Study Protocol and Statistical Analysis Plan

Title of Study: Online Mindfulness Training for Adolescents with 22q11.2 Deletion Syndrome
ClinicalTrial.gov Identifier: NCT05849441
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Study Protocol

Objectives:

To date, there are very few non-pharmacological, behavioral interventions that have been developed and evaluated specifically for adolescents with chromosome 22q11.2 deletion syndrome (22q11DS). Thus, there is a need for effective interventions that are tailored for this population to improve their health and well-being. Practicing mindfulness on a daily basis is one possible avenue to build self-regulatory abilities and has been associated with beneficial health outcomes. The *Aware Program* is an online mindfulness education program for adolescents with 22q11DS designed to enhance their coping skills and ability to manage stress and anxiety in healthy ways. The main objective of the study is to test the effectiveness of the *Aware Program* with adolescents with 22q11DS and their parents. This study will examine if the *Aware Program* increases adolescents' use of healthy coping strategies, emotion regulation abilities, and global health, as well as reduces adolescents' anxiety and executive functioning difficulties.

Design:

The study is a parallel group randomized controlled trial with a 1:1 allocation ratio and superiority framework to test the efficacy of the *Aware Program* among parent-adolescent pairs. The randomized controlled trial will be conducted online at two time points: 1) baseline/pre-test and 2) post-test (four weeks after pre-test). The study questionnaires will be programmed into an online data collection system and the intervention itself is also completed online.

Participants will be randomized to one of two conditions: 1) intervention (pairs will receive access to the Aware Program right away) or 2) wait-list control (pairs will not have access to the intervention between pre-test and post-test assessments; after completing the post-test questionnaire, pairs will be given the option to use the *Aware Program*).

Participants are randomized and enrolled based on: 1) time study forms (e.g., consent) were completed and 2) confirmation of email addresses. A statistician will generate the allocation sequences using a random number generator in Excel. After eligibility is determined, the PI will assign participants to condition (either intervention or wait-list control) according to those sequences and then enroll participants in the study. All participants will be assigned a unique ID number that will be associated with their data in place of a name.

Methods:

Sample and Recruitment. Sixty (N = 60) parent-adolescent pairs (adolescents with 22q11DS between the ages of 12 and 19 years) will be recruited to participate in the study. To be eligible to participate in the study, **adolescents** must: 1) Have received a diagnosis of 22q11.2 Deletion Syndrome; 2) be between the ages of 12 and 19 years old; 3) have an IQ of greater than or equal to 55; 4) have regular internet and computer access; 5) speak and read English (all study and program materials are in English). To be included in the study, **parents** must: 1) Have a participating adolescent in the study and 2) read fluently in English (all study and program materials are in English). Only one parent per youth may participate. Parent-adolescent pairs will

be recruited from across the United States. A study recruitment website will contain information about the research study that interested parent-adolescent pairs can review. The website will also have the study team contact information and a link to the eligibility screening questionnaire. Parent-adolescent pairs will also be recruited via a study flyer and with the help of expert consultants, as well as help from organizations that work with families of individuals with 22q11DS and diagnostic clinics or centers that specialize in 22q11DS. Recruitment materials may also be shared on social media, through word of mouth, via email listservs, and other online methods in order to reach families of adolescents with 22q11DS.

Procedure. Interested parents and adolescents will visit the recruitment website to learn more and respond to the study eligibility questions. Parents will be notified onscreen immediately if the pair is eligible to participate in the study, and if so, they will then be provided with a link to the electronic study forms to review and sign. For adolescents aged 12-17 years and their parents: The parent will be asked to complete a parent permission and consent form and adolescents will be asked to complete a youth assent form. For youth aged 18 and 19 years and their parents: Prior to reviewing the forms, parents of 18- and 19-year-olds will be asked to respond to the following question: "Is there legal guardianship in place between you and your teen?". If there is a legal guardianship in place, the parent will be asked to complete the parent permission and consent form and the adolescent will be asked to complete the youth assent form. If there is not a legal guardianship in place, the parent will be asked to complete the parent consent form and the adolescent will be asked to sign a youth consent form. The permission, consent, and assent forms will describe the goals of the study, as well as the minor potential risks and the benefits of participation. Permission, consent, and assent forms will also state the participant may discontinue their participation at any time. Potential parent-adolescent pairs will be provided with the contact information of the researchers and may contact them to ask any questions they may have about the study. Parent-adolescent pairs will read the permission, consent, and assent forms and provide online permission, consent, and assent by typing their names into a text box, providing contact information, and clicking a button to indicate permission/consent/assent rather than providing a signed hard copy of the forms. They will have the option to download and/or print the forms to retain a copy for their files. Only parent-adolescent pairs with completed study forms will be permitted to participate in the study.

