review by the un-blinded WASABI Clinician, Study Coordinator, Posit Science study team, and/or other study personnel through a secure web portal. The WASABI Clinician in particular will use the secure web portal to regularly check on usage and progress of each active participant to customize their weekly phone/in-person and dCBGT discussions to provide helpful guidance and coaching.

G-Suite Google Chat and Meet: This platform allows participants to communicate with others via the app without having to share their full name, mobile phone number or email to do so. Participants also have the opportunity to personalize their profile, by entering a short bio and a picture of their choice. In order to access the Google Meet and Chat apps, participants will have a unique username/login that contains no personally identifiable information. Once logged in, they will be operating within the Google Meet and Chat HIPAA-compliant digital environment, and data that are produced, transmitted, and shared among users will be exclusively visible/readable to the research participants and authorized University of Minnesota and Posit Science staff. These data will include personally identifiable information–such as faces, first names or aliases, biographical and medical information–similar to what happens during all in-person group therapy sessions. The Google Meet and Chat API will allow participants to exchange end-to-end encrypted instant and group messages, as well as make end-to-end encrypted group voice and video calls. Participants will be aware that research team members at the University of Minnesota and Posit Science will have access to the group chat history and will be monitoring its contents throughout the intervention period. As such, participant are informed that any personally identifying information voluntarily shared on this platform will be viewed by staff at both the University of Minnesota and Posit Science. Google Meet and Chat use end-to-end encryption for voice and video calls, as well as instant messages. Google Meet and Chat's voice calls are encrypted with DTLS and SRTP, its video calls with RTP, and its instant messages with RTP. In addition to this, client-server communication is protected by Transport Layer Security. More information about how Google Meet and Chat protects privacy can be found here: https://support.google.com/a/answer/3407054

Participants assigned to the Active Control condition will not be asked to use the Google Chat app, as it is unique to the WASABI intervention. Participants in both groups will be able to download other Google apps associated with their deidentified study assigned G-Suite account, such as Google Calendar and Gmail, to facilitate communication with the Site Study team and

set reminders for weekly dCBGT sessions and study activities. The Site Study Coordinator will assist participants in downloading these apps, as needed. Participants loaned a study-device will have these applications available on the study device.

Laboratory Specimens

There are no laboratory specimens collected for this study.

Sample Size Justification

Within-group effect sizes (Cohen's *d*) will be computed using the mean change scores for primary quantitative outcomes (post-intervention minus baseline) and the change score SDs. With 24 participants fully evaluated, we will not have enough power to detect a treatment augmentation effect ascribable to WASABI. However, data from this pilot RCT will suggest whether there is feasibility, acceptability and usability of WASABI, as well as an incremental difference in secondary outcomes between groups, with greater improvement in the WASABI+dCBGT arm, and will be used to power a pivotal RCT in Phase II. To test whether WASABI induced greater improvements in social anxiety ratings compared to the active control condition, we will conduct the analysis based on the pre-intervention (baseline) and post-intervention data. Finding a significance level of $p < 0.05$ on the outcome measures will support the statement that the intervention improves social anxiety in the population.

Data Analysis

Standard data quality procedures will be used, including double-scoring and random spot-checking of cognitive assessments, electronic data capture, and external data monitoring. Acceptability of the program will focus on the functional effectiveness of the program (validation that it functions as intended). Evaluation of the actual acceptability of WASABI will be based on adherence rates, engagement patterns, EMA completion rates, SPAI-B completion rates, overall program completion rates, usability ratings (exit survey data), clinician burden, and reported adverse effects. Rate of referral to enrollment and average program completion rate will be used to evaluate adherence rates. *Assessment adherence* (percentage of assessment sessions attended) refers to assessments completed by all participants who have participated in the minimum required intervention activities (attended at least 2 group calls, completed EMAs at least five times). We expect successful data collection of baseline and post-intervention outcome measures for ≥90% of participants. *Engagement with the digitally delivered Cognitive Behavioral Group Therapy (dCBGT) and with group Instant Messaging (IM)* refers to the number of group sessions attended and number of messages sent per week on the group chat. We hypothesize WASABI+dCBGT will participate in 80% of the dCBGT sessions, and send at least 8 messages/week in the group chat.

We do not anticipate dCBGT within WASABI being associated with greater adherence rates and engagement patterns compared to the control condition. Due to the inter-individual differences in participant engagement found in the pilot study, we will also use bivariate correlations to test whether changes in outcome measures correlate with engagement metrics. If so, we will use repeated measures linear mixed modeling to determine whether changes in outcome measures were mediated by engagement with the intervention. Finally, enjoyment, usability, perceived benefits, and ease of fit into schedule, and qualitative user feedback will also be evaluated. Based on our previous findings, we hypothesize exit survey ratings of at least ≥4.5 ±1.5 on the 7-point Likert scale items.

