Title: Pilot RCT to Evaluate the Effects of a Trust-Building Depression Management Intervention on Moderate Depressive Symptoms in Low-Income Adolescents

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PROTOCOL TITLE: Study comparing two depression management interventions for teens with depression

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Study Comparing Two Depression Management Interventions for Teens with Depression

Objectives

(1) Our purpose is to test the **Tru**st-building depression **S**elf-Management **T**ogether (**TRUST**) intervention among adolescents with moderate depressive symptoms. Our premise is that trust can be learned, that increasing trust will improve self-regulation, and improved self-regulation will influence depression management behaviors, which will decrease depressive symptoms and increase quality of life (QOL). **The study aims are:**

Aim 1. Compare the effects of the TRUST intervention with a depression management intervention on depression management behaviors (sleep, stress management, medication adherence, appointment keeping) and health status (depressive symptoms, QOL) in adolescents with moderate depressive symptoms.

Aim 2. Assess whether the effects of the TRUST intervention on depression management behaviors (sleep, stress management, medication adherence, appointment keeping) and health status (depressive symptoms, QOL) are mediated by (respiratory sinus arrhythmia [RSA], behavioral interaction assessment, adolescent/parent trust self-reports, relationship quality, self-regulation, family cohesion, social support, decision making, self-efficacy, rumination, decentering).

Aim 3. Assess the effects of potential moderators (gender, race, perceived stress, parental monitoring, household income, parent level of education, parenting style, parent stress) on the relationship between the TRUST intervention and depression management behaviors and health status (depressive symptoms, QOL).

(2) **Hypothesis:** We hypothesize that variations in adolescent/ parent trust-building will predict response to the TRUST intervention and depression management behaviors as evidenced by change in depressive symptoms and QOL.

Background

(1) Depressive symptoms are a serious concern affecting the social, academic, and health outcomes of 36% of Cleveland adolescents.[2] Health disparities exist in depression management—with low-income and minority adolescents more likely to forego treatment for depression.[3] Students enrolled in Cleveland Metropolitan School District (CMSD) schools are 100% low-income and 84% ethnic minority.[6] We are collaborating with CMSD to address health disparities in depression management among low income and minority adolescents. Our team has an 8-year ongoing relationship with CMSD schools to improve the health of Cleveland's children and their families.

Depression among adolescents is affected by health behaviors such as sleep, stress management, medication adherence, and appointment keeping, as well as quality of relationship with parents. Family focused interventions are well established for reducing emotional and behavioral problems in adolescents, and function in part, by fostering positive adolescent-parent relationships.[7] Rotenberg describes adolescents' trust of their parent as made up of: (a) honesty, which is telling the truth and engaging in benign and genuine behaviors; (b) reliability, which is perceived compatibility between one's words and actions; and (c) emotional connection, which is the dependence on others to be receptive to disclosures and maintain confidentiality of disclosures.[8] We are applying this theory as a basis for the TRUST intervention used in this study that builds trust between adolescents and their parents, alongside depression management behaviors.

(2) **Preliminary data.** In this pilot RCT, we are evaluating the effects of the novel TRUST intervention to improve depression management behaviors in adolescents with depressive symptoms. PI Hardin has shown that low interpersonal trust is associated with risky health behaviors[5] and high depressive symptoms in low income adolescents.[4] Recent studies indicate

that self-regulation is a core aspect of positive relationships,[9] trust,[10] and healthy behaviors.[11] RSA is an indicator of heart rate variability in response to respiration,[12] which is a marker of self-regulation.[11,13] We will assess RSA during a behavioral assessment of the quality of adolescent-parent interaction using microsocial coding approaches.[14,15] Co-I Connell has shown that RSA is associated with mutual positive affect[16] and emotion regulation[15] in adolescent-parent behavioral interactions.

Inclusion and Exclusion Criteria

(1) **Screening.** Using an existing collaboration with the CMSD school system, participants will be recruited via advertisements in parent meetings at CMSD schools and social media. Candidates whose parents indicate interest by phone call, email, message, or completing an online prescreening tool will be contacted using an IRB approved script to recruit, screen, and enroll participants. Adolescents will complete the PHQ-8 measure of depressive symptoms over the phone or by REDCap link on a tablet computer. A PHQ8 score >8 and <20 will be considered for study inclusion. Screening the adolescent with the PHQ8 confirms that the adolescent currently has moderate depressive symptoms and will occur during the screening process, prior to consent/assent. We have requested a waiver of consent on page 7 for screening purposes.

	(2) **Inclusion (adolescent)**
1.	A Cleveland Metropolitan School District student
2.	Ages 14-17 years old
3.	Reports diagnosis of depression
4.	Reports moderate depressive symptoms (PHQ-8 score >8 and <20)
5.	Able to read, speak, and understand the English language
	Inclusion (parent/guardian)
1.	Female parent/guardian
2.	Able to read, speak, and understand the English language

	(3) **Exclusion (adolescent)**
1.	Current suicide risk
2.	Diagnosis with bipolar disorder, schizophrenia, or a personality disorder
3.	Sever behavioral problems that preclude group participation (as reported by parent)
4.	Family plans to move from the region within one year
	Exclusion (parent)
1.	Family plans to move from the region within one year

Number of Research Participants

(1) N = 30 adolescent/parent dyads
(2) Single site study, N/A

Vulnerable Populations

(1) Vulnerable populations included are:

- ☐ **Adults unable to consent**
- ☒ **Minors (infants, children, teenagers)**
  - ☐ Wards of the state
  - ☐ Foster Children
- ☐ **Pregnant Women**

- ☐ **Neonates**
- ☐ **Employees of CWRU or UHHS**
- ☐ **Prisoners**
- ☐ **Illiterate Individuals**
- ☐ **Non-English Speaking**
- ☐ **University Students**

(2) Minors will be recruited with permission of the parent/guardian during the process of informed consent with assent designated for acceptance by the minor. Minors are the participant of interest, since this is a pediatric study targeting adolescent participants with depression. The consent/assent document was designed with adolescents in mind, including simple and clear lay language to promote respect for (minor) persons with shared consent/assent decision-making between parent and adolescent. Drs. Hardin and Connell have conducted previous research protocols that involve adolescent-parent dyads and have experienced research assistants and established protocols for quality assurance, crisis intervention and referral, as well as initial and ongoing staff training. The research assistants hired for this project will have prior experience working with adolescent-parent dyads.

