PROTOCOL AND STATISTICAL ANALYSIS PLAN

An Interactive Education Program to Reduce High Risk Behavior in Adolescents Phase I (1R42HD110333-01)

NCT05607784

09/27/2022

Note. We have highlighted information in the protocol relating to Phase 2 activities in grey. Such information is included for reference but does not pertain to the current package submission. We are only seeking approval for Phase 1 activities at this time.

SIGNIFICANCE

Early Adolescence is a Critical Time for Sexual Health Intervention. Partnered sexual behaviors often begin in early adolescence (ages 12-14 years). Youth Risk Behavior Surveillance data indicate that while only 3% of adolescents have had intercourse before age 13, by 10th grade, over a third have had sex, highlighting the importance of the early adolescent years.[2] The behavioral patterns established in adolescence have powerful implications for current and future health,[3] yet CDC data indicate that only 53% of Americans receive formal sex education before age 18.[144] Those who have sex in early adolescence continue to exhibit greater sex risk (more sex partners, substance use with sex, less condom use) than their peers as they age,[4-6] suggesting a persistent lifestyle pattern with negative outcomes. Indeed, early sexual debut is associated with more unintended pregnancies[7]**Error! Hyperlink reference not valid.** and STIs.[8] Early adolescent girls who have sex are also less likely to use contraception and wait longer to start doing so.[9] These effects extend to other health behaviors; early adolescent sex predicts higher frequency of alcohol use at age 16 and problematic use at age 22,[10] even controlling for confounds such as puberty, parental monitoring, and antisocial behavior. Delaying sexual initiation and enhancing skills related to decision making can have profound effects on long-term health.

Early adolescence is a critical time to intervene, as attitudes about sex change dramatically in this developmental window.[11] Cognitions about sex change before adolescents engage in sex,[11] and values and intentions in early adolescence are predictive of sex in middle adolescence.[12] The relationship between positive feelings about sex and sexual initiation is strongest when adolescents are younger.[13] Intervening during early adolescence is an opportunity to target sexual values, cognitions, and feelings before they are well established.

Biological changes in early adolescence also put youth at risk via both sexual development and emotion regulation (ER). Physical changes during puberty can elicit sexual advances, and hormonal changes are linked to adolescent sexual behavior.[14,15] Relatedly, brain development in early adolescence may affect skills related to self-regulation, often leading to impulsive decisions. MRI data show that teens' frontal lobes, which manage executive functions such as impulse control, ER, and reasoning, mature later than other brain areas.[16,17] For example, young adolescents' performances on tasks of emotion recognition tend to be poor in early adolescence, and this poor performance has been linked to high activation of the amygdala and low activation of the frontal lobes when processing these tasks. Performance improves as teens age, when their frontal lobes become more active in this processing.[18] These difficulties in emotion processing likely impact early teens' understanding of their own (and others') feelings, making it difficult to recognize and regulate emotions in affect-laden situations, such as those involving sex or substance use (which has been shown to influence sexual risk).[19-21] Indeed, poor ER in adolescence is related to more sex partners[22] and more substance use.[23-25] Because psychosocial and biological factors predispose early adolescents to emotion dysregulation and sexual risk, improving ER during this developmental period is likely to affect their lifetime health trajectories.

Emotion Regulation (ER) Mitigates Risky Behavior. The most widely used and supported model[26] of ER is Gross' process model,[27] which conceptualizes ER as the process of "shaping which emotions one has, when one has them, and how one experiences or expresses these emotions."[27] ER uses multiple skills, including identifying affect in others, recognizing one's own emotions, and using strategies to manage one's emotional response. Targeted emotions are often negative, but positive emotions can require regulation too, as when curiosity or attraction leads to sex. The process model identifies five families of ER strategies: situation selection, situation modification, attentional deployment, cognitive change, and response modulation. These target emotion management at various points in the emotion process (e.g., attending to a stimulus, appraising a stimulus, physical/ cognitive responses).

Research has demonstrated that when people experience high levels of negative emotion, they act impulsively and prioritize short-term soothing to decrease distress.[28] Indeed, many studies document a lack of relationship between knowledge of potential negative outcomes and behavior,[29-31] suggesting that other processes interfere with the use of facts. Teens who engage in risk behaviors are more likely to report difficulty with ER,[32] and better ER has been longitudinally associated with less adolescent risk taking.[33] Moreover, poorer self-regulation of emotions and behavior in early adolescence is associated with sexual risk in later adolescence.[22,34] These relationships likely exist because adolescents' ER difficulties increase the likelihood of impulsive self-soothing behaviors, such as sex. However, this work is hampered by a preponderance of associational studies and few developmentally tailored interventions that examine ER.

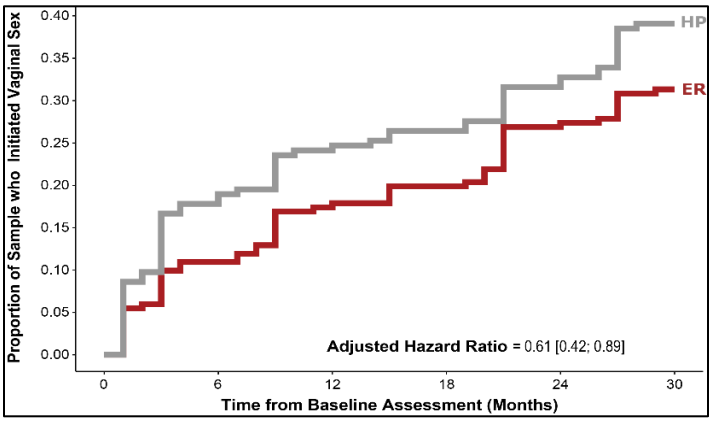
Most sexual risk prevention interventions target knowledge and behavioral skills.[35] Without ER skills training, these approaches are unlikely to influence the ways in which teens respond to risk situations. Poor ER may short-circuit effective use of knowledge and behavioral skills in risk situations, which are typically marked by high emotionality. This is particularly important because decision making surrounding risky sexual behavior

occurs during strong positive *and* negative emotions. ER training addresses the heightened emotions of these situations, enabling teens to implement knowledge and skills to better navigate these moments. The proposed intervention moves the field forward by focusing on emotion regulation to enhance sexual health education to reduce negative health outcomes. While a few digital sexual health interventions have been developed for adolescents, they do not focus on ER, and do not show impact on sexual initiation,[36-38] leaving a gap in the field. Other recent interventions have focused on brief face-to-face interventions with parents to encourage sexual health communication[39,40] or group educational interventions for high risk adolescent subgroups,[19,41] but they do not target ER. Similarly, programs targeting social emotional learning (SEL) exist, but these typically have lengthy curricula administered in groups, with a wide range of goals (e.g., organizational skills, personal goal setting, compassion, conflict resolution) that do not explicitly connect to health behaviors. These broad reaching programs serve important but distinct functions to those directly teaching efficacious, evidence-based ER skills. Without ER skills training, sexual health education is unlikely to influence the ways in which teens act in high-emotion risk situations. Learning facts is not enough; ER training teaches adolescents to regulate emotions in ways that allow them to implement other skills (e.g., communication skills, condom use skills) to positively influence sexual health and outcomes.