We hypothesize that the innovative features of WASABI will improve the quality of treatment delivery and facilitate the generalization of trained skills into real-world settings. The measures collected to determine the efficacy of the program for this trial are clinical ratings of anxiety and social anxiety symptoms (LSAS-CA), self-report inventories of social anxiety symptoms (SPAI), broad measures of anxiety (MASC-2), self-report inventories of social skills (SSQ), and self-report inventories of social functioning (ASSES). To test this hypothesis, we will use a linear mixed model approach. We will first compare treatment and active control groups in the ITT population to determine if any differences in baseline demographic, characterization, outcomes variables, or total program use time remain after the randomization process. Any such factors that show trend level significant differences ($p < 0.1$) will be noted and used as covariates in the linear mixed model analysis. The criterion for statistical significance is $p < 0.05$. Results with $p < 0.1$ will be described as trends.

Performance on the attention bias and interpretation bias assessments will be modeled longitudinally to examine if these measures can serve as potential moderators and mediators. To test if the attenuation of attention and interpretation biases mediates improvements in outcome measures, we will use repeated-measures linear mixed modeling to test in the active group the effects of WASABI on LSAS-CA, SPAI, SSQ and ASSES, and then model outcomes as a function of performance improvements on the attention bias and interpretation bias assessments.

Because we are interested in examining the ecological validity of WASABI, we will not restrict the analyses only to participants who adhered to all intervention requirements. Within-group effect sizes (Cohen's d) will be computed using the mean change scores (post-intervention minus baseline) and the change score SDs.

These measures will be analyzed to power the pivotal study proposed for Phase II. For the FDA, we will collect data documenting that WASABI meets its design requirements when used in the field by clinicians and patients, and that clinicians deem its risk/benefit ratio as acceptable and view it as adequate/appropriate for the target population.

Data Management

Data collected in this study may include paper forms for consent/assent forms and some assessments from clinician- or psychometrician-administered structured interviews, neuropsychological or functional assessments. Other assessments will be administered remotely and collected electronically through REDCap servers (hosted on HIPAA compliant UMN servers) or the program platform (hosted on Posit Science servers). Fully executed consent/assent forms completed by Site Study personnel and securely stored at the Study Site will not be shared with Posit Science. With the exception of dates that assessments are completed, personally identifying information collected by UMN Site Study personnel will not be collected or stored with study assessment or performance data on the BrainHQ app on Posit Science Servers and will not be shared with Posit Science. Personally identifying information voluntarily disclosed by participants on BrainHQ (EMA questionnaires) and the Google Meet and Chat platforms during the intervention will be accessible to the Posit Science research team. Participants are informed that both the UMN and Posit Science research teams will be monitoring their chat history on the Google Meet and Chat platforms. Prior to entering the participant's study record, direct identifiers (names, email addresses) will be redacted. De-identified, study-related data collected on paper and shared with Posit Science will be recorded into a secure, web-based electronic case report form (eCRF). This system meets all relevant privacy and security standards for electronic clinical trial data entry and storage, as well as the Health Insurance Portability and Accountability Act (HIPAA) standards for confidentiality and privacy.

Following consent, each participant will be assigned a standardized Participant Identification Number (PIDN) composed of digits to identify the study and 3 digits to identify the participant. The digits will begin with "001" for the first consented participant and ascend thereafter. All eCRF data entry will be de-identified, using the PIDN only and not the participant name, but will include the date of the assessment administration.

Study personnel will transcribe and upload de-identified data and de-identified source documentation into the study database for the purpose of data monitoring. PSC data entry personnel and Site Study personnel will interact frequently throughout the study to accomplish the quality goals of the data management process through the below process.

Participants may email Site Study personnel with questions or concerns, or to make arrangements for study visits. If deemed significant and relevant to the participant's study record, de-identified emails may be saved to the participant's study file. To de-identify emails, all direct identifiers (name, email address, date of birth, etc.) will be redacted from the email in PDF format. Site Study personnel will place black bars over any directly identifying information. The redaction will be verified by a secondary staff member for accuracy and completion to ensure patient privacy prior to being uploaded for permanent storage at the Site and shared with Posit Science. The dates of communication will be maintained in the emails to provide context for the conversation.

Periodic analysis of the data will be performed in order to examine the expected distributions of data, and to identify outliers for possible data mistakes. PSC data management personnel and Site Study personnel will interact frequently throughout the study to accomplish the quality goals of the data management process through the below process.