After completing and submitting the study forms, parents will receive an email confirmation that will ask parents to confirm their email address in order to receive emails about the study. If parents do not confirm their email address, reminders will be sent to parents via iRT's study management system. iRT project staff will determine whether or not the address the parent has provided for the pair in the consent forms is real using a Google map search. Eligible parent-adolescent pairs who have completed all study forms and confirmed their email address will receive a welcome email that will provide more information on the timeframe and tasks for the study. Participating parent-adolescent pairs will be randomly assigned to either the intervention group (immediate access to Aware Program) or the wait-list control group (delayed access to program). When the study starts, parent-adolescent pairs will receive an enrollment email from iRT's study management system via the parent's email address with a link for the participating parent to complete the online parent pretest questionnaire within one week. This enrollment email will also indicate that the parent will receive a second message with a unique link for their adolescents to use to complete the online teen pretest questionnaire within one week. Completion of the pretest questionnaires may take up to 30 minutes for participants. Upon

completion of the pretest questionnaires, parent-adolescent pairs will see a message at the end of the questionnaire indicating that the parent will receive an email regarding the pair's next steps in the research study.

- Pairs in the intervention group will receive an email that they are able to access the Aware Program immediately with instructions on how to access and review the Aware Program. There are four courses in the Aware Program and each course has 5 brief lessons. It is expected that adolescents will complete one course per week. For the purposes of the study, adolescents (and their caregivers) will be instructed that they have four weeks to complete the Aware Program but that it can be done at their own pace and schedule. Parents will have access to the parent resources as part of the program. Parent-adolescent pairs may also subscribe to the mobile messaging service associated with the Aware program; this optional service includes progress reminders, encouragement, and practice content sent to their phones. The mobile messages will not be sent after 9pm or before 8am, and families may opt out at any time from their phone by texting "STOP" in response to a message. Parents may opt their teen and themselves in mobile messaging from the parent dashboard, as well as opt out if needed.
- Pairs in the wait-list control group will receive an email telling them that they will be asked to complete another set of questionnaires in about four weeks. Participants in the wait-list control group will not have access the Aware Program during this time and will receive business as usual, which in this case is no mindfulness education. The wait-list control group will later receive access to the Aware Program once they have completed the posttest questionnaires.

Project staff members will monitor usage of the Aware Program through iRT's Learning Management System (LMS). Approximately five weeks after completing the pretest questionnaire, participating parents will receive an email with a link for the parent to access the online parent posttest questionnaire to be completed within one week. This parent email will also indicate that the parent will receive another message with a unique link for their adolescents to use to complete the online teen posttest questionnaire within one week. Completion of the posttest questionnaires may take up to 30 minutes for participants. Participants in the intervention group will receive the Consumer Satisfaction Questionnaire at the end of their posttest questionnaire. Completion of the Consumer Satisfaction Questionnaire may take approximately 15 minutes. Participants in the wait-list control group will have the option of reviewing the Aware Program after their posttest data have been collected. Adolescents will have access to the four courses and parents will have access to the parent dashboard, in which parents can opt in or out of mobile messages for themselves and their teens. After 4 weeks, the wait-list control group will have the opportunity to complete the Consumer Satisfaction Questionnaire about the Aware Program. Completion of the Consumer Satisfaction Questionnaires by participants in the wait-list control group is optional and those participants will not receive an incentive for completing these questionnaires. Parents (in the wait-list control group) will receive an email with a link for the parent to access the online parent Consumer Satisfaction Questionnaire to be completed within one week. This email will also indicate that the parent will receive another message with a unique link for their adolescents to use to complete the online teen Consumer Satisfaction Questionnaire within one week. Participants will receive automatic email reminders from the study management system if they have not completed the

questionnaires or not accessed the Aware Program. The research team will also call a parent or send a check-in email to a parent if there is no response following the automatic reminders. Incentives for completing the pretest questionnaires and for completing the posttest questionnaires will be physically mailed to parent-adolescent pairs using the address provided on their study forms. At the end of the study, responses on the online questionnaires will be downloaded from the online data collection system and saved on a secure, password-protected network in preparation for statistical analyses.