Risks associated with study procedures (surveys, behavioral interaction, RSA) are not greater than encountered in daily life and will be minimized with careful attention to adolescent participant needs. There is the potential for stigmatization due to depression diagnosis; however, measurements are taken in private and all results are reported privately in a sensitive and culturally appropriate manner. If questionnaires indicate symptoms suggestive of severe depression or suicidal ideation, the results will be reviewed with Dr. Arin Connell, Ph.D. (co-investigator, licensed clinical psychologist, #6732) who will consult with the adolescent and/or parent/guardian to determine whether the adolescent or parent/guardian is in need of a referral for further evaluation and treatment. The nature of this study includes adolescents with a diagnosis of depression. If the adolescent becomes upset during study procedures, a study research assistant and the participant's parent will be available to support and comfort the adolescent participant if needed. The adolescent/parent dyad will be given an information sheet with the number of United Way First Call (211) to access on call mental health professional services in their local area or Cuyahoga County 24-Hour Mental Health Crisis Information and Referral Hotline (216-623-6888). If the participant is unable to be comforted by the research assistant or the parent and further assistance is required, the Mobile Crisis Team from the Cuyahoga County 24-Hour Mental Health Crisis, Information, and Referral Hotline will be contacted immediately. In addition, our Data and Safety Monitoring Committee (DSMC) will include an individual with expertise and experience conducting research studies with minor participants.

(3) Pregnant women are not targeted for inclusion in this study, but will not be excluded in this study. Non-English speaking individuals will be excluded in this study. At this time, our study does not have the means to accommodate non-English speaking participants. This is a small (N=30), proof of concept, pilot study conducted by an early stage investigator. Once our team has evidence that trust-building interventions are effective, we will expand our reach with larger studies, which will include non-English speaking families.

Recruitment Methods

(1) The target population are CMSD school students 14-17 years old diagnosed with depression and a parent. CMSD has 41 high schools enrolling approximately 10,000 students 14-17 years old. According to a recent screening, approximately 36% of CMSD high school students reported depressive symptoms, which is approximately 3,600 students ages 14-17 years old.

(2) Using an existing collaboration with the CMSD school system, participants will be recruited via mailed invitation letters, advertisements in parent meetings at CMSD schools, community events/locations, on the public bus system, and social media. Due to COVID-19 safety restrictions, in person recruitment will follow all guidance made by local government (wearing masks, washing hands, or stay at home when appropriate). Parents of participants in our previous studies that have consented to notifications of future research will be mailed or emailed study information letters and study flyers.
(3) Frances Payne Bolton School of Nursing investigators have used this recruitment approach in a depression management study in which 52 adolescents were recruited in one year. Our study aims to enroll 30 adolescent/parent dyads. Candidates whose parents return a phone call, message, or online prescreener indicating interest will be contacted using an IRB approved script to recruit, screen, and enroll participants.
(4) Study flyers will be provided to school nurses, school administrators, and school guidance counselors for distribution to parents either electronically or, once restrictions associated with the COVID-19 pandemic are lifted, in-person. Similarly, once restrictions associated with the COVID-19 pandemic are lifted, we will also use traditional methods of recruiting and flyer drops, targeting community venues including branches of the local public library, commercial retail outlets, and community parks, recreational facilities, and places of congregation (e.g., churches, temples). Public bus advertisements will include paid advertising on the interior of the bus, aimed at bus riders. These materials will be used to recruit participants during visits with school staff, during visits to community venues, and while riding the public bus system.
(5) Advertisements on public buses and Facebook will include a brief description of the study eligibility and study contact information, while flyers and brochures will include greater details about the study, eligibility, and contact information. The study recruitment materials are attached with this application.
Facebook advertisements will be used to advertise the study and evaluate potential eligibility for the study (See Facebook Level Up study advertisement attached). This Facebook advertisement will be targeted to parents of adolescents 14-17 years old attending a Cleveland Metropolitan School District school. The Facebook advertisement will be linked to a prescreening tool in REDCap to evaluate potential eligibility for the study. Facebook advertisements will take four forms: 1) study advertisements, 2) fun posts, 3) page shares, and 4) targeted advertising. Examples of Facebook advertisements and the prescreening form are attached with the study application.

A. Study advertisements. We plan to periodically post the following Level Up study advertisements on our study Facebook page to assist in recruitment and keep the page active:
    a. “Greetings from the Level Up team at Case Western Reserve University Frances Payne Bolton School of Nursing! We are actively recruiting for our program helping parents and teens feel better. If you have a 14-17 year-old teen enrolled at a Cleveland Metropolitan School District school and would like more information about our program, please give us a call. Our office phone is 216-368-5129, and our email address is levelup@case.edu. We look forward to hearing from you!”
    b. “Are you the parent or guardian of a teen ages 14-17 years attending a Cleveland Metropolitan School District school? Would you and your teen like to join a program to learn how to live healthier and feel better? Simply click the blue “Sign Up Now” button, fill out the form, and one of our study team members will be in contact with you soon. Participants will be compensated for their time.”
    c. “We are looking for parents and guardians of teens ages 14-17 years living in the Cleveland Metropolitan School District who are interested in joining our healthy

living program. If you are interested, please feel free to contact us or click on the "Sign Up Now" button. Participants will be compensated for their time."

B. Fun posts. We will make fun Facebook posts to maintain presence and activity of our Facebook page. For example, we may make posts about secular holidays such as, "Wishing Cleveland families a Happy New Year!"
C. We will ask other pages to share our page or recruitment posts with their followers. These other pages include Frances Payne Bolton School of Nursing, the Cleveland Metropolitan School District, local parent groups, local community groups, local churches, and national parenting groups.
D. We will also use paid, targeted advertising on Facebook. These ads will target parents of high school age children in Cleveland.

With the online prescreener form, parents will be contacted for further screening if the following conditions are met: 1) parent indicates interest in the study, 2) parent indicates concern about their teen's stress/mood, and 3) parent provides their contact information.