Periodic analysis of each data field (across all cases) will be performed in order to examine the expected distributions of data, and to identify outliers for possible data mistakes. Particular attention will be paid to the following:

- *Data Cleaning:* All eCRFs are automatically reviewed to check for omitted data and data inconsistencies. These deficiencies are required to be resolved at the point of data entry to prevent errors from entering the system.
- *Data Editing:* Each data record is evaluated on a regular interval. Any discovered error is then referred to the clinical site Investigator Designee within the Electronic Data Management (eCRF) System via the Data Monitor. The Investigator Designee will review the queries and make the corrections through the eCRF system. All such changes are automatically logged to allow a complete audit trail and recovery to any point in the change log if required.
- *Data Update:* The cycle of data editing will be ongoing until all the data are clean. If further data entry or source documentation errors are discovered during review, the corrections will be made at that time through the eCRF system.
- *Data Back-up:* The eCRF system employs an automatic continuous replication system to ensure that all data including change logs and access logs are replicated to two independent remote servers. At any point, the system is capable of emitting the entire store of eCRFs as paper CRFs for offsite storage or auditing if required.

We will take all standard and appropriate steps to protect the privacy and confidentiality of participants in this trial. At enrollment participants will be assigned a PIDN as described above, and all study data collection derived from that participant will be coded by PIDN. All

eCRF pages, including those with demographic as well as assessment data, will have the PIDN on them rather than the participants name. No personally identifying information will be shared with Posit Science, with the exception of dates that assessments are completed and date of birth. However, personally identifying information voluntarily disclosed by participants on the BrainHQ (EMA questionnaires) and Google Meet and Chat platforms during the intervention will be accessible to the Posit Science research team. Prior to entering the participant's study record, direct identifiers (names, email addresses) will be redacted. Accurate and complete study records will be maintained and stored in a confidential manner so as to protect the confidentiality of participant information.

The eCRF system runs on remote servers not physically accessible to any study staff (including PSC staff); all electronic access to the eCRF system is logged and regularly reviewed for any inappropriate access. All study related paper materials will be stored in locked file cabinets inside of locked rooms when not in use. During remote procedures, study personnel may shred the original paper documents after Posit Science has completed the data monitoring and reconciliation process and approved shredding of documents. Until documents are ready for shredding, they will be stored by the respective study personnel with limited access until the documents are shred or transferred to the Study Site. All participant use of the BrainHQ program will use a login based on the PIDN, and study programs will not collect or store any personally identifiable information, with the exception of any volunteered information included in EMA questionnaires, on the laptop or on PSC servers, with the exception of dates that assessments are completion. Participants will choose whether to use their first name or an alias for the Google Meet account.

We note this protocol does collect sensitive information, i.e. when assessing suicidal ideation, that may result in a reporting requirement to state or local authorities. The Study Site is expected to follow standard institutional policies in such cases to ensure the protection of participants and proper reporting. If Site Study personnel become aware of specific issues outside of the ordinary data collection procedures (e.g., child abuse) they will follow established institutional procedures already in place as appropriate for their local jurisdiction to report such knowledge.

Confidentiality

Participation in research may involve a potential loss of privacy. All records and documents pertaining to participation in this study will be handled as confidentially as possible. However, absolute confidentiality cannot be guaranteed.

All information, if collected on paper, will be kept in areas of limited access available to approved study personnel only. Any physical records will be maintained in locked cabinets in locked offices, until the appropriate time at which documents may be shredded. Access to these cabinets will be limited to the study team. During remote procedures, study personnel may shred the original paper documents after Posit Science has completed the data monitoring and reconciliation process and approved shredding of documents. Until documents are ready for shredding, they will be stored by the respective study personnel with limited access until the documents are shred or transferred to the Study Site.

Electronic data will be password protected and securely stored. The servers maintained by both Posit Science and UMN are HIPAA compliant, secure servers, that will require permissions from the study team to access.

Absolute confidentiality in therapy groups is difficult to achieve irrespective of the delivery method (in-person, video-conference, etc.), as there is no guarantee that other group members will maintain confidentiality about sensitive information. However, in order to decrease the likelihood of breaches of confidentiality among group members, we will 1) provide informed consent about confidentiality; 2) educate group members about confidentiality; and 3) make the discussion of confidentiality an ongoing process.