Targeting ER during early adolescence, when ER and cognitions about sex are developing and dynamically interacting, increases the likelihood of improving ER throughout adolescence and increasing healthy decision making. While a few other group-based programs have been developed to specifically target ER constructs (rather than broader SEL) among adolescents[42-44], the proposed program goes beyond existing ones by directly relating ER to sexual behavior and eliminating challenges inherent in group-based interventions.[45] It is based on the only proven efficacious program to target ER and demonstrate longitudinal impact on sexual risk reduction among adolescents from middle school into high school (Project TRAC). Our team has demonstrated that ER skills can be effectively taught at the developmental level of early adolescence and that these skills change sexual behavior over 2.5-year follow-up. We seek to extend this work by completing the technology translation of our novel, effective intervention and testing it in a randomized controlled trial.

Preliminary Studies. Project TRAC (Talking about Risk and Adolescent Choices; R34 MH07875, R01 NR011906) is an efficacious, developmentally tailored intervention teaching ER skills for early adolescents that focuses on strategies to use in moments of sexual decision making (e.g., peer pressure to have sex, decisions to use a condom). It contains 3 main components: ER training, sex education, and the link between emotions and risk behaviors. The program was developed using qualitative research with early adolescents[46] and emphasizes emotion recognition and labeling, connecting emotions and behavior, and the use of ER strategies (Get Out, Let It Out, and Think It Out) consistent with Gross' process model. Sexual health information, including sexual development, safer sexual behaviors, and condoms, is also included in the program. Project TRAC integrates ER into all topics (e.g., discomfort with condoms, managing emotions that occur in sexual possibility situations, managing peer pressure) as the key construct that is absent from previous adolescent sexual health interventions. In an efficacy trial (n=420) of urban early adolescents (ages 12-14), **Project TRAC's ER condition outperformed a rigorously matched health promotion (HP) comparison, which provided sexual and general health education without ER content, in delaying sexual initiation and reducing sexual risk.[47-49]** The sample was diverse in terms of ethnicity (38% Latino), race (28% Black), and SES (30% ≤ $20,000) and balanced in terms of gender (53% male). The study targeted those at highest risk due to mental health symptoms. There were no significant differences between the conditions on baseline demographics, sexual activity, emotional and behavioral symptoms, or attendance at the 12 after school sessions (9.1 vs. 9.0).

Figure 1. TRAC Sexual Initiation by Intervention



The TRAC ER condition was efficacious in slowing the time to sexual initiation. Time-to-event analyses showed that ER participants were significantly less likely to begin having vaginal sex (the primary outcome) over the 1-year follow-up (Adjusted Hazard Ratio [AHR]=.58 [95% CI: .36 to .94])[49] and this effect maintained to 30 months (AHR=.61 [.42 to .89];[47] See **Figure 1**). Further analyses indicate relatively similar effects between those with and without clinically significant mental health symptoms ($AHR_{sub-clinical}$= .60 [.31-1.17]; $AHR_{clinical}$=.65 [.42-.99][47]), suggesting a promising intervention that works for multiple audiences, including those at higher risk.

The intervention also reduced sexual risk behavior. ER participants reported significantly fewer condomless vaginal or anal sex acts (Adjusted Rate Ratio [ARR]= .36 (.14-.90) and fewer total vaginal or anal sex

acts (ARR=.39 [.20-.77]). They also were less likely than HP to endorse multiple partners (Adjusted Odds Ratio [AOR]=.54 [.30-.99]) or substance use before sex (AOR=.42 [.23-.75] during the 30-month follow up.[5] In short, TRAC ER delayed sexual initiation and reduced sexual risk when youth became sexually active.

TRAC ER also affected measures of ER abilities, the targeted mechanism. On a computerized measure of distress tolerance, ER participants were more likely to persist through 80% of the task than those in HP (OR= 1.55, *p*= .05), suggesting better ER skills. Similarly, on a validated task of emotion recognition[49,50] ER participants correctly labeled more emotions based on facial expressions than HP (Rate Ratio= 1.10, *p*<.01).[49] These findings provide performance-based evidence of the efficacy of TRAC ER in affecting emotional competence that correspond to adolescent self-reports of greater use of ER strategies, Cohen's *d*= .30 [.25-.34].[48]

Barriers to Implementation and Solutions. TRAC ER reduces adolescent sexual risk, but is time-, resource-, and training-intensive, and thus possesses challenges to dissemination. Its interactive activities were designed for coordinated, small groups and require significant facilitator training in ER concepts. Our school partners have indicated that while they want to continue offering this program, these challenges are prohibitive. Indeed, it is common for evidence-based interventions (EBIs) to encounter problems during broader dissemination due to passive diffusion techniques.[51-53] Active techniques, such as technology use, offer an opportunity to expand EBI reach.[54-56] The mood and anxiety literatures for both adults and children have demonstrated that the translation of traditionally delivered EBIs to technology 1) can be effective,[57-67] 2) has high feasibility and acceptability,[68-70] and 3) can achieve high retention and adherence.[41, 66, 69, 70] Technology is nearly ubiquitous in teens' lives, and over 90% report playing video games.[71] Further, middle schoolers' preferred device for learning at school is tablets.[72] A tablet-based adaptation of TRAC offers many advantages over group-based training. Logistically, a tablet intervention reduces staff and training in addition to long-term costs as tablets become more accessible. For learning uptake, tablet administration provides all individuals opportunities to practice skills, whereas the group format often could not accommodate practice for everyone. It also provides individualized feedback at the participant's pace, improving comprehension, and allows evaluation of interaction with the program. Scheduling barriers are removed, so participants do not miss groups and thus receive all content. Finally, some adolescents may prefer sexual health content that is provided in a less public setting than group. Findings for the preliminary development of an internet-based TRAC (iTRAC) support that the ER constructs can be taught through these games and that early adolescents liked it. In fact, as expected, findings support that our tablet-based intervention had stronger effects on ER constructs than the group format.

iTRAC Pilot Study (R21 HD089979). To establish that the ER skills training from TRAC ER could be effectively translated to a game format, the investigative team completed a study to 1) translate the ER components of TRAC ER into interactive web app activities, 2) assess usability and acceptability, and 3) conduct a small, randomized trial to assess intervention feasibility and the impact on ER constructs. Due to the focus on demonstrating feasibility and preliminary efficacy of digital ER training, as well as the scope of funding, sexual health components were not developed. With the help of two youth advisory boards (YABs; one male, one female) and input from an expert panel (psychologists and school professionals), TRAC ER components (only) were adapted to develop the foundation of an internet-based TRAC (see **Table 1**). With guidance from the YABs (14 meetings) and expert panel (3 meetings), activities comprising four 30- to 45-minute modules were developed to target TRAC's core ER constructs. Using YAB feedback, an engaging space theme was chosen. Users are "cadets" in a mandatory training on a planet in which the young aliens are making unhealthy decisions because of unmanaged feelings; they must complete a series of challenges to learn ER skills. After the translation phase, two rounds of acceptability testing were conducted with ten more 7th graders to incorporate their feedback on program functionality, usability, and acceptability. The iTRAC modules were judged to be easy to use and acceptable, with average ratings of 4.7 (on a 5-point scale) for ease of use, 4.3 for information helpfulness, and 4.3 for "overall experience." After establishing usability and acceptability, 85 7th graders (58% female; 33% White) were randomized to iTRAC or a waitlist control. Participants completed study procedures after school under supervision. Modules were completed about 1 week apart. This format proved highly feasible; 88% (37/42) of those randomized to iTRAC completed all 4 modules (93% completed at least 3).