Measures.

Adolescents:

Background information. Adolescents will be asked to provide some basic demographic information (e.g., age, gender, race, ethnicity).

Self-Report Coping Measure (SRCM; Causey & Dubow, 1992) assesses coping in response to stressors across five coping domains (e.g., Seeking Social Support, Problem Solving, Distancing, Externalizing, and Internalizing). Adolescents will respond to 34 items on a 5-point Likert scale (1 = Never to 5 = Always) to indicate how often they use a given coping strategy (e.g., "Try to think of different ways to solve it) when facing stress. Additionally, 3 items related to mindfulness skills (e.g., "Stop and notice how I am feeling") will be included as a mindfulness subscale in this measure.

Emotion Regulation Questionnaire (ERQ; Gross & John, 2003) assesses differences in the use of two emotion regulation strategies: Cognitive Reappraisal and Suppression. Adolescents will respond to 10 items (e.g., "I keep my emotions to myself") using a 7-point Likert rating scale (1 = Strongly disagree to 7 = Strongly agree).

Emotional Self-Efficacy Scale for Youth (Youth-ESES; Qualter et al., 2015) assesses youth's beliefs about their ability to understand and manage emotions in themselves and others. Adolescents will rate their confidence in each of the 27 items (e.g., "I can tell when my feelings change") using a 5-point Likert Scale (1 = Not at all confident to 5 = Very confident). The measure has four factors: Using and managing your own emotions; Identifying and understanding your own emotions; Dealing with emotions in others; Perceiving emotion through facial expressions and body language.

Generalized Anxiety Disorder (GAD-7; Spitzer, Kroenke, Williams, & Lowe, 2006) assesses general anxiety in youth. Adolescents will respond to 7 items (e.g., "Over the last two weeks, how often have you been bothered by the following problems… feeling nervous, anxious, or on edge,") using a 4-point Likert scale (0 = Not at all, 1 = Several days, 2 = More than half the days, 3 = Nearly every day).

Social Anxiety Scale for Adolescents (SAS-A; La Greca & Lopez, 1998) assesses social anxiety in youth. Adolescents will respond to 18 items (e.g., It's hard for me to ask others to do things with me) using a 5-point Likert scale (1 = Not at all, 5 = All the time). The measure has three

factors: Fear of Negative Evaluation, Social Avoidance and Distress-New; Social Avoidance and Distress – General.

PROMIS Pediatric Global Health Measure (PGH-7; Forrest, Bevans, Pratiwadi, Moon, Teneralli, Minton, & Tucker, 2014) assesses overall health and wellbeing across 7 items. Adolescents will respond to 4 items (e.g., In general, would you say your quality of life is…) using a 5-point Likert scale (5 = Excellent, 1 = Poor); 1 item (e.g., How often do you feel really sad) using a 5-point Likert scale (5 = Never; 1 = Always); and 2 items (e.g., How often do you have fun with friends?) using a 5-point Likert scale (5 = Always; 1 = Never).

Parents:

Background information. Parents will be asked to provide some basic demographic information (e.g., age, gender, race, ethnicity, personality).

The Emotion Regulation Checklist (Shields & Cicchetti, 1997) assesses parent reports of their adolescents' emotion regulatory abilities. Parents will respond to 24 items (e.g., "Responds positively to neutral or friendly overtures by peers) on a 4-point Likert scale (1 = Never; 4 = Always). There are two subscales: Emotion Regulation (e.g., appropriate displays of emotion, awareness of emotions) and Negativity (e.g., lack of flexibility and regulation of emotion).

Childhood Executive Functioning Inventory (Thorell & Nyberg, 2008) assesses parent ratings of their adolescents' executive functioning. Parents will respond to 24 items (e.g., "Has difficulty thinking ahead or learning from experience.") using a 5-item Likert scale (1 = Definitely not true; 5 = Definitely true). There are four subscales: Working Memory, Planning, Inhibition, and Regulation.