Setting

(1) Due to restrictions associated with the COVID-19 pandemic, this study will be delivered in a remote format. Enrolled families will complete surveys via an electronic device connected to the internet, and intervention sessions will similarly be offered in a virtual (phone or video conferencing) format. When restrictions associated with the COVID-10 pandemic are eased, the survey, behavioral, RSA, and intervention components of this study will be conducted in research laboratories at the Frances Payne Bolton School of Nursing and the Department of Psychology at Case Western Reserve University. The intervention session component of this study will be conducted at private community locations (e.g., library meeting rooms) that are convenient for enrolled study participants once covid-19 restrictions are eased. (2) Using an existing collaboration with the Cleveland Metro School District, participants will be recruited from parent meetings, the community at large, public bus system, and Facebook advertisements. (3) Due to the COVID-19 pandemic, assent/consent will be obtained online using a REDCap survey facilitated by a phone call with a research assistant to verify understanding of the study. When restrictions associated with the COVID-19 pandemic are eased, assent/consent will be obtained in-person using the following process. First, consent/assent will be obtained at either PI Hardin's research space at the School of Nursing or Dr. Arin Connell's research space at the Department of Psychology. Next, participants will complete surveys on tablet computers either PI Hardin's research space at the School of Nursing or Dr. Arin Connell's research space at the Department of Psychology. Parent/teen dyads will then be taken to Co-I Connell's lab at the Department of Psychology where they will be seated in comfortable chairs in separate, quiet research rooms. Research assistants will then provide an overview of the physiological equipment, including the manner of attaching all recording sensors.

Consent Process

Indicate whether you will be obtaining consent:

☒ Yes ☐ No

We will recruit participants using an IRB-approved protocol. All participants will be required to give informed written assent/consent to participate in the project. Assent will be obtained from adolescent participants and consent will be obtained from the parents. No waiting period will be required between screening and consent. Trained research personnel will read, review, and discuss assent/consent forms with all potential participants prior to asking them to sign. It is anticipated that it will take approximately 30 minutes to complete the consent/assent process, but participants may take as long as they need to make a decision. Participants that seem

unsure about consent/assent will be encouraged to discuss it at home and contact us once a decision is made. If the candidate appears confused or indicates a lack of understanding, the interviewer will attempt to identify the misunderstanding and to explain the form again. Any candidate who still does not comprehend the form will be excluded from the study. We will ask questions to confirm understanding of the material covered in the assent/consent procedure (e.g., "Could you tell me what's going to happen if you take part in the study?"). Trained research personnel will witness and date the signed forms. Assent/consent procedures will take place in a private room or office. PI Hardin will keep assent/consent forms in a secured file cabinet within a locked room. At each study visit, study personnel will ask participants about their experience in the study (i.e. "How are things going for you in the study?") and ask if they understand what is happening in the study (i.e. "Do you know why you're here today?" or Do you have any questions about the study?").

As consent is an ongoing process, subjects in the study may need to be re-consented/re-assented to inform them of new study information and reaffirm their willingness to continue participating in the research. National and local guidance recommends the use of the least burdensome approach for re-consenting/re-assenting a subject.[42,43] The Office of Human Research Protections (OHRP) guidance for re-consent/re-assent will be followed,[44] which includes re-consenting/re-assenting active participants and verbal communication with documentation in the study record for participants who have already completed all study activities.

The following is a list of how data will be handled following attempts to re-consent/re-assent. In the event that an active participant does not complete re-consent/re-assent, their participation in the study will be ended and their data will not be used for analysis. For subjects who have completed all study activities and select not to re-consent/re-assent, their data will not be used for any new analyses. With a subject who has completed all study activities and cannot be contacted for re-consent/re-assent, only the survey data included in previous IRB approvals (depressive symptoms, covid-19 anxiety) will be used for data analyses. Finally, all subjects who are re-consented/re-assented and reaffirm their willingness to continue participating in the research will have all data included in data analyses.

Waiver or Alteration of Consent Process or Documentation

☒ I will obtain consent, but request a waiver for pre-screening purposes.

(1) The online prescreener and screening phone call cannot be practicably conducted without a waiver of consent/assent for a number of reasons. The information collected for the prescreen does not involve any actual intervention or experimentation. Families will only have a prescreening done if they are volunteering to learn more about participating in the study. The purpose of the pre-screening is to clarify the dyad's eligibility for the study prior to arranging a baseline visit to the lab space at Case Western Reserve University. This is necessary to avoid scheduling dyads for baseline visits only to find that they are not eligible, a situation that, if avoidable, would anger and disappoint families. Our community advisory board recommended that the process of prescreening be efficient and non-burdensome for families, and the proposed approach is designed to be consistent with their recommendations. It also avoids inappropriate use of CWRU resources. Further, no data will be collected except those pertaining to eligibility. To require full consent/assent would create temporal and perceptual impediments for families who would otherwise be interested in participating and would likely reduce community engagement in the project substantially. Furthermore, the waiver applies only to the

prescreening by phone, online, or in person visit. All those eligible and wanting to take part in the project will compete a full consent/assent prior to beginning the study.

Additional Considerations for Consent Process with Adults

Non English Speakers: Not applicable. With this small (N=30), proof of concept, exploratory pilot study, we are including only those who can speak, read, and understand the English language. Once effectiveness of the intervention has been established, we will include non-English speakers. We intend to develop a Spanish version of this intervention for use in future replication studies, once effectiveness of the intervention has been established.

Adults Unable to Consent: Not applicable. The interventions under evaluation in this study are social/behavioral in nature and require the ability to read, speak, and understand language, in addition to interacting one-on-one and in a group setting.

Research Participants Who Are Not Yet Adults (teenagers)

Parental permission be obtained from:

☒ One parent even if the other parent is alive, known, competent, reasonably available, and shares legal responsibility for the care and custody of the child.

(1) With the non-invasive, low-risk nature of this study with potential for participant benefit, we will require parental/guardian permission and involvement of only one parent/guardian. The screening form will ask both the parent/guardian and adolescent for confirmation that the parent providing consent is a legal parent/guardian of the child. Parental consent will be recorded with the either the selection of the "yes" checkbox in the electronic consent process during the COVID-19 pandemic or with the parent's signature on the assent/consent form once restrictions associated with the COVID-19 pandemic are eased.

(2) All minor adolescents (ages 14-17) will require consent of a parent or legal guardian. All minor adolescents (ages 14-17) will require assent.