Results from the final, 3-month follow-up showed moderate to strong effect sizes on ER constructs (*d*=.36-.72), **stronger than the small to moderate effect sizes on ER measures observed in the original TRAC trial, suggesting better efficacy on ER for the tablet-based intervention.** Specifically, emotional competence for ER participants improved relative to the control group on scales assessing belief in emotions as malleable (Implicit Theories of Emotion Scale; *d*=.72), emotional self-efficacy (Children's Self-Efficacy Questionnaire; *d*=.63), emotional awareness (Difficulties in Emotion Regulation Scale (DERS); *d*=.59), access to ER

strategies (DERS; *d*=.36), and use of ER strategies taught in TRAC (Emotion Regulation Behaviors Scale-Revised (ERBS-R); *d*=.45). These data indicate that teaching TRAC ER's constructs in a technology format can affect emotional awareness and regulation in this developmental period. The proposed STTR will improve upon the rigor of the pilot R21 by completing the iTRAC program to include the sexual health content and content linking ER to sexual health from the original program. It will evaluate its ability to influence self-efficacy for sexual risk prevention, a key construct related to sexual risk among adolescents. The study will also collect preliminary data regarding whether it delays sex, which was not collected during the short pilot study. The completion of iTRAC to include sex education and its content linking ER to health represents a novel, efficacious strategy (ER) for promoting healthy behaviors that can reach a wider audience than group-based interventions and has substantial commercialization potential given societal interest in healthy sexual development to avoid unintended pregnancy, relationship violence, and sexually transmitted diseases in adolescence and beyond.

TABLE 1: Content of developed iTRAC game modules

Module	Constructs	Sample Activities
1	Introduce feeling and behavior connection Develop emotion vocabulary Expand emotion knowledge Identify emotions in others Connect somatic cues to emotions	Connect feelings to behavior through a frustrating shape matching game Brainstorm emotion words Decide which statements about emotions are true/false Determine others' feelings based on body cues displayed in vignettes Identify somatic cues for personal emotional experiences
2	Connect feelings to behavior in others Connect feelings to behavior in self Recognize triggers for feelings Identify personal triggers Introduce model: Triggers, feelings, actions	Identify how feelings may lead to unhealthy/risky behaviors Identify feelings that cause their own regretful/troublesome actions Label triggers for risk behaviors illustrated in vignettes Identify their own triggers for problematic behaviors Prevent triggers from increasing emotional intensity in a Pong-like video game
3	Introduce ER strategies Get Out Let It Out Think It Out Practice ER strategies	Separate healthy ER behaviors from unhealthy ones Practice Get Out (i.e., getting mind off triggers) with images that elicit disgust Practice Let It Out (i.e., deep breathing, venting) while playing a timed game Practice Think It Out during an emotionally challenging sad video Integrate all three strategies (metaphorically) during a video game to keep their spaceship at a navigable speed
4	Connect ER strategies to desirable outcomes Apply ER strategies Consider ER strategies for personal situations	Practice using ER strategies and observing resulting outcomes Apply newly acquired ER skills to frustrating game from Module 1 Identify future personalized risk situation and apply ER model

History of successful collaboration between the study teams. Dr. Houck has collaborated with Klein Buendel on three previous federally-funded projects involving the creation of digital products teaching ER skills to adolescents (2014-MU-CX-0002, R21 HD 089979, R01 HD 097126). These teams have established work processes that have led to successful completion of these projects that was built on a foundation of communication of the sophisticated concepts of ER and digital translation of behavioral interventions. Similarly, the Rhode Island Hospital (RIH) team has a 20-year history of collaboration with Dr. Hadley, previously at RIH and now at the University of Oregon, with whom they continue to collaborate (R01 HD 097126; R01 DA 050603).

INNOVATION

Integrating ER Training in Sexual Health Education for Early Adolescents: Project TRAC innovated the field as the first program to target ER in the context of sexual risk for early adolescents, leading to positive sexual health outcomes. Although ER is touted as a promising approach for health interventions (primarily from work with preschoolers or clinical adults),[73,74] it has been rarely implemented in sexual risk prevention, which has typically focused on cognitions or skill building,[45,75] thus weakening the rigor of previous prevention research**Error! Hyperlink reference not valid.**. Only two other programs[76, 77] have used ER to address sexual risk; both targeted older teens with severe mental health problems in group formats. While a few other group-based programs have been developed to target ER constructs generally (e.g., Learning to Breathe,[42] Mindfulness-based cognitive behavioral therapy[78]), TRAC goes beyond existing programs by directly relating ER to sexual health.

While we recognize that digitizing an efficacious in-person intervention is not innovative in itself, creating a marketable tool that can be used by schools and/or other agencies and does not require staff training to administer does represent an innovation to the field and the commercial landscape. Although there are a number of programs designed to scaffold Social Emotional Learning (SEL) within school settings, the vast majority are resource intensive, require trained facilitators, and do not integrate sexual health education. A search of 61 of the most popular SEL programs (most of which are focused on SEL constructs that emphasize social skills for positive school climate) indicates that about half (31) distribute materials relevant to early adolescents. Of

those, only 12 are primarily web-based, and only one (Get Real) focuses on sexual risk behaviors[79]. Though there are significant distinctions that set iTRAC-Sexual Risk Prevention (SRP) apart from this program, most notable is iTRAC's focus on teaching ER skills and practicing those skills within the program. Get Real describes itself as comprehensive sexual education that includes elements of SEL such as "relational skill-building," but does not teach ER skills. iTRAC has innovated the teaching of ER skills through technology by including activities that provide opportunities to regulate emotions through experiences that evoke feelings (e.g., watching a sad video clip, looking at "gross" pictures, playing stressful video games while receiving negative feedback) while coaching participants to use the strategies they have been taught. In this way, teens develop self-efficacy for emotion regulation, which is key to its use in daily life and is reflected in the moderate effect sizes observed in adolescents' self-efficacy for emotion regulation (SEQ; *d*=.63), beliefs that they are able to change their emotions (ITES; *d*=.72), and their use of the strategies taught (ERBS-R; *d*=.45). iTRAC-SRP will further enhance these opportunities by connecting ER skills to sexual situations.

For example, standard sexual health education includes learning about reproductive anatomy of both sexes with visual aids for understanding. This often elicits feelings of discomfort that can interfere with engagement with programs and, thus, knowledge acquisition. Connecting the ER strategies learned in the program to this content may enhance understanding and improve application of this information to later sexual health content. Other examples of connecting ER to sexual health education include recognizing and regulating emotions evoked when learning how to use a condom or managing emotions during conversations with partners in which one is negotiating sex or condom use. Explicitly making these connections for young adolescents, before patterns of behavior around sex are entrenched, can improve the likelihood that they will apply the ER skills they are learning to sexual situations. Sexual activity is an emotional experience for people, especially in the developmental period of adolescence, and the absence of emotion regulation skill building in sexual health education represents a key opportunity for innovation.

COMMERCIAL POTENTIAL

iTRAC-SRP has strong commercial potential, having few direct competitors in the diverse landscape of SEL and ER curricula for middle school students (see Commercialization Plan). The vast majority of existing programs are resource-intensive, require trained facilitators, and do not integrate sexual health education. Foresight Science & Technology, Inc. will serve as a Technical and Business Assistance vendor for this Fast-Track application. Additionally, we secured a letter of interest from Cranston Public School District to aid in implementation of research activities as well as evaluate the program for future adoption (see Letters of Support).