- First, study participants will learn about confidentiality during the informed consent process. The consent form will clearly describe the roles and responsibilities of all parties and the limits of confidentiality.
- Second, individual sessions will be held between the Site Study Coordinator and/or WASABI Clinician and each participant to educate them regarding confidentiality prior to entering the intervention. Participants will be informed that 1) they have the right to choose an alias rather than their first name and decide at any point what information they choose to disclose; 2) the WASABI Clinician will respect the patients' ability to choose what they disclose, and keep the promises of faithfulness and loyalty to all participants, including not revealing information participants disclose; 3) the WASABI Clinician cannot promise that other group members will maintain confidentiality; 4) the WASABI Clinician may have a legal obligation to break confidentiality in certain circumstances (e.g., child abuse), and those circumstances will be fully explained. The WASABI Clinician will follow established procedures appropriate for their local jurisdiction to report such knowledge; 5) the UMN and Posit Science research teams will be monitoring the BrainHQ (EMA questionnaires) and Google Meet and Chat contents, including chat history, throughout the intervention and as such any volunteered information that may be personally identifying will be available to both UMN and Posit Science monitors.

- Third, participants will be asked to read, sign and agree to be bound by a modified version of the American Psychological Association procedures and guidelines for group therapy (http://www.apadivisions.org/division-49/publications/newsletter/group-psychologist/2011/04/group-procedures.aspx), adapted for the target population, while in the intervention.
- Finally, during the first group therapy session, the WASABI clinician will encourage group members to embrace the concept of confidentiality, making it their own rather than a mandatory rule.

Given that one of the goals of WASABI is to enhance social functioning in people with social anxiety, we will not discourage group members from sharing contact information and befriending other study participants. Research shows that peer-to-peer interactions occur naturally on social media platforms and serve many purposes, such as establishing new relationships, maintaining relationships, reconnecting with people, disclosing personal experiences of living with social anxiety, seeking and sharing information related to symptoms and medications.

Representatives of the Sponsor, the reviewing Institutional Review Board, and the National Institute on Aging will be permitted to audit study-related data and related materials. Personally identifiable information will not be used in any study reports or publications; data contained in these will only be presented or published in aggregate form.

Disposition of Data

The following study records will be retained by the Study Site for minimum of two years following the conclusion of the study:

1. signed participant informed consent forms (securely held at UMN and stored with limited access),
2. patient medical records, including all significant diagnostic reports,
3. supporting documentation of all adverse events,
4. completed eCRFs, and;
5. study related correspondence and study reports.

Paper records from this study must be stored in locked areas of limited access. During remote procedures, documents will be stored by the respective study personnel in a safe location with limited access until the documents can be shred or transferred to the Study Site. Electronic data must be securely held with restricted access available to personnel on a need-to-know

basis only. Google Team Drive access will be restricted to authorized study personnel by invitation only.

Research staff will comply with the requirements of UMN (i.e., the enrolling institution) data storage and disposition policies at the conclusion of the record retention period.

Sharing Research Results

Overall study results will be available to participants through ClinicalTrials.gov and when such results are completed and accepted for publication. At enrollment, information is collected that, if appropriate, we will share with the participant to ensure they are receiving appropriate health care (i.e. suicidality) as assessed by the C-SSRS. Any participant presenting a safety concern for any of these medical issues will be referred to ensure they are receiving appropriate treatment. We do not intend to share individual assessment data with participants, as the assessment battery is not intended to be the type of comprehensive battery a rehabilitation psychologist would use to guide treatment. Any participant interested in such comprehensive assessment will be referred to an appropriate clinician.

Foreseeable Risks, Risk Management & Emergency Response

Participation in the study presents minimal risk. The probability and magnitude of harm or discomfort anticipated in this research study are not greater than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

Serious adverse effects from prior studies of the treatments under study have not been reported. The protocol details potential risks related to study participation and includes assessments of increased risk of suicidality.

The following foreseeable risks will be discussed with potential participants during the enrollment visit, as will the following measures taken to minimize such risks:

- *Diagnostic interview and self-report measures*. Participants may feel uncomfortable or embarrassed due to sensitive questioning about their psychiatric condition and medical history during the diagnostic interview or on self-report measures. Participants will be reminded during each appointment that their participation in the study is voluntary and that as such, they are not required to complete any assessments and may skip individual questions or assessments entirely.