(3) Assent will be recorded with the either the selection of the "yes" checkbox in the electronic consent process during the COVID-19 pandemic or with the adolescent's signature on the assent/consent form once restrictions associated with the COVID-19 pandemic are eased. Assent will be recorded with the adolescent's signature on the consent/assent form. The consent/assent form has been designed with simple language appropriate for both adults and teens. A single consent/assent form treats participants ages 14-17 as autonomous individuals able to make decisions for their participation, while reducing burden on families with multiple documents.

(4) Re-consent/assent addendum.

Sharing of Results with Research Participants

We will not be providing individual results to participants', however, general group results will be shared with participants at the end of the study, or as needed if the results may influence their decision to remain in the study.

Study Design, Procedures, and Timeline

(1) Study Design. We will use an exploratory 2-group pilot RCT to investigate the hypothesized effects of the TRUST intervention on depressive symptoms, QOL, sleep, stress management, medication adherence, and appointment keeping at 3 months and 6 months in comparison to the effects of a Depression Management Intervention.

(2 & 3) Research Procedures will include:

a. **Recruitment and Informed Assent/Consent***:* We will recruit participants using an IRB-approved protocol. All participants will be required to give informed written assent/consent to participate in the project. During the COVID-19 pandemic, we will be

obtaining assent/consent online via REDCap. Research assistants will read, review, and discuss assent/consent forms with all potential participants prior to asking them to sign. If the candidate appears confused or indicates a lack of understanding, the interviewer will attempt to identify the misunderstanding and to explain the form again. Any candidate who still does not comprehend the form will be excluded from the study. We will ask questions to confirm understanding of the material covered in the assent/consent procedure (e.g., "Could you tell me what's going to happen if you enroll in the study?"). Interviewers will witness and date the signed forms. Assent/consent procedures will take place in a private room or office. PI Hardin will keep assent/consent forms in a secured file cabinet within a locked room. Participants will be enrolled in blocks of 10 dyads, using a block randomization scheme to assign each of the 10 dyads to either study group. Once a group of 5 is filled, weekly intervention sessions will begin.

b. **Questionnaires**: Survey data will be collected using REDCap on a tablet computer. Measures used in the study are listed in the Table below. Due to restrictions associated with the COVID-19 pandemic, parents and adolescents will be asked to answer questions privately and at approximately the same time point on an electronic device connected to the internet in their homes. If, for example, only one electronic device is able to connect to the internet, the adolescent can complete the survey and then pass the device to the parent for survey completion. We are assessing families for internet access and device availability in the screening form. For families that do not have a device, we will mail them a tablet that they will mail back to us at the end of the study.

Study Variables, Measures, and Data Collection Points

ADOLESCENT SURVEY

Variable	*Instrument*	*Title on Survey*	B	3M	6M
Depressive symptoms	Patient Health Questionnaire-8[19]	Depression Questions	X	X	X
Quality of life	Youth Quality of Life-Short Form[21]	Quality of Life Questions	X	X	X
Sleep	PROMIS sleep disturbance-4[25] Children's Report of Sleep Patterns[22]	Sleep Questions More Sleep Questions	X X	X X	X X
Stress management	Adolescent Lifestyle Questionnaire—stress management subscale[23]	How do you handle your stress?	X	X	X
Medication adherence	Extent of Medication Adherence[24]	Medication Questions	X	X	X
Appointment keeping	Hill-Bone Compliance Scale[25]	Appointment Questions	X	X	X
Biologic Trust	Respiratory sinus arrhythmia[13]	Not applicable—assessment in lab	X	X	
Behavioral Trust	Behavioral interaction assessment[14]	Not applicable—assessment in lab	X	X	
Cognitive Trust	Children's General Trust Scale[26]	Children's Trust Questions	X	X	X
Cognitive Trust	Parent Trust of Child Scale—Adolescent perceived[27]	Parental Trust Questions	X	X	X
Relationship quality	Inclusion of Other in Self[28]	How close are you with your parent?	X	X	X
Self-regulation	Positive and Negative Affect Schedule[29]	Emotion Questions	X	X	X

Family cohesion	Brief Family Relationship Scale[30]	Family Relationship Questions	X	X	X
Rumination	Children's Response Style Questionnaire[32]	How do you handle sadness?	X	X	X
Self-efficacy	PROMIS Self-efficacy - Youth[31]	Getting stuff done questions	X	X	X
Decentering	Experiences Questionnaire[33]	Self-awareness Questions	X	X	X
Demographics	Demographics questionnaire	Who are you?	X		
Perceived stress	Perceived Stress Scale-Peds[34]	Stress Questions	X	X	X
COVID anxiety	COVID anxiety-5	COVID anxiety	X	X	X
Anxiety symptoms	PROMIS-25 Pediatric[19]	Health Questions	X	X	X
Executive function	Pediatric Cognitive Function Short Form[35]	Thinking Questions	X	X	X
Parenting monitoring	Parental Monitoring Scale[36]	How much do your parents keep an eye on you?	X	X	X
PARENT SURVEY					
Biologic Trust	Respiratory sinus arrhythmia[13]	Not applicable—assessment in lab	X	X	
Behavioral Trust	Behavioral interaction assessment[14]	Not applicable—assessment in lab	X	X	
Cognitive Trust	Parent Trust of Child Scale—Parent[27]	Parent's Trust of Child Questions	X	X	X
Relationship quality	Inclusion of Other in Self[28]	How close are you with your teen?	X	X	X
Relationship quality	Parent-Child Coercion Scale[37]	Parent-Child Communication Questions	X	X	X
Demographics	Demographic questionnaire	Who are you?	X		
Parenting style	Alabama Parenting Questionnaire-Shor)[38]	Parenting Style Questions	X	X	X
Parent stress	PROMIS Perceived Stress Scale[34]	Stress Questions	X	X	X
General health	PROMIS-25[19]	General Health Questions	X	X	X

Note. B = baseline, 3M = 3 months, 6M = 6 months

We are also providing families with information about free or reduced cost internet access and free internet hot spots in the community (attached). Once restrictions associated with the COVID-19 pandemic are eased, in-person data collection will resume. Parent and adolescent will simultaneously answer questions on separate computers in a private room. This is intended to allow both to answer questions privately and to prevent parents from interfering with adolescent responses. During social distancing due to novel coronavirus-19, we will email a link to the questionnaire to participants. All materials will be assigned a unique number that will be used to link data over time. A master list linking the ID number to the participant's name will be kept in a password-protected computer file, in a locked office, at the local site. This list will be kept entirely separate from the data so that responses cannot be linked to the individual participant.