RESEARCH PLAN

We propose a Fast-Track STTR research project. We have already developed the efficacious iTRAC intervention to enhance emotion regulation competencies (based on the original efficacious group intervention). This was well-received and resulted in high uptake, even without the sexual health content (which is often of high interest to middle schoolers). Thus, we believe the potential feasibility of iTRAC-SRP (with its sexual health content) is high. We propose to achieve Phase 1 milestones of conducting focus groups with advisory boards, updating the TRAC sexual health content using current sexual health education standards, creating prototypes of the iTRAC-SRP intervention and receiving approval from the advisory boards and creating a specifications document that will guide Phase 2 production. Milestones in Phase 2 include full production of iTRAC-SRP followed by acceptability testing with 16 students and a randomized trial with 120 more.

Research Team: The investigative team brings a wealth of complementary experience to their roles (see **Biosketches**). Drs. Houck and Hadley developed TRAC ER and collaborated with Klein Buendel on the development and pilot testing of iTRAC, providing experience with the procedures of the proposed application. Dr. Houck has successfully recruited and retained participants for several middle school-based projects, including the pilot. Each investigator brings necessary expertise. Dr. Houck will oversee the adaptation and the clinical trial with expertise in ER interventions and early adolescence. Dr. Hadley will assist in the translation of the remaining content as well as assist in the oversight of the clinical trial design and execution. Dr. Barker will direct the statistical analyses. Ms. Berteletti will contribute expertise in the technology transfer of interventions. She will oversee the KB development team during the Translation phase as well as during the management of the intervention during the RCT. Dr. Houck and Ms. Berteletti have collaborated previously on an intervention to prevent adolescent dating violence (R01 HD097126) that integrated emotion regulation concepts into health behavior content. Thus, we are uniquely positioned to successfully achieve the goals of this program.

Overview of Fast-Track Research: To fill a need in the area of sexual education, which fails to integrate emotion regulation skills training, the goal of this study is to complete adaptation of TRAC to a web app format and assess its efficacy for improving self-efficacy for sexual risk prevention behaviors (e.g., sexual refusal, condom use). Consistent with the process of the pilot study (R21 HD089799), this will be accomplished through three stages. In the Translation Stage (Phase 1), the remaining core constructs of the original TRAC

sessions will be adapted and iteratively reviewed by community advisory panels (2 adolescent advisory boards, 1 expert panel of health professionals). In the Acceptability Testing Stage (Phase 2), participants (n=16) will provide feedback on acceptability and usability for the completed iTRAC for Sexual Risk Prevention (iTRAC-SRP), followed by revisions. Finally, the RCT Stage (Phase 2) will individually randomize 120 participants to iTRAC-SRP or a waitlist control group. Teens will complete 8 tablet-based modules after school in small, monitored groups. Adolescent assessments (baseline, post-intervention, 6-month follow-up) will include computer-administered self-interviews (ACASI) and computerized performance tasks. Parents will also complete ratings of adolescent ER. The effect size of iTRAC-SRP relative to the waitlist control group will be examined, and results will be published. See **Timeline**.

Settings and Participants (for both Phases 1 and 2): Subjects will be recruited from four public schools in Providence County, which is rated a Level 1 Urban Influence Code by the U.S.D.A. Health and Education Professionals Panel (HEPP) members in Phase 1 will also be recruited through a Rhode Island Department of Health (RIDOH) school nurses listserv and the Planned Parenthood Federation of America. Eligibility criteria will include 1) attending the 7th grade and 2) being 12-14 years of age. Adolescents will be excluded if they are unable to read at a 4th grade level, have a sibling who has participated in the program, or have developmental delays. The proposed schools have previously participated in our studies and are familiar with our procedures (see **Letters**). Racial and ethnic minorities represent 50% of students, and 45% are from socioeconomically disadvantaged homes. Thus, these data will generalize to large segments of the population. Together, these schools serve over 750 7th graders each year. The RCT will enroll 120 participants (and their parents), requiring a recruitment rate of 16%. This is feasible; our rate of recruitment in Project TRAC was 40% from a sample that presented additional challenges (i.e., teens with mental health symptoms), and the pilot study recruited 86 students in 4 months from fewer schools (see **Recruitment**).

Overview of Phase 1: Translation Stage (months 1-12): This phase will complete the TRAC adaptation to a web app. The pilot study (R21 HD089979) effectively translated the ER content of TRAC (see **Table 1**) and the same procedures will be used to translate the remaining content. In month 1, protocols will be reviewed and approved by the Institutional Review Boards. In months 1-4, content will be reviewed and advisory boards will participate in focus groups to guide development of iTRAC-SRP. Wireframe prototypes will be developed in months 5-8. Advisory boards will review prototypes and provide approval of feasibility and acceptability in months 9-12. Finally, a specifications document will be created in month 12 to guide full development in Phase 2, if approved by the advisory boards.

Phase 1a- Sexual Risk Prevention Content Development Updates: The TRAC content to be translated will include sexual health information such as reproductive anatomy, pubertal development, STIs, sexual identity, pregnancy, abstinence, condom use and contraception, accessing healthcare, and sexual behaviors that confer risk of STIs. TRAC content will be updated with consideration of the National Sex Education Standards (NSES) published by the Focus on Sex Education Initiative[80], which emphasize functional skills through a lens that recognizes the influences of inclusivity, intersectionality, trauma, and social justice. Other sources will be consulted (e.g., Gender, Sexuality & Inclusive Sex Education Tip Sheet[81], Vermont Agency of Education Sexual Health Education Resource Guide)[82] as well as input from the HEPP of middle school health professionals. This information will guide decisions related to adapting sexual health content for iTRAC-SRP and will ensure consistency with professional recommendations for inclusive sexuality education. Possible technology translations include a digital anatomy game in which participants are asked to label body parts and match their biological functions and a game in which teens correctly order videos of steps for condom use. Similarly, content connecting emotions and sexual behavior from the TRAC intervention remains to be translated. Examples include the influence of sexuality in the media on feelings, attitudes, and behavior; emotions' influences on decisions to have sex and/or use condoms; and the influence of perceived peer norms on emotions and their influence on risk behaviors. Other content includes connecting these concepts with the ER strategies taught in the intervention. For example, an activity might include coaching participants to use previously learned ER strategies while watching a video in which a condom is correctly placed on a plastic penis model, which can be dysregulating to some and interfere with learning in many settings. As in the R21 iTRAC pilot, games, puzzles, quizzes, and video scenarios used in the original TRAC intervention to convey these concepts will serve as the starting point for translation ideas with the advisory groups for the current study. Per NSES recommendations, inclusive language that recognizes the spectrum of gender and sexuality will be used throughout. Further, we will not be including content that may be upsetting for individuals with a history of trauma (e.g., descriptions of sexual violence), within this digital program (See also *Trauma-informed Approach* in **Human Subjects**).

Deliverable 1: A summary report of the recommended content based on review of sexual education standards, integrated with recommendations from advisory groups, will be developed.

Phase 1b- Formative Research through Advisory Focus Groups: The iTRAC program created during the pilot R21 study was developed using principles consistent with Designing for Dissemination (D4D), which

promotes the design of interventions with consideration of the elements most important to external validity.[83] Stakeholders from the target population (early adolescents) were included as key advisors in the adaptation of the program and testing of delivery approaches (after school). This proposal will continue this approach and form a Health and Education Professionals Panel (HEPP) of middle school health professionals to complement two Adolescent Advisory Boards (AABs; 1 male, 1 female, n=16) during translation. Research summaries will also be generated to communicate with participating communities. Using these recommended D4D processes, the research will be better positioned for dissemination (and commercialization).