- *Discomfort During Assessments:* Assessments may be fatiguing for some individuals, particularly for those with persistent cognitive symptoms. To minimize this potential discomfort, breaks are encouraged and scheduled within the session. In the event that a participant appears to be under undue strain, test sessions are discontinued.
- *Lack of Assessment Feedback:* Participation in this study does not include feedback to participants on their individual assessment results. Though participants are informed of this policy during consent, some participants may find the lack of feedback to be frustrating.
- *Discomfort During Intervention/Program Use:* The following risks may be reasonably anticipated as the result of intervention and/or program use: fatigue, mood complaint, headache, tremor, eye strain, neck/shoulder discomfort, leg/hip discomfort, arm/wrist discomfort, back discomfort, headache and sleep difficulty. To minimize the fatigue participants are encouraged to sit ergonomically correctly while completing study activities on their device. The program is also designed to be entertaining and enjoyable. In addition, assessment and self-report sessions may be paused at any time and participants are encouraged to take breaks.
- *Other Risks:* Although it has not been previously documented, it is possible that the use of the investigational program or participation in the study activities may cause symptoms to worsen. There may also be risks related to the use of the computer program that are unknown at this time.
- *Loss of Privacy*: The most significant risk to the participants are those that would follow a breach of confidentiality and the disclosure of clinical information. Participation in any research study, including this one, may involve a loss of privacy, and absolute confidentiality cannot be guaranteed. Procedures designed to maintain data confidentiality include (1) formal protocol training sessions for all study team members emphasizing the importance of confidentiality, (2) adherence to specific procedures developed to protect participants' confidentiality, and (3) formal mechanisms limiting access to information that can link data to individual participants. One reason for breaking confidentiality is that the study personnel are required by law to report cases of physical or sexual abuse to local law authorities; and another is that despite all procedures, an error may occur. To mitigate this risk, data forms that include identifying information, with the exception of dates assessments are completed, date of birth, and dates associated with other data collected, and personally identifying information volunteered by participants in the BrainHQ (EMA questionnaires) and Google Meets chat forum, will be kept in locked cabinets or secure servers at the study site, accessible only to authorized site study personnel, and will not be shared with Posit Science. Only the unique ID number, assigned by the study coordinator, will represent participants during participation in the study. In the Google Meet platform, participants will have the choice

to self-identify with their first name or an alias. To facilitate tracking, a password-protected computer file will be maintained containing the identity of participants, their ID numbers, and contact information. This file, however, will contain no clinical data. Electronic data will be password protected and stored on a secure network. All data keys will be stored separately and securely. Only study personnel (specifically, the PSC study steam, study site collaborator, and Data Management designee) will have access to the study data. No participant names will be used in study reports or publications.

- *Risks of Email Communication*: This study will rely on the use of email communication between Site Study personnel and research participants as part of their participation in the intervention. Site Study personnel may expected to email participants about their upcoming appointments, provide weekly updates on program usage, or communicate other important study information. Participants may also ask questions of Site Study personnel using email. There are risks associated with email communication, and these risks increase when emails are sent without an encryption service. Risks of sending or receiving unencrypted emails include, but are not limited to:
    - Others can intercept messages
    - If messages are sent or received on an employer-owned device, the employer may have the right to save and read the messages. The internet or cell-phone provider may also have the right to save and read email messages
    - A copy of the message may be saved on a device or computer system, even if it is deleted
    - If an email address is not typed correctly, it can be sent to the wrong person
    - Emails can spread computer viruses
    - Others may be able to access messages on devices that were lost, stolen, or thrown away
    - If a participant changes emails without notifying study personnel, they may miss communications.

Participants will be encouraged to report any adverse effects occurring during the duration of the study to the Site Study point of contact.

<u>PSC does not provide compensation</u> for research-related injuries and will not reimburse or pay medical expenses for the treatment of research-related injuries.

Although there is little chance for a study-related emergency, Site Investigators and Site Study

personnel are required to following institutional standard operating procedures for obtaining emergency care or treatment for adverse effects requiring such. This study has adequate personnel and equipment to respond to expected adverse effects, and maintains working knowledge of the nearest treatment facilities available to patients enrolled into this study.

Potential Benefits

Two levels of benefit will be described to participants:

1. Benefit to Science: Results from this study will directly benefit the applied science in social anxiety disorders. Understanding if the scientific design principles of WASABI drive superior outcomes to current evidence-based treatments will provide considerable insight to scientists and clinicians working in social anxiety disorders.

2. Benefit to Participants: This study has the potential to directly benefit the participant, in terms of symptom alleviation and improved social functioning. We will emphasize that this is the level of benefit that is most speculative in this study, and that potential participants in any randomized controlled trial should join if the benefits to participants like them and to science from the overall trial results are compelling to them, and should not expect that the trial provides treatment benefits as such.

Study Personnel

PSC will serve as the coordinating and data management center for this clinical trial.