c. The risks associated with gathering information from participants by properly trained and supervised research assistants are low. Participants may experience discomfort by

some questions assessing stress and depression. In prior research, we have used these measures or similar measures with this adolescent-parent dyad population and found that adolescent-parent dyads were comfortable with the interviews. However, all participants will be instructed that they can stop the interview at any time or can choose to skip any question that they wish. Our investigators and staff are experienced interviewers in research involving adolescent-parent dyads, and we have rarely encountered participant reactions more adverse than transient awkwardness, embarrassment, or mild discomfort. If questionnaires indicate symptoms suggestive of severe depression or suicidal ideation, the results will be reviewed with Dr. Arin Connell, Ph.D. (co-investigator, licensed clinical psychologist, #6732) who will consult with the adolescent and/or parent/guardian to determine whether the adolescent or parent/guardian is in need of a referral for further evaluation and treatment. The nature of this study includes adolescents with a diagnosis of depression. If the adolescent becomes upset during study procedures, a study research assistant and the participant's parent will be available to support and comfort the adolescent participant if needed. The adolescent/parent dyad will be given an information sheet with the number of United Way First Call (211) to access on call mental health professional services in their local area or Cuyahoga County 24-Hour Mental Health Crisis Information and Referral Hotline (216-623-6888). If the participant is unable to be comforted by the research assistant or the parent and further assistance is required, the Mobile Crisis Team from the Cuyahoga County 24-Hour Mental Health Crisis, Information, and Referral Hotline will be contacted immediately.

d. **Cheek swab DNA test**: The cheek swab DNA test is canceled due to COVID-19. The cheek swab DNA test includes swabbing the parent and adolescents' cheek with separate sterile cotton swabs. Participants can remain in the study, but opt out of the DNA test, if they choose. Participants will be assured that we will not use the data for paternity testing. The sensation of a cotton swab in the mouth may feel uncomfortable for some. We will allow participants to swab their own cheek under guidance of study staff, if they prefer.

e. **Saliva sample collection**: The saliva sample portion of the study is canceled due to COVID-19. Saliva will be collected in a tube to measure salivary oxytocin. Fifteen minutes pre/post the dyadic behavioral interaction, measures of salivary oxytocin levels of both adolescents and parents will be collected using Salivattes and stored at -80 degrees centigrade until processed and analyzed. Study staff will provide guidance to participants on how to provide the saliva sample. Spitting into a tube may be uncomfortable for some participants. Participants can remain in the study, but opt out of the salivary sample collection, if they choose.

f. **Behavioral interaction assessment**: The behavioral interaction is currently on pause and will only occur following the easing of restrictions associated with the COVID-19 pandemic. During the behavioral interaction assessment lab visit, adolescents and parents are seated facing each other and will first complete a five-minute paced breathing task, which serves as a baseline period for physiological indices, and four 5 minute discussions tasks on family-related matters. The tasks include discussion of family problems, and planning a positive family activity, and have been used in prior trials and shown to relate to emotion self-regulation capacity and adaptive coping by members of our study team.[28,31] Interaction tasks will be digitally recorded using a Noldus video capture system. The behavioral interaction assessment may seem awkward and uncomfortable to some participants. The paced breathing task and a practice discussion question are intended to help participants acclimate to the behavioral interaction assessment. Participants may opt out of the use of audio/video capture of the

interaction. If participants refuse the use of the audio/video recording, study staff will make notes of the interaction instead.

g. **Respiratory sinus arrhythmia**: The RSA is on pause and will only occur following the easing of restrictions associated with the COVID-19 pandemic. Heart rate and respiration will be collected simultaneously during the paced breathing and discussion tasks, from parent and adolescent, using a Biopac MP150 system and Acqknowledge Software.[72] To collect heart rate and respiratory rate, we will apply cardiac leads to the bare chest of both parent and adolescent. This may be uncomfortable for some participants. To reduce discomfort and maintain privacy, the cardiac leads will be placed on the participants in a private room and by a same gendered study staff member, if requested.

h. **Intervention group protocol**: Due to restrictions associated with the COVID-19 pandemic, we will deliver both types of interventions in remote format wherein parents and adolescents will review video recordings of the materials, engage in exercises, and complete pre- and post-test to ensure engagement. Following the easing of restrictions associated with the COVID-19 pandemic, we will resume offering in-person sessions with parent-adolescents in groups of approximately five dyads. Each of eight 90-minute weekly sessions of the TRUST intervention will include both a trust-building topic and a depression management topic. Trust-building topics include honesty, reliability, and emotional connection.[8] The honesty portion will include discussion and practice of disclosing personal truths and receptivity of others' disclosures. The reliability portion will include discussion and practice of making and keeping promises. The emotional connection portion will include discussion of adolescent-parent similarities and bonding activities like hugging and eye contact. The depression management portion will focus on sleep, stress management, medication adherence, and appointment keeping skills. The intervention will build depression management knowledge, set personal and dyad goals, and practice self-monitoring. Goal-setting and self-monitoring of progress are also forms of making and keeping promises, thus connecting and reinforcing the concepts of trust and depression management techniques. The **Depression Management group** will receive 8 sixty-minute weekly sessions that include the only the depression management training (sleep, stress management, medication adherence, appointment keeping) described above. Both intervention groups will be led by interventionists with health behavior change training.

The interventionist will have a teaching plan with guidelines on time use for TRUST topics. Each session will include a trust-building topic and a depression management topic, a discussion portion and a practice portion. With the trust building portion, we will focus on honesty, reliability, and emotional connection. For example, the Honesty portion will teach adolescent and parent to share personal details about themselves without judging one another. Parents often get upset when their adolescent shares personal details with them and then jump to conclusions, judgment, and reprimands, which breaks down trust. The intervention will discuss this, then have adolescent-parent dyads practice sharing small truths and being receptive to those disclosures. With the Reliability portion, we'll discuss that reliability means following through on your word. Dyads will make small promises to one another, then try to follow through on keeping the promises in the week between sessions. Emotional Connection is built when each person is receptive to disclosures and keeps promises.