Content translation will be guided by the AABs, who will meet 2 times to assist with brainstorming translation of content and 2 times to review the wireframe prototypes generated from that process. AABs will contribute ideas for translation, provide feedback about appeal, and attend to cultural, developmental, and gender considerations. The HEPP will provide feedback on the proposed content and ensure contextual acceptability (i.e., schools). Each time an AAB or HEPP meeting is scheduled, participants will be notified in advance of the time, data, and location to minimize conflicts. At least 50% of participants will need to indicate their ability to attend each meeting. Otherwise, meetings will be rescheduled for a more convenient time. If municipal, state, or federal guidelines prohibit face to face communication, or if it is not logistically feasible to get the majority of participants together in the same physical space, AAB and HEPP meetings will be conducted virtually using secure video-conferencing technology. Research staff will provide portable wireless internet and a video-compliant device to all participants who require them in order to fully participate. As in the R21, the design development cycles will begin with advisory focus group feedback about how the existing activities convey the content (i.e., what and how they are learning). They will advise on activity design for the remaining content (sexual health and content connecting this with ER) to ensure these are engaging, appropriate, and informative. They will also provide perspectives about design, structure, navigability, and approach. Established protocols, successful in previous projects, will be used and led by Dr. Houck. Groups will be recorded, transcribed, and analyzed for content and themes, as in the pilot.

Deliverable 2: A report of the focus group data summarizing and integrating recommendations for the development of remaining modules will be created.

Phase 1c- Prototype Development: *Theoretical frameworks.* The technology design process will use a multi-theoretical framework to guide production. Persuasive System Design (PSD) is a well-established guide for translating clinical aims to technology frameworks for supporting health-related behavior change.[84-86] Along with PSD, User-Centered Design (UCD)[87, 88] and the ADDIE Model,[89-91] a user interface and instructional design approach, will be used. Design elements such as space (colors, sounds, visual space), components (characters, objects), and mechanics (actions) will be determined for program features (i.e., activities).

Iterative design process. The conceptual and technological web architecture will be developed using PSD. The AABs, HEPP, and investigative team will identify key elements to be translated. Using UCD, AAB input will be solicited through iterative cycles, with adjustments based on feedback,[92] resulting in greater user experiences and more effective results.[93, 94] Game design theory and the MDA framework will guide intervention "gamification." Consistent with mHealth research with teens,[95-99] adaptation will emphasize gaming as a teaching strategy and interactive components will be the centerpiece of the intervention, complemented by role play simulations and hosted videos. To reward learning and bolster adherence, "badges" (visual reward icons), will be awarded intermittently. Badges are a highly effective tool used to encourage user engagement and build game "loyalty."[100-103] Quizzes for the modules will also provide corrective normative feedback. TRAC content will be integrated into 8 (approx. 45-minute) modules in Phase 2. Though full programming will not be completed in Phase 1, the formative research and iterative design process will guide plans for future development.

Multimedia programming will follow standard production steps. Investigators will develop instructional and behavioral objectives based on focus group results, the previously validated intervention, and existing web platforms. Interface design ideas will be created in writing, combined with scripts, flowcharts, mock-ups, and storyboards using Adobe XD wireframing tools in Phase 1. Acceptability of the prototypes will be determined with a second round of advisory board meetings to review the wireframes generated from the ideas provided during the first round. A specifications document, with a full outline of modules and activities, will be created to guide full development in Phase 2.

Deliverables: Deliverable 3a: Prototype wireframes for use in a second round of advisory board meetings

will be created. Deliverable 3b: A summary report of advisory board feedback will be generated to guide final scripting. Deliverable 4: Specification documents for the digital modules to complete the iTRAC intervention for sexual risk prevention (iTRAC-SRP) will be created.

Summary of Phase I Milestones:
1. **Milestone 1**: Review of Sexual Education Standards. TRAC sexual health content will be updated using the recommendations of the health and education professional advisory board and by a review of the National Sex Education Standards[80]. **Deliverable 1**: A summary report of the recommended content based on review of sexual education standards, integrated with recommendations from advisory groups, will be developed.
2. **Milestone 2**: Focus Groups. Each of three advisory boards (female adolescents, male adolescents, health and education professionals) will meet to provide recommendations for the adaptation of the intervention, including key sexual health content and content linking sexual health to ER as well as approaches to translating this material via technology. **Deliverable 2**: A report of the focus group data summarizing and integrating these recommendations for the development of remaining modules will be created.
3. **Milestone 3**: Prototype wireframes. Static screenshots will be created to show the look and feel of the new content (aiming to match that of the existing content), demonstrate storyboards of the proposed games and activities, and illustrate the user interface via wireframes. These will be used in a second round of advisory board meetings to get feedback. **Deliverable 3**: a) Prototypes of intervention modules will be created. b) A summary report of advisory board feedback will be generated to guide final scripting.
4. **Milestone 4**: Specifications Document. Scripts of the remaining iTRAC module content will be created, integrating the existing emotion regulation content with the identified sexual health skills and education content. **Deliverable 4**: Specification documents for the digital modules to complete iTRAC-SRP will be created.

Completing the Phase 1 Specific Aims and these milestones will provide measurable outcomes reflecting a successful trajectory of the project indicating a high probability of accomplishing the Phase 2 goals.

Overview of Phase 2: Acceptability Testing and Randomized Trial (months 13-36): This phase will create iTRAC-SRP as a web app from the specifications document created in Phase 1, thus completing the translation of the original group program to a mobile intervention that can be more easily disseminated and fill a content gap (emotion regulation) in the area of sexual education. Once completed, acceptability testing will be completed with early adolescents in two rounds to allow for modifications based on participant feedback. Once finalized, a small RCT will assess impact on adolescents' self-efficacy for preventing sexual risk as well as engagement in sexual behaviors. All of these activities will follow procedures successfully used in prior collaborations between the research institution (RIH) and technology partner (KB).

Phase 2a- Full Program Development (months 13-18): will take place at the beginning of Phase 2, using content outlined in Phase 1 and approved by the advisory boards. For this STTR Fast-Track study, the sexual health and connecting ER to risk decisions content will be completed using the same successful procedures of the pilot study (including D4D principles).[83] The iTRAC-SRP program will be produced for mobile platforms, including smartphones, tablets, and desktop computers. It will be alpha tested in-house for stability and code errors, beta tested (see below), and revised following KB's iterative design process. Federal Section 508 standards for accessible information technology will be considered so program functionality can be compliant in future dissemination trials and commercialization. **Web app production** will use a Responsive Web Design approach that provides an optimized user experience for tablets. The web app front-end interface components will be developed using HTML5, CSS and JavaScript. A Microsoft SQL database will enable user identification and store and deliver tailored content. Server-side components will be developed on the Microsoft dotNet platform using the C# programming language. Hosting will occur on KB's state-of-the-art server farm (see **Resources**). Click stream data will be tracked and monitored on the backend. Sensitive information is protected by a hardware firewall (Cisco ASA 5505) and daily backups protect against data loss. The program will be developed for tablets for the current project but optimized for use on desktops and smartphones as well, which will enhance commercialization opportunities.

The iTRAC intervention aims to enhance ER skills to reduce poor decision making that can lead to risk behaviors. Incorporating the ER content developed in the pilot, we plan to create 45-minute digital modules, time consistent with computerized executive function training programs used with adolescents (e.g., Cogmed, Braingame Brian) and typical class lengths. This length was acceptable in the pilot trial. Consistent with research on mHealth strategies for adolescents,[95-99] the design emphasizes gaming as a teaching strategy.