Key study personnel at PSC include:

- Principal Investigator (Bruno Biagianti): responsible for the overall design of the study protocol and data analysis plan as well as the eventual publication of the result (with input and authorship from all investigators). He is also responsible for the execution of the study protocol, and coordinating activities with all PSC and UMN staff participating in the trial. Additionally, Dr. Biagianti will monitor, flag and/or remove inappropriate content on the Google Meet chat and report and discuss the content with the appropriate team members, including the WASABI Clinician(s).
- Sponsor Study Coordinator is responsible for assisting the PI with the execution of the study protocol and for data management. She will also be responsible for monitoring all submitted data for consistency and integrity, monitoring, flagging, removing and/or discussing the Google Meet chat content with the appropriate team members, including the WASABI Clinician(s). The Sponsor Study Coordinator will also be responsible for discussing all qualifying criteria with Site

Study personnel, leading virtual training sessions, and holding meetings and with the Site Study personnel. S/he will be responsible for ensuring that the Site meets regulatory compliance requirements and executes the protocol, as IRB approved.
- Sponsor Clinical Trials Manager will provide oversight, advise on regulatory procedures, and support the sponsor study coordinator with her responsibilities, as needed.

Dr. Biagianti and research staff at PSC disclose a conflict of interest: all are paid employees of PSC and may be shareholders, and could benefit if this intervention for Social Anxiety is shown to be an effective treatment in this trial.

This conflict will be mitigated by ensuring that the complete investigator team, including Dr. Biagianti, other PSC study personnel, and UMN Site personnel have joint and overlapping responsibility for the design of the protocol, the execution of the protocol, the *a priori* design of the data analysis plan, the execution of the data analysis plan, the interpretation of the study results, and the authorship of publications emerging from the study. In addition, this conflict of interest will be disclosed to all study participants, and through standard mechanisms for all publications.

Key study personnel at UMN include:

- Principal Investigator (Gail Bernstein): responsible for the overall execution of the study protocol at the Study Site, including overseeing participant recruitment, enrollment and intervention delivery in conjunction with the Site Study team for this clinical trial. She will provide support and coordinate activities between PSC and UMN staff participating in the trial. She will be involved in the data analysis as well as the eventual publication of the result (with input and authorship from all investigators). Additionally, she will ensure that the Site meets regulatory compliance requirements and executes the protocol, as IRB approved. Dr. Bernstein will be blinded to participant randomization assignments.
- Site Clinical Research Coordinator is responsible for assisting the Site PI with the execution of the study protocol, recruiting, screening, enrolling and monitoring participant progress when active in the study. She will also be responsible for entering data into REDCap, reviewing data for consistency and integrity, reconciling data queries, and may randomize participants. She may serve as a back-up WASABI clinician and may be responsible for removing and/or discussing the Google Meet chat content with the appropriate team members, including other WASABI Clinician(s) and the Posit Science research team. Additionally, she will

assist in ensuring that the Site meets regulatory compliance requirements and executes the protocol, as IRB approved.

- Site Clinical Assessor will serve as the blinded psychometrician and clinical rater. She will conduct eligibility and clinical assessments with participants and will be blinded to their randomization assignment. S/he may assist with conducting preliminary screening interviews with participants and conducting consent discussions, as needed. The assessor may assist with connecting with different community organizations, clinics, schools or other sources of recruitment.
- Site WASABI Clinician will lead the group CBT sessions, for treatment and control. She will monitor the Google Meets forum and may be responsible for removing and/or discussing the Google Meet chat content with the appropriate team members, WASABI Clinician(s) and the Posit Science research team. For participants assigned to the WASABI treatment, she will manage the clinician dashboard, and engage participants in ecologically valid interactions. The WASABI Clinician may assist with connecting with different community organizations, clinics, schools or other sources of recruitment.
- Volunteers may be recruited to assist Study Coordinator with study activities, including, but not limited to, recruiting, contacting and conducting a preliminary screening of participants.
- Site Regulatory Study Monitor may be required to access study documents and data capture systems to conduct study monitoring visits to ensure adherence to institutional requirements.

Blinding

Un-blinded Site Roles: At each site, *WASABI Clinicians* are un-blinded in order to provide lead dCBGT sessions and support for participants using their assigned programs. They will be distinct from staff administering and scoring follow-up assessments. Additionally, designated personnel that are un-blinded may not participate in the assessment and evaluation at follow-up assessments (V3) of study participants.

Blinded Site Roles: All site staff responsible for the administration and scoring of participant assessments visits conducted after randomization will remain blinded to participant treatment. Site Principal Investigators will be required to complete a Delegation of Authority Form, indicating which activities individual site research team members will be authorized to complete. Site Principal Investigator will also remain blinded.

Depending upon the extent to which they are responsible for data collection and/or entry, *Clinical Research Coordinators* may or may not remain un-blinded to participant treatment. This will be clarified on a site-by-site basis and will be noted on the Site Principal Investigator Delegation of Authority Form.