With the depression self-management portion, we will focus on stress management, sleep, medication adherence, and appointment keeping only. We will discuss why these topics are important to health and identify ways to improve them. Each adolescent-parent dyad will set goals to improve in each of these areas, then

identify a way to do that. For example, with stress management it could be taking a walk to de-stress, with sleep it might be giving up screen time one hour before bed. Making goals and keeping them is also a form of making promises and keeping them--thus connecting and reinforcing the concepts of trust and a healthy lifestyle.

We will conduct fidelity monitoring of the intervention groups. Each session of the TRUST intervention will be audio-recorded. Half of the sessions will be randomly selected for review using an investigator-developed fidelity checklist composed of the key elements of the intervention [26]. Fidelity will be assessed by checking that each of the assigned topics from the teaching plan are discussed during the appropriate meetings.

This is a social/behavioral research study. No drugs or devices will be tested as interventions with the research participants. No source records, such as medical or educational records, will be used to collect data about participants.

(4) Study Procedures and Time Requirement:

	Estimated time requirement	
Study Procedures	**Group 1**	**Group 2**
Prescreening	5 minutes	5 minutes
Screening	30 minutes	30 minutes
Study Visit 1 (Baseline)	30 minutes	30 minutes
Intervention week 1	45 minutes	1 hours
Intervention week 2	45 minutes	1 hours
Intervention week 3	45 minutes	1 hours
Intervention week 4	45 minutes	1 hours
Intervention week 5	45 minutes	1 hours
Intervention week 6	45 minutes	1 hours
Intervention week 7	45 minutes	1 hours
Intervention week 8	45 minutes	1 hours
Study Visit 2 (3 months)	30 minutes	30 minutes
Study Visit 3 (6 months)	30 minutes	30 minutes
Total	**8 hours 5 minutes**	**10 hours 35 minutes**

ClinicalTrials.gov Information

Has this study been registered on ClinicalTrials.gov?

☒ Yes. Provide the following:

i. The ClinicalTrials.gov identifier: 00220503

ii. Investigator/sponsor responsible for registering: Heather K. Hardin

☐ No. Explain if there are plans to register or why registration is not required.

List of Data to be Collected

1. *Indicate what identifiers you will collect*

☒ Name

☒ Address

☒ Dates related to an individual *(birthdate)*

☒ Telephone number

☐ Fax number

☒ Email address

- ☐ Social security number
- ☐ Medical record number
- ☐ Health plan beneficiary number
- ☐ Account number
- ☐ Certificate/license number
- ☐ Any vehicle or other device serial
- ☐ Device identifiers or serial numbers
- ☐ Web URL
- ☐ Internet protocol (IP) address
- ☒ Finger or voice prints
- ☒ Photographic (video) images
- ☐ Other: Any characteristic that would uniquely identify the individual

Data Analysis Plan

(1) Statistical Analyses. Each participant will be assigned a unique identifier for tracking purposes and all raw data will be uploaded to the secure database in REDCap. We will explore all variables using descriptive statistics. To address the Aims 1-2, we will use a linear mixed effects model. To address Aim 3, we will apply usual mediation techniques.

Confidentiality of Specimens and Banking

Salivary specimens and cheek swabs are canceled due to Covid-19. Specimens collected prior to Covid-19 were handled as follows. Salivary specimens and cheek swabs will be collected and banked until full processing can occur. The specimens will be stored in the Frances Payne Bolton School of Nursing biomarker laboratory. Specimen testing is funded with internal monies; therefore, specimens will not be transferred to other researchers at this time.

Saliva specimens will be obtained from each adolescent at baseline and 3-month data collections. The saliva samples will be collected by study personnel and labeled with the participant's alpha-numeric study identification code. Fifteen minutes pre/post the dyadic behavioral interaction assessment, measures of salivary oxytocin levels of adolescents will be collected using SalivaBio passive drool salivary collection kits (Salimetrics LLC, State College, PA). Salivary samples will immediately be placed on ice, transported to the laboratory by study personnel, and transferred to a locked -80°C freezer until processed and analyzed. Time from collection to freezing will be less than 1 hour. Salivary specimens will be processed per standard operating protocols to minimize non-biological technical bias. Salivary specimens will be stored for approximately 1 year, until enough samples have been collected to fill a single assay plate. Only study personnel will have access to the specimens. The remainder of the specimens will be destroyed after analysis. The salivary oxytocin testing is funded with internal funding and will not be transferred to other researchers.

Cheek swabs obtained by a Registered Nurse research assistant will be collected only a single time during the study and will be used for *OXTR* genotyping. The Registered Nurse research assistant will obtain the cheek swabs, label them with the participant's alpha-numeric study identification code, transport them to the lab at the Case Western Reserve University Frances Payne Bolton School of Nursing, and preserve them in lysis buffer until DNA extraction. *OXTR* rs53576 will be genotyped using the TaqMan genotyping platform. The TaqMan Genotyping Assay and TaqMan Genotyping Master Mix will be ordered from Thermo Fisher Scientific (Thermo Fisher Scientific, Waltham, MA, https://www.fishersci.com). Genotyping will be performed in a 20-µl system containing 10 µl of TaqMan Genotyping Master Mix, 1 µl of

TaqMan Genotyping Assay, and 1 µl genomic DNA using the StepOne Plus real-time PCR system (Applied Biosystems, Foster City, CA). Allele determination will be performed using StepOne Plus software v2.3 (Applied Biosystems). Cheek swab specimens will be stored for up to 10 years and may be used for other genetic analyses. The remainder of the specimens will be destroyed after 10 years or when they are no longer viable. Only study personnel will have access to the specimens. The OXTR genotyping is funded with internal funding and will not be transferred to other researchers. Cheek swabs will be labeled only with study id and date; no master list will be made of identities and no attempt will be made to re-identify the specimens.

Are you storing the specimen for future use for other research projects?

☒ Yes
☐ No

Confidentiality of Data

(1) To maintain the confidentiality of the data, I will use a unique study identifier (not derived from the participants' personal identifiers) to code individuals' data and I will store this ID log separate from study data.

(2) How are you storing your electronic data?