These interactive components (4-6 per module) are the centerpiece of the intervention, complemented by hosted videos connecting the games. As in the original TRAC group program, each module will include activities related to emotions, sexual health, and the link between the two (the iTRAC pilot modules contained emotion content only). As with the pilot, the complete iTRAC-SRP intervention will begin each module with teens labeling their feelings that day (to practice emotion recognition and labeling skills) before moving on to a brief review of previous module content. The first four modules will focus on illustrating the relationship between emotions and behaviors and providing education about emotions, such as strategies for labeling feelings in others, identifying emotional arousal in oneself through somatic cues, labeling these feelings, and recognizing their source ("triggers"). The last four modules of the program will focus on teaching developmentally appropriate strategies for regulating emotions during difficult situations, particularly those related to health risks, using three primary groups of strategies identified during qualitative work in the development stage of Project TRAC (R34 MH078750)[45]: 1) getting away (physically or cognitively) from triggers for strong emotions, 2) releasing emotional energy in healthy ways (verbally or physically), or 3) changing cognitions and appraisals about emotional triggers. These strategies, labeled "Get Out," "Let It Out," and "Think It Out," correspond to four of the "families" of ER processes in Gross's process model.[27] Activities also emphasize practice with the unique focus of the intervention, managing emotions as they occur, as cued by frustrating games or emotionally arousing visuals. Much of this content exists through the pilot study (**see Table 1**), including games navigating a spaceship through emotional triggers, a virtual slingshot target game highlighting places in the body where somatic emotional cues are experienced, and activities exposing adolescents to emotional cues with coaching to regulate these emotions. Emphasis is also placed on activities that encourage participants to personalize this information. This existing ER training will be integrated with the rest of the program content (sexual health education and activities linking ER to health behaviors) to be developed with guidance from the AABs and HEPP. This content will include strategies for (and practice with) recognizing and managing emotions in sexual health situations, such as those involving peer pressure, condom use, media/pornography exposure, or sexual decision making, to enhance the likelihood that the ER and sexual health education provided can be applied to experiences that are emotionally arousing and lead to risk.

Deliverable: A complete digital version of the adapted TRAC intervention for sexual risk prevention, iTRAC-SRP, will be created.

Phase 2b- Acceptability Testing and Finalizing Revisions (months 15-18): A pilot test of the completed iTRAC-SRP will be conducted to confirm that the components perform as designed. Assessment and intervention procedures to be used in the RCT will also be tested. Sixteen 7th grade students (50% female, racially and ethnically diverse) will be recruited from the study schools in two cohorts to test iTRAC-SRP and make iterative revisions. These participants will be excluded from the RCT.

Acceptability will be assessed several ways for each module. First, teens will complete a brief standardized questionnaire (used in the pilot project) to assess acceptability (e.g., How much did you like the program?) and feasibility (e.g., How easy was it to use?). Mean scores of 3.5 or greater (on a scale of 1-poor to 5-excellent), will be deemed acceptable (the existing iTRAC received scores over 4). Second, adolescents will complete the System Usability Scale (SUS)[104]. This validated, 10-item scale provides a global view of subjective usability for programs such as web tools. SUS scores above 68 will be considered acceptable. Third, researchers will observe participants playing the program using screen sharing software (e.g., GoToMeeting) to assess for confusion with functionality. In the pilot, this proved informative for identifying usability concerns. Finally, a brief interview with teens after each module will collect impressions of the primary messages conveyed in each of the developed activities. Interviews will be reviewed for consistency of themes and content comprehension by Drs. Houck and Hadley; both have experience in qualitative methods.[46] Each activity will have an identified primary message to which participant responses will be compared for understanding, as in the pilot. This interview will also collect feedback regarding suggested improvements. Recruitment will occur in two groups of eight, to allow for iterative changes in response to participant feedback. The final revisions will incorporate all feedback and resolve remaining technical issues prior to the RCT. This process was successful in the pilot study.

Deliverable: A summary report of quantitative and qualitative data from the Acceptability testing questionnaires and interviews will accompany a table of recommended changes that will guide Klein Buendel's revisions to the program, leading to the finalized iTRAC-SRP program.

Phase 2c- Randomized Control Trial (months 19-36): **Recruitment:** For the RCT, project staff will recruit 120 7th grade students from two waves of enrollment over an eight-month period that will span across two school years, providing two unique cohorts of 7th graders from which to recruit. We will examine sample demographics after the first cohort to ensure diversity in terms of race, ethnicity, and SES. Oversampling will be conducted if sampling is not representative of diversity at the schools, though our previous projects have not experienced this. Participants will be recruited through several methods consistent with those used to successfully recruit in the pilot trial and in our other school-based studies (see **Form F**- **Recruitment and Retention**). 1) Students will be introduced to the program at school via small-group presentations emphasizing the content (sexual and

emotional health) and approach (gaming), both of which are of interest to this age group. The introductions will be conducted by project staff, who will distribute flyers with QR codes that connect to a REDCap link to the "consent to contact" form, to avoid students having to remember to return the form. Parents can also sign and return the forms to the school. 2) Principals will introduce the project to parents via school announcement emails that contain the REDCap link to the consent to contact form. 3) Project staff will recruit at school events attended by parents (open houses, sporting events, etc.).

Once permission to contact the family is received, trained staff arrange a meeting to describe the project, obtain parental consent, and complete baseline parent measures. Separate meetings for adolescents are arranged to explain the project and obtain assent (separate from their parent). The Translation and Acceptability stages will also use the classroom recruitment procedures described above. Parents and teens will be compensated for time and effort in all stages of the project.

Randomization: Participants will be individually randomized to either iTRAC-SRP or waitlist control after baseline, following consent. Per recommendations for achieving between-group comparability in clinical trials,[105] randomization will be stratified by school and gender and blocked using predetermined size-4 blocks. Individual randomization avoids nesting of conditions within schools by each school hosting both conditions, which is feasible given individual program completion. We considered randomization by school, but a group randomized design would require >30 schools to achieve adequate power. Minor concern exists that teens from different conditions may discuss the intervention; as in Project TRAC, we will measure this "cross-talk" via assessment. Project staff will log participants into the password-protected site to avoid outside access. Accessibility will be an ultimate goal of iTRAC, but use will be monitored during the study to control for dose.

Intervention Condition: iTRAC-SRP will consist of eight, approximately 45-minute, "gamified" digital modules of 4-6 activities (games, videos, etc.). Teens will complete modules in after-school supervised groups. Students will be allowed to complete 1-2 modules each week (total intervention completion time 4-8 weeks); project staff will be present at each school at least three days per week, allowing flexible scheduling/attendance. No instruction is needed to use the program. Teens will come to a common area (e.g., classroom, library) where they will be provided a project tablet connected to Wi-Fi. They will have an individual account for the program (password controlled by project staff to prevent outside use), by which they will resume where they left off at the previous module (thus allowing flexible administration and breaks, as needed). We have chosen this strategy for the research for pragmatic reasons; after-school formats are common in schools, and this time, location, and format were successful in TRAC and iTRAC. However, we recognize that the program may be administered differently (e.g., during class time, in waiting rooms, or at home) once it is commercialized.

Content will use gender- and sexuality-inclusive language and avoids heteronormative descriptions of risk. All modules will include activities that personalize main concepts (some were developed in the pilot). iTRAC's programming structure does not permit the skipping of content (unless configured to allow it in predetermined instances). Modules will conclude with a quiz (with corrective feedback) that must be passed before moving on.