To prevent un-blinding, the following controls will occur at the site level:

1. The treatment condition and the control condition will be identified as "two forms of dCBGT."
2. Participants will be reminded not to discuss details related to treatment with blinded psychometricians and/or clinical evaluators during the informed consent process as well as prior to initiation, and at the conclusion of, each assessment visit;
3. Site personnel will be instructed to <u>not</u> discuss details of either treatment arm during open participant groups or forums outside of the assigned dCBGT sessions or cohort discussions;
4. Sites will be required execute the protocol in a manner that minimizes the possibility of accidental un-blinding of psychometricians or clinical evaluators (e.g. unintended viewing of treatment sessions).

Research Monitor

This is a minimal risk protocol. There is no significant risk to using either of the web-based programs in this study, beyond the minor discomfort and tedium risks noted above. Previous studies in healthy aging, schizophrenia, and spatial neglect have not noted any significant adverse events arising from program use. Nonetheless, to follow best practices for treatment trials in medical indications, we will employ a central Research Monitor to review all unanticipated problems involving risk to participants, serious adverse effects, and any participant deaths associated with the protocol, and provide an unbiased written report of the event within ten calendar days. The research monitor will comment on the outcomes of the adverse event and relationship of the event to the protocol or test article. The research monitor will also indicate whether they concur with the details of the report provided by the PI. Reports for events determined by either the PI or Research Monitor to be possibly or definitely related to participation, and reports of events resulting in death will be promptly forwarded to the IRB.

Withdrawal from the Protocol

Study participants may withdraw from the study at any time, for any reason, or for no stated reason. We anticipate that a common reason for study withdrawal will be the time required to complete the intervention. For participants seeking to withdraw for that reason, we will offer the alternative of discontinuing the intervention and scheduling and completing the post-intervention assessment (*End of Study, V3)* visit, given they have met the minimum sessions required to complete the post-assessment visits. The data analysis plan is structured so that their data will be valuable even if they do not complete the intended number of sessions. Participants who still wish to withdraw following that option will withdraw. Other than time required to use the program, we do not anticipate any common reasons for withdrawal that we will plan for in advance.

In rare cases, a Principle Investigator may decide to prematurely discontinue a participant's involvement in the study for any of the following reasons:

a) Safety,
b) Participant non-compliance,
c) A change in circumstance that would prevent completion of protocol-required assessments,
d) Participant relocation to an area that, due to great distance, would prohibit a participant from receiving follow-up at the study site,
e) Participant displays inappropriate behavior toward study staff members or other participants,
f) Participant is hospitalized for psychiatric reasons;
g) Loss of funding, or;
h) A clinical determination, by the Principal Investigator, that continuation in the study is not in the participant's best interests.

Across all reasons for withdrawal, we will ensure an orderly end to the participant's involvement in the study by arranging for the Site Study Coordinator or WASABI Clinician to recover the mobile device (if it has been issued to the participant), conducting an informational interview with the participant to understand the reasons for study withdrawal and identify any issues with study conduct or adverse events that are relevant, and arrange study compensation for sessions that the participant completed.

Modifications to the Protocol

Any significant changes to the protocol, including changes to inclusion/exclusion criteria, changes to assessments, changes to recommended intervention and/or program use, changes that could potentially increase risk to study participants, and additions or removals of key personnel and/or recruitment sites will have to be approved by the grant-recipient and Sponsor PI, Dr. Bruno Biagianti, PSC. Changes requiring approval by the Institutional Review Board will be submitted for review in the form of a protocol amendment or revision prior to implementation.

Protocol Deviations

Protocol deviations will be noted and recorded by Staff (PI, Clinical Coordinator, Study Coordinator, Psychometrician, or WASABI Clinician) if they detect the deviation, or the Study Data Monitor if they detect the deviation during a site visit. All protocol deviations will be reviewed by the Study PI (Bruno Biagianti) on a monthly basis and must be signed off by the Study PI; any such deviations suggesting systematic problems with the protocol procedures as implemented by the site will be reviewed and corrective action determined and implemented by the site.

Reporting of Serious Adverse Effects & Unanticipated Device Effects

The intervention activities and WASABI-program assessments are conducted remotely and primarily computerized. The WASABI protocol has minimal risk, and previous studies of similar approaches in psychiatric populations have not reported significant adverse events arising from intervention and program use. Additionally, computerized treatment studies using Posit Science software in healthy aging, schizophrenia, and TBI have never reported adverse events attributable to study activities. Nonetheless, to follow best practices for treatment trials in medical indications, we will employ a central Medical Research Monitor to review all unanticipated problems involving risk to participants, serious adverse events, and any participant deaths associated with the protocol, and provide an unbiased written report of the event within ten calendar days. The Medical Research Monitor will comment on the outcomes of the adverse event and relationship of the event to the protocol or test article. The Medical Research Monitor will also indicate whether they concur with the details of the report provided by the Site Study staff member. Reports for events determined by designated study personnel, i.e. Medical Research Monitor, to be possibly or definitely related to participation, and reports of events resulting in death will be promptly forwarded to Western IRB. Further, serious adverse events attributable to study activities and/or the intervention and/or program use, will be

documented and reported immediately to the Western IRB. An event that is serious must be recorded on the case record and requires expeditious handling to comply with regulatory requirements. In the event that a patient becomes ill or injured as a direct result of participation in the project, necessary medical care will be made available.