Spence Children's Anxiety Scale: Parent Report, Brief Version (SCAS-P-8; Reardon, Spence, Hesse, Shakir, & Creswell, 2018) assesses parent report of their adolescents' anxiety. Parents will respond to 8 items (e.g., "My child worries about things.") using a 4-point Likert scale (1=Never, 4 = Always).

The PROMIS Pediatric Global Health Measure (PGH-7 Parent Proxy Report; Forrest et al., 2014) assesses parent reports of their adolescents' overall health and wellbeing across 7 items. Parents will respond to 4 items (e.g., In general, would you say your child's quality of life is…) using a 5-point Likert scale (5 = Excellent, 1 = Poor); 1 item (e.g., How often does your child feel really sad) using a 5-point Likert scale (5 = Never; 1 = Always); and 2 items (e.g., How often does your child have fun with friends?) using a 5-point Likert scale (5 = Always; 1 = Never).

Implementation:

Dosage. iRT's LMS will record the number of program lessons completed by adolescents and amount of time that adolescents spend in the program.

Engagement. iRT's LMS will record the number of Likert-type rating scale questions that adolescents respond to as part of the lesson activities in the Aware Program.

Consumer Satisfaction:

Consumer Satisfaction Questionnaire for Adolescents (CSQ-A) will assess adolescents' satisfaction with the Aware Program in terms of: (1) content (e.g., I think the information provided in this program is important for teens like me.); (2) format (e.g., The games and activities in the Aware program were fun.); and (3) usability (e.g., I found it easy to go through the program.). Overall quality will also be assessed (e.g., I would recommend the Aware program to a friend or another teen.). Participants will rate each item on a 5-point Likert scale. Participants will also be asked an open-ended question for improving the program (e.g., Is there anything you think we could do to make the Aware Program better?).

Consumer Satisfaction Questionnaire for Parents (CSQ-P) will assess parents' satisfaction with the Aware Program. The questions will include (1) content (e.g., The information on the My Teen's Course Progress page was helpful to me.), (2) format (e.g., The design of the My Teen's Course Progress page was pleasant.), and (3) usability (e.g., It took a long time for the pages to load in the Parent Dashboard). Overall quality will also be assessed (e.g., I would recommend the Aware Program to another parent of a teen with 22q11DS). Participants will rate each item on a 5-point Likert scale. Parents will also be able to share open-ended feedback about their experience using the Aware program (e.g., What did you like best about the text messaging system?).

Statistical Analysis Plan

Data will be analyzed using SAS 9.4.

***Preliminary analyses*.** Psychometric and other descriptive analyses will be conducted of the reliability, validity, and distributions of key measures. Summary scores will be created and distributions, internal consistencies, and intercorrelations of these scores will be reviewed as indices of reliability and validity. In addition, the impact of random assignment on producing essentially equivalent groups for the intervention and control conditions will be analyzed in a series of t-test and chi-square models estimated for each demographic variable at outcome variable at baseline. Missing data at each time point will also be examined using the appropriate imputation method and estimates and standard errors adjusted for imputations, if warranted.

Main Analyses. Multiple regression analyses will be used to investigate differences in outcomes (i.e., coping strategies, emotion regulation, global health, executive functioning, and anxiety) using condition (intervention; wait-list control) as the independent variable of interest. A series of multiple regressions will be used to examine if using the Aware Program impacts the post-test coping, emotion regulatory abilities, global health, executive functioning, and anxiety of adolescent participants. Pre-test scores for each outcome will be included as predictor variables; thus, outcome variable means will be reported as adjusted post-test scores. Demographic variables found to be non-equivalent between groups will be included as covariates in these models. The effect sizes will be calculated by dividing the appropriate contrast parameter by the sample standard deviation of the outcome. Analyses will be intent-to-treat, so

that participants who do not adhere to the protocol will be still included in the analysis in their assigned condition.

Fidelity and Consumer Satisfaction. The process data recorded for the intervention group by the LMS (e.g., lessons completed, time spent using the program, number of activities completed) will be examined to determine dosage and engagement. In addition, consumer satisfaction responses will be examined including mean scale scores on the CSQ (e.g., format, usability). Responses to qualitative items will be summarized, and similar patterns of responses will be grouped by content.