Waitlist Control Condition: Control participants will be assessed on the same schedule as the treatment condition and offered the intervention after 6-month follow-up. This is an appropriate strategy given that adolescents will still be in the developmental window of early adolescence at the conclusion of the follow-up window, thus the intervention will still be age appropriate.

Fidelity: To preserve internal validity, assurances for consistent delivery will be taken. 1) Research staff complete comprehensive training to assure proper administration, and drift will be monitored through regular team meetings. 2) The computerized nature of iTRAC-SRP will ensure standardized delivery of content. 3) A trained RA will be available to answer questions and problem solve at all appointments. 4) Each module will conclude with a quiz of key content, with corrective information that re-presents concepts relevant to incorrect responses. Participants will not be able to advance to the next module until successfully answering all quiz items. Results will also be saved as data to inform regarding program comprehension. 5) The iTRAC program prevents advancing through video content, to ensure that teens do not skip challenging material. 6) Tracking software will track time spent on each module and activity to assess dose. Summaries of these data (means, ranges) will be reviewed to understand usage patterns that may also inform commercialization.

Intervention Retention: Retaining participants and ensuring a maximum intervention dose is critical to assessing efficacy. 1) The gaming approach to the interventions will encourage participants to return weekly. Pilot teens were easily engaged; 88% completed all modules. 2) The health content, especially that related to sex, is of interest to this age group. 3) In-program reinforcers (e.g., "badges," virtual prizes) mark progress and encourage completion, especially as they relate to knowledge valued in this developmental period (e.g., sexual anatomy, STI knowledge). Badges were noted by participants during the pilot project. 4) As in the pilot, the sessions will be held at a convenient location and time (after school), with options to accommodate special circumstances (e.g., library meetings during school breaks). 5) Snacks will be provided. 6) Finally, providing multiple chances to complete modules on a flexible schedule is an advantage over traditional group formats, which are restricted to a specific time and can lead to missed content when participants miss group. Mobile delivery

allows teens to receive 100% of the content at their own pace, which may enhance intervention effects.

Follow-up Retention: The investigative team has previously demonstrated strong retention capacity (e.g., Project TRAC: 86% of adolescents, 77% of parents through 30-months; iTRAC pilot: 94% through 3-months). We will facilitate retention over the proposed two-year follow-up using successful methods from our own work and the literature.[106-111] 1) The value of their participation will be conveyed (teen and parent compensation; education during consent regarding the importance of follow-ups; problem solving barriers). 2) Rapport will be established (contacts conducted by the same staff over time; follow-ups conducted at times/locations convenient to families; holiday cards). 3) Participant relocation will be monitored (assessment of potential moves at all contacts; families complete locator forms). 4) Logistic barriers will be minimized (parent assessments kept brief; scheduling to include evenings/weekends). See **Form F- Recruitment and Retention** for details.

Assessment Procedures: Assessments for both conditions will occur at baseline, post-intervention (2 months) and 6 months after baseline. They will minimize participant burden while assessing key constructs of the intervention. Assessments will be administered in a quiet location at school; we expect the battery of self-report and performance measures will take 60-90 minutes. Questionnaires will be administered via tablet, using REDCap to reduce errors and missing values. We will use calendar-aided recall cues and anticipate that recall will be excellent given the salience of risk events for early adolescents. The proposed battery is shorter than that of Project TRAC, which was well-tolerated. Performance measures of emotional competence will be collected via laptop computer. The brief parent battery will be collected via REDCap and can be administered in person, via email link, or, if needed, by phone.

Measures

Primary Outcome: It is well-established that sexual self-efficacy (SSE) is correlated with positive sexual behavior outcomes and sexual well-being among a diverse array of populations[112-115] . As such, measuring self-efficacy for safer sexual activity as a main outcome will indicate iTRAC-SRP's efficacy and ability to promote healthier sexual behaviors with the full sample (not just those who are sexually active). Adolescents' perceived abilities to engage in behaviors that mitigate sexual risk will be assessed by the Self-Efficacy for HIV Prevention scale (12 items)[116]. This continuously scaled measure includes items such as "If you decide to have sexual intercourse with your girlfriend/boyfriend, how sure are you that you could talk to your girlfriend/boyfriend about safer sex?" The measure assesses a range of behaviors related to prevention of HIV, other STIs, or unintended pregnancy, including refusing sexual behaviors, discussing sexual histories with partners, buying condoms, taking free condoms, carrying condoms, and asking a partner to use a condom. Participants respond on a 4-point scale (couldn't do it, unsure, sure, very sure). This measure demonstrated good reliability in the TRAC study with this age group (α= .90).

Secondary Outcomes: *Sexual Risk Cognitions:* The intervention is expected to have an impact on other cognitive constructs related to sexuality (e.g., knowledge, attitudes), as well as behaviors. The Sexuality Questionnaire for Adolescents (34 items) is a multiple choice test to assess sexual health knowledge and has been shown to be sensitive to intervention impact.[12] The Abstinence Attitudes (10 items[117]) questionnaire assesses agreement with values related to abstinence (α= .86).

Sexual Behaviors: The Adolescent Risk Behavior Assessment (ARBA)[118] is a computer-assisted structured interview for self-reported sexual and drug behaviors, successfully used in Project TRAC. The ARBA employs a skip structure so that questions answered in the negative are not followed by more detailed questions. Questions are asked in behavioral terms, without reference to sex of partner. Except at 2-month follow-up (which will use an abbreviated version), the ARBA will assess sexual behavior occurrence and frequency in the past 6 months. Given the relative infrequency of these behaviors and their significance to adolescents, we anticipate that recall will be excellent for this time frame. For early adolescents, we have modified the ARBA to include behaviors relevant to this developmental period (e.g., genital fondling) using previously validated items from the Psychosexual Development Interview (PDI)[119]. Other questions cover condom use and number of partners. It is expected that, as in TRAC, the ER skills taught in iTRAC-SRP will result in less sexual behavior and less sexual risk when compared to the waitlist control group over the same time period. Occurrence of vaginal, anal, and oral sex, as well as condomless sex, multiple partners, and substance use before sex, assessed via ARBA, will be examined. We recognize that the study will be underpowered to detect significant group differences on these variables, given that most early adolescents will not transition to sex in this 6-month time frame of 7th grade and that larger studies with longer follow-ups will be needed to demonstrate effects on these variables. Nonetheless, gathering preliminary information will be useful for understanding the impact of iTRAC-SRP and planning for future studies.

Non-sexual risk behaviors may also be impacted by a generalized effect of ER on health behavior. Thus, we will conduct brief assessment of behaviors that may be more common in this developmental window. Youth Risk Behavior Surveillance System[1] items (n=9) will be used to assess tobacco/vape use, violence (e.g., fighting), and substance use behaviors. Further, acceptability of the program will be assessed at immediate posttest using the acceptability questionnaire used in stage 2b, to provide additional information for commercial

viability and marketing direction.