☐ UH Redcap
☒ CWRU Redcap
☐ Secure Research Environment (SRE)
☒ CWRU Box
☐ OnCore
☐ UH Secure Network Drive (S:)
☐ CWRU Secure Network Drive
☐ Other: List storage method and provide justification

(3) ☒ I acknowledge that paper research data and documents will be stored in a double-locked secure environment in the following location:
Location: Locked file cabinet in PI Hardin's locked research office located in the School of Nursing

(4) Data Sharing: N/A

HIPAA Authorization

If you are going to be accessing PHI (Protected Health Information), indicate how HIPAA authorization will be obtained (check all that apply):

☐ HIPAA authorization is in the consent form
☐ Requesting a full or partial waiver of HIPAA for prescreening
☐ Requesting a full or partial waiver of HIPAA

(1) We are not collecting data from a covered entity; therefore, HIPAA authorization is not necessary.
(2) Research records will be kept in a locked file and access will be limited to the researchers. In addition, research guidelines require that we provide access to regulatory bodies such as the

University IRB, regulatory agencies, and the Center for Reducing on Health Disparities at MetroHealth to evaluate the safety of this project.
(3) Personal identifiers will be kept for 6 years after giving study consent, which is approximately 5 years after the study ends and data analysis begins.

Risks to Research Participants

(1) The level of risk from the proposed trial is no more than encountered in daily life and is minimal relative to other clinical trials that test drugs, devices, or medical procedures. Of note, we will not be completing the behavioral interaction, RSA, salivary samples, or cheek swabs portions of the study while restrictions associated with the COVID-19 pandemic are in-place. We will resume this part of our study when public health recommendations allow for this in-person data collection. There is a small risk of loss of confidentiality by participating in this study. Our team takes participant confidentiality serious and implements several safeguards against loss of confidentiality. However, it is possible that being seen on campus with members of our team will identify participants' role in the Level Up Study to passersby.

The risks associated with gathering information from participants by properly trained and supervised research assistants are low. Participants may experience discomfort by some questions assessing stress and depression. In prior research, we have used these measures or similar measures with this adolescent-parent dyad population and found that adolescent-parent dyads were comfortable with the interviews. However, all participants will be instructed that they can stop the interview at any time or can choose to skip any question that they wish. Our investigators and staff are experienced interviewers in research involving adolescent-parent dyads, and we have rarely encountered participant reactions more adverse than transient awkwardness, embarrassment, or mild discomfort. We are prepared to deal with such events and have a protocol that instructs the data collector how to obtain assistance for psychological issues should they arise.

There is the potential for stigmatization due to depression diagnosis; however, measurements are taken in private and all results are reported privately in a sensitive and culturally appropriate manner. The nature of this study includes adolescents with a diagnosis of depression. If the adolescent becomes upset during study procedures, a study research assistant and the participant's parent will be available to support and comfort the adolescent participant if needed. If questionnaires indicate symptoms suggestive of severe depression or suicidal ideation, the results will be reviewed with Dr. Arin Connell, Ph.D. (co-investigator, licensed clinical psychologist, #6732) who will consult with the participant to determine whether the participant is in need of a referral for further evaluation and treatment.
(2) Although this study is deemed as having minimal risk, we recognize there are some unanticipated risks. An example on an unanticipated risk is that participants may be disappointed with the intervention group to which they are assigned.
(3) As a social/behavioral intervention study, no procedure in this study is a risk to an embryo or fetus should the research participant may or may become pregnant.
(4) There are no known risks to others who are not research participants.
(5) Drs. Hardin and Connell have conducted previous research protocols that involve adolescent-parent dyads and have experienced research assistants and established protocols for quality assurance, crisis intervention and referral, as well as initial and ongoing staff training. The research assistants hired for this project will have prior experience working with adolescent-parent dyads. If questionnaires indicate symptoms suggestive of severe depression or suicidal ideation, the results will be reviewed with Dr. Arin Connell, Ph.D. (co-investigator, licensed clinical psychologist, #6732) who will consult with the youth and/or parent/guardian to determine whether the youth or parent/guardian is in need of a referral for further evaluation and treatment.

Provisions to Protect the Privacy Interests of Research Participants

To protect participants' privacy, several measures will be taken. During COVID-19 data collection, adolescents and parents will be encouraged to complete the surveys in private spaces. Following the easing of restrictions associated with the COVID-19 pandemic, in-person data collection will resume and the following precautions will be taken, All study procedures will be carried out in private rooms. As participants are completing questionnaires, study staff will remain available for questions, but avoid moving around the room in any way that would allow the staff to see the participants' questionnaire responses. Both parents and adolescents will receive separate tablet computers to complete the questionnaires simultaneously, so that participants are each engaged with their own questionnaires and promote privacy of the other participant. If participants are uncomfortable with the tablet computer, we will make arrangements to complete the questionnaires by participant's choice of interview by study staff or by paper and pencil. During the cheek swab, participants will be allowed to swab their own mouths with direction from study staff, if the participants' desire. When placing the heart rate monitoring leads on participants' chests for the respiratory sinus arrhythmia testing, this will be done in a private room and by same gendered study staff, if desired by participants. During the behavioral interaction assessment, study staff will remain nearby but step out of the room, in order to help adolescent and parent participants' feel comfortable during the discussion.

Paper and pencil questionnaire completion will be a rare event. In the event of participant's choice or internet connectivity problems, survey data will be collected through paper and pencil surveys. Research staff will be responsible for entering survey data directly into REDCap once internet connectivity has become a non-issue. Paper and pencil surveys will be stored in a locked, filing cabinet in PI Hardin's locked research office. Only key research staff will have access to this office and access to the key to the filing cabinet.

Potential Benefit to Research Participants

Participants participating in this research may learn new skills for better managing their stress and sleep quality; medication adherence and appointment keeping skills may improve their health; and trust-building exercises may improve the quality of the adolescent-parent relationship. These improvements may be short-term or long-term changes. We anticipate that our findings will demonstrate the linkages between a trust-building behavior change strategy and health behavior change that will help adolescents and parents improve their health.

Withdrawal of Research Participants

Research participants will be withdrawn from the intervention without their consent under these circumstances:

1. participants display disruptive behavior during the group intervention sessions,
2. evidence of abuse between parent and adolescent dyad, or
3. indication that a participant may be a harm to themselves or others.