The Site Study Coordinator and WASABI Clinician will ask about any deterioration in symptoms during each contact with participants, and will be alert to any volunteered episodes of suicidality. All events of this nature will be documented on a standardized form and will be classified by the PI to their degree of seriousness and their relationship to the study protocol. Participants will be referred to appropriate clinical care should there be any concerns for safety or increasing symptoms. If deemed clinically necessary, the PI may elect to remove participants from the study if they find that it is no longer in the participant's best interests to continue participation in the study.

Finally, we will also conservatively follow guidelines for medical devices (i.e., computerized assessments) in the reporting of adverse events in this trial, which defines unanticipated adverse device effects (UADEs) in The Code of Federal Regulations in 21 CFR 812.3(s) as any serious adverse effect on health or safety associated with, a device.

Continuing Review and Final Report

In accordance with NIA SBIR guidelines, a continuing review report(s) as well as a Final report will be submitted via eRA Ccommons.

The knowledge of any pending compliance inspection/visit by the FDA, Department of Health and Human Services Office for Human Research Protection, or other Government agency concerning clinical investigation or research, the issuance of Inspection Reports, FDA Form 483, warning letters, or actions taken by any Regulatory Agencies, including legal or medical actions, and any instances of serious or continuing noncompliance with the regulations or requirements will also be reported.

Surveys, Questionnaires and Other Data Collection Instruments

*Complete paper versions are available upon request.

Diagnostic Assessment

MINI-KID

https://eprovide.mapi-trust.org/instruments/mini-international-neuropsychiatric-interview-for-children-and-adolescents

Cognitive Status

WASI-II

https://www.pearsonassessments.com/store/usassessments/en/Store/Professional-Assessments/Cognition-%26-Neuro/Wechsler-Abbreviated-Scale-of-Intelligence-%7C-Second-Edition/p/100000593.html

Anxiety and Social Anxiety

SPAI-B

https://www.mhs.com/MHS-Assessment?prodname=spai

LSAS-CA

Masia-Warner, C. *et al.* The Liebowitz Social Anxiety Scale for Children and Adolescents: An Initial Psychometric Investigation. *Journal of the American Academy of Child & Adolescent Psychiatry* **42**, 1076–1084 (2003).

MASC-2

https://www.mhs.com/MHS-Assessment?prodname=masc2

Social Functioning

ASSES

Connolly, J. Social self-efficacy in adolescence: Relations with self-concept, social adjustment, and mental health. *Canadian Journal of Behavioural Science/Revue canadienne des sciences du comportement* **21**, 258–269 (1989).

SSQ

Nelson, W. Social Skills Training – Enhancing Social Competence With Children and Adolescents, S.H. Spence; U.K.; NFER Nelson; 1995; Kit; $160.00 (ACER). *Australian Journal of Guidance and Counselling* **6**, 102–103 (1996).

Suicidality

C-SSRS

https://cssrs.columbia.edu/the-columbia-scale-c-ssrs/cssrs-for-research/

Case Report Forms: this study employs both an electronic case report form system and a paper-based case report form system (i.e., source documentation records to support the EDC System).

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Appendix I. Table of Assessments

Assessment	Screening	V1	V3
Informed Assent/Consent	X		
Demographics	X		
Medical History Questionnaire and Screening	X		
Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID)	X		
Social Phobia and Anxiety Inventory-Brief version	X		
Wechsler Abbreviated Scale of Intelligence (WASI-II)	X		
C-SSRS, Baseline	X		
Medications, Baseline	X		
Liebowitz Social Anxiety Scale for Children and Adolescents (LSAS-CA)		X	X
Social Phobia and Anxiety Inventory (SPAI)		X	X
Multidimensional Anxiety Scale for Children 2nd Edition (MASC-2)		X	X
Adolescent Social Self-Efficacy Scale (ASSES)		X	X
Social Skills Questionnaire (SSQ)		X	X
Medications, Since Last Visit		X	X
C-SSRS, Since Last Visit		X	X
Adverse Effects		X	X
Unanticipated Adverse Effects	As needed		
Study Exit	As needed		

Appendix II. Sample Debit Card Information

Attached separately.