Treatment Mechanisms (Mediators): *Emotion regulation* will be measured via self-report, performance measures, and parent observation. Teacher measures were considered; our experience in Project TRAC was that students changed teachers too frequently for long-term follow-ups and that short-term follow-ups (2 months) did not provide time for the ER skills learned for risk situations to generalize to non-risk settings, like the classroom[48]. ***Self-report:*** The Difficulties in Emotion Regulation Scale (36 items[120]) uses six subscales (e.g., lack of emotional awareness, limited access to ER strategies; all α ≥ .80) to assess perceptions of skill in ER based on Linehan's theoretical work.[121] The Affect Dysregulation Scale (6 items[122]) assesses the frequency of difficulties with ER (α= .72), and is shown to be related to adolescent risk behaviors.[122] The Emotion Regulation Behaviors Scale- Revised (9 items[123]) measures use of the specific emotion regulation strategies taught in iTRAC (α= .73). The emotional self-efficacy subscale of the Self-Efficacy Questionnaire for Children (8 items[124]) assesses perception of one's ability to cope with negative emotions (α= .83). It has been shown to be valid, reliable, and related to risk behaviors among adolescents.[124] The Implicit Theories of Emotions for Children- Self subscale (6 items)[125] is based on Dweck and colleagues' work on implicit theories of intelligence[126] and Tamir's adult measure of emotion malleability._ENREF_146[127] It assesses adolescents' beliefs about the controllability of their emotions (α=.86). All of these measures were successfully used in the iTRAC study. ***Performance measures:*** a) Diagnostic Analysis of Nonverbal Accuracy–2[50] (DANVA2) is a computer-based measure that asks participants to identify the emotion of facial expressions displayed in photographs. The measure has shown one-month test-retest reliability over .8[50] and had an alpha of .83 in Project TRAC. b) Behavioral Indicator of Resiliency to Distress (BIRD)[128] is a 5-minute computerized distress tolerance task in which participants are given the option to quit at any time. It generates a score of time spent persisting on a frustrating task that provides negative feedback (aversive noise) when users fail at the task.[128-130] ***Parent report:*** The Adolescent Self-Regulatory Inventory (29 items)[131] measures perceptions of adolescents' abilities to regulate over the short-term and long-term, separately; both adolescents and parents will complete it about the adolescent (α= .75-.90). Parents will complete this measure at baseline and 6-months, to reduce burden.

Treatment Moderators: Demographic information will be collected, allowing for analysis of demographic factors, including sex as a biological variable, as moderating influences of treatment effects. Self-Rating Scale for Pubertal Development (PDS; 5 items)[132] will be used, as pubertal status and sexual activity are related. The PDS uses gender-specific items to assess physical maturation. It is reliable (α= .67) and strongly correlated with pediatrician-rated physical development.[132] The Columbia Impairment Scale (CIS; 13 items)[133] provides a global measure of functional impairment with good reliability and validity.[131, 133] A score of ≥ 15 suggests clinically significant impairment. Intervention Cross Talk will be assessed with 3 items from our previous studies that ask whether participants have talked with others about the intervention, how often, and about what content.

Other constructs shown to influence early adolescent sexual behavior will be measured to assess moderators of intervention impact.[29, 134-140] Perceived Peer Approval (3 items)[141] measures perceptions of peer approval of sexual behaviors (α= .81). Normative Beliefs (5 items)[142] assesses perceptions of peers' experience with and attitudes toward sexual behaviors (α= .76). The Neighborhood Environment Scale (6 items)[143] assesses conditions of an adolescent's neighborhood (α= .83).

Data Analysis: A more detailed description of the analytic plan and justification for power calculations is presented in Section *4.4 Statistical Design and Power*, including approaches to evaluate model assumptions, potential imbalance between treatment groups in baseline characteristics, and missing data. Analysis of covariance will be used to evaluate changes in self-efficacy for sexual risk prevention skills over 6-months post intervention with baseline as a covariate. All participants who were randomized will be included in all analyses (i.e., intent-to-treat). The size of the treatment effect will be estimated using standardized mean differences. The same approach will be used to evaluate sexual health knowledge and emotional competencies. Sexual behaviors (number of sexual behaviors, number of condomless sex acts) will each be aggregated across the two- and six-month follow-up assessments and analyzed using generalized linear models with log link functions and negative-binomial distributions for behavioral counts that are expected to follow a zero-altered count distribution. Exploratory analyses: *Mediation:* Causal mediation models will be used to test how much of the treatment effect is accounted for by measures of emotional competencies and sexual attitudes. Causal mediation provides a general framework for evaluating mediation in both linear and nonlinear models, including count outcomes[1]. *Moderation:* To better understand who is benefiting most from the intervention we will use causal random forests, a non-parametric data-mining procedure[2]. Although this principled exploratory approach cannot definitively define subgroups, it has better statistical properties than looking at individual moderators and will help suggest subgroups that differ in terms of their response to the intervention.

Power and Sample Size: This trial was powered to the primary and other continuously scaled outcomes (self-efficacy, knowledge, and emotional competencies). With 120 participants, this study is powered at .80 to detect moderate effect sizes (standardized mean difference $d \geq .47$). The power analysis was run using the R package simstudy v0.2.1 and assumed a two tailed type-1 error rate of .05 and a correlation between baseline and

the 6-month outcome of *r*=.6. Effect sizes from our previous work with TRAC and iTRAC showed effect sizes ranging from .20 to .70.

Deliverable: A summary report of the trial data will be created and submitted for publication.

Summary of Phase 2 Milestones:

1. **Milestone 5**: Digital Modules. Based on the specifications document, Klein Buendel will create the digital activities that will be integrated with the existing iTRAC intervention. **Deliverable 5**: A complete digital version of the adapted TRAC intervention for sexual risk prevention, iTRAC-SRP, will be created.
2. **Milestone 6**: Acceptability Testing. Acceptability of iTRAC-SRP will be assessed by recruiting youth in the target age range to complete the full intervention and provide feedback after each module via questionnaires and interviews. **Deliverable 6**: A summary report of quantitative and qualitative data from the Acceptability testing questionnaires and interviews will accompany a table of recommended changes that will guide Klein Buendel's revisions to the program, leading to the finalized iTRAC-SRP program.
3. **Milestone 7**: Efficacy Data. A randomized controlled trial with assessments at baseline, post-intervention (2 months), and 6-months follow-up will provide information regarding adolescents' perceived self-efficacy for sexual risk prevention behaviors, an important construct at the intersection of emotion regulation and sexual health. Other variables of interest will include sexual health knowledge, sexual behaviors, and emotion competencies. Further, acceptability of the program will be assessed at immediate posttest, to provide additional information for commercial viability. **Deliverable 7**: A report of the trial data will be submitted for publication.

RECRUITMENT AND RETENTION PLAN

The approach for recruitment will be similar for both phases of the project, with the exception that, given the small numbers of students needed for the Translation and Acceptability stages of the project and adolescent enthusiasm for participation, sufficient numbers of participants can be recruited with a few classroom presentations (described below).

Adolescent Recruitment: Several considerations for recruitment have been included in the proposed plan, including the time needed to enroll the target number of participants. First, to maximize the number of students approached, we will recruit over 8 months, crossing two school years. In this way, two cohorts of 7th graders at each school will be eligible for participation during the recruitment period. Participants will be approached during the school year, and school vacations during summer have been accounted for in the recruitment plan.

Our team has successfully recruited diverse families in previous projects, including the pilot trial (33% White; 30% endorsed Latino ethnicity). The participating schools serve students from diverse racial and ethnic backgrounds (see **Planned Enrollment Table**). Our participant sample will reflect current Cranston school demographics; we expect at least 50% of the sample to endorse racial or ethnic minority identity.

As noted in the application, participants will be recruited through several methods, all of which are facilitated by our excellent relationships with the participating schools. All of the methods described have been used in our intervention research laboratory to successfully recruit samples. First, project staff will introduce students to the study of iTRAC-SRP via