In the event that participants are removed from the intervention, PI Hardin will notify participants of their removal. Participant dyads will receive a closeout packet, which will contain a list of community resources for further depression symptom management treatment. Participants will also receive study personnel contact information to follow up on study outcomes. At this time, we will also update participants' contact information and ask if they are willing to be contacted for further study visits, if appropriate.

Alternatives to Participation

(1) No one will be required to participate in our study. Other available clinical treats are individual, family, or group therapy. Community self-management treatments available include stress management classes, such as yoga.
(2) Standard of care therapy, including depression medication and counseling, should be continued regardless of participation. Self-management treatments are considered adjuvant to clinical treatment. We anticipate and encourage our participants to continue standard of care therapy.
(3) Since self-management training is adjuvant to standard of care treatment, another option is to not participate.

Costs to Research Participants
(1) There are no costs to participation in this study. Our study compensates participants for their time and travel costs.
(2) Participants' health insurance will not be charged for any services provided in this study.
(3) This study will pay for the costs of transportation to study visits; cost of group intervention sessions including healthy snacks and small gifts; time to complete study visits; costs of surveys; and costs of respiratory sinus arrhythmia/behavioral interaction testing.

Research Participant Compensation
Participation in the study requires time and effort. Because of this, compensation for time spent completing the study surveys, respiratory sinus arrhythmia (RSA), and behavioral interaction assessment will be provided. Each adolescent and parent participant will receive a $25 gift card for completing each structured interview and each behavioral interaction assessment with RSA. Thus, adolescent-parent dyad participants who complete all interviews ($150 total) and undergo two behavioral interactions with RSA ($100 total) may receive a total up to $250. This amount is consistent with our previous work and is not perceived to be coercive by members of the community advisory board.

During the intervention groups, participants may receive small gifts (each valued at less than $15) intended to assist them in meeting intervention goals. Participants may receive small gifts such as an eye mask to promote sleep, a 7-day medication box to promote medication adherence, a book about parent/teen communication, and a yoga mat. Healthy snacks will be made available to participants during the group sessions. A schedule of compensation is listed below.

	Compensation	
Study Procedures	**Adolescent**	**Parent**
Study Visit 1 (Baseline) Questionnaires RSA/behavioral interaction	Transportation (paused) **$25 gift card** $25 gift card (paused)	Transportation (paused) **$25 gift card** $25 gift card (paused)
Intervention week 1	Small gifts	Small gifts
Intervention week 2	Small gifts	Small gifts
Intervention week 3	Small gifts	Small gifts
Intervention week 4	Small gifts	Small gifts
Intervention week 5	Small gifts	Small gifts
Intervention week 6	Small gifts	Small gifts
Intervention week 7	Small gifts	Small gifts
Intervention week 8	Small gifts	Small gifts
Study Visit 2 (3 months) Questionnaires RSA/behavioral interaction	Transportation (paused) **$25 gift card** $25 gift card (paused)	Transportation (paused) **$25 gift card** $25 gift card (paused)
Study Visit 3 (6 months) Questionnaires	Transportation (paused) **$25 gift card**	Transportation (paused) **$25 gift card**
Total	**$75 gift cards + small gifts;** transportation + snacks (paused)	**$75 gift cards + small gifts;** transportation + snacks (paused)

Compensation for Research Related Injury

Describe who will pay for the costs of medical treatment and/or compensation in the event of a research related injury:

☐ Funding agency is providing some/all payment for injury

☒ Funding agency is providing no payment for injury

☐ Not applicable

Provisions to Monitor the Data to Ensure the Safety of Research Participants

(1) The data and safety monitoring plan for this study includes an official committee. The committee members who are outside the study team will review data on the study as provided by Drs. Hardin and Connell and conduct random auditing of the research records to assess study safety and regulatory compliance. Twice annually throughout the project, this committee will review data on this study regarding 1) study safety, including auditing selected cases for compliance with IRB requirements, conformance with informed consent requirements, verification of source documents, and investigator compliance; 2) minimizing research-associated risk; and 3) protecting the confidentiality of participant data. In addition, it will review all causes of mortality and issues with participation. The rate of recruitment refusal (percent and reasons) and participant attrition (percent and reasons) will be tracked and reported at these reviews. Differential attrition from the intervention arms also will be monitored. If concerns or problems are identified by the Data and Safety Monitoring Committee (DSMC), they will be reported to the IRB and the sponsor via email by Dr. Hardin and Dr. Douglas, respectively, within 3 business days after they are identified. If there are recommendations made by the DSMC, the action plan for response or notice of any actions taken by the IRB regarding the research and any responses to those actions will be provided to sponsor officials within 2 weeks.

At the onset and across the duration of the study, all staff and Investigators will have instructional review of the nature and types of unanticipated and adverse events as described

by the sponsor and the CWRU IRB. As they occur, all unanticipated events and adverse events will immediately be reported to the PI who will report them to the IRB according to the IRB protocol reporting procedures for both serious and non-serious adverse event and unanticipated problem reporting. These will be summarized in the twice annual reports to the DSMC. Annual progress reports to the IRB and the sponsor will include a summary of the DSMC's activities and findings as well as any adverse events regarding human participants. Program Officials of the sponsor will be informed in a timely manner (3 business days) of unanticipated problems (e.g., a data breach) or unexpected serious adverse events that may be related to the study protocol or IRB-approved revisions to the study protocol that indicate a change in risk for participants.

(2) A Data and Safety Monitoring Committee (DSMC) will be established for this study. This DSMC will independent of the study sponsor and will meet every 6 months of the study. Dr. Daly will chair the committee and be responsible to submit reports to the study sponsor and IRB within 2 weeks of the meeting. DSMC members include:

Dr. Sara Douglas, an experienced family researcher (sld4@case.edu)
Dr. Val Toly, an NIH-funded researcher with parent/child dyads (vab@case.edu)
Dr. Chris Burant, a statistician not involved with the project (cxb43@case.edu)
Dr. Michael Decker, neuroscience of health behavior researcher (mjd6@case.edu)
Dr. Heather Hardin, PI (hkh10@case.edu)
Dr. Arin Connell, Co-I (arin.connell@case.edu)

Community-Based Participatory Research: N/A
Non-Local Recruitment Methods for Multi-Site Studies: N/A
Multi-Site Research Communication Plan: N/A
Drugs or Devices: N/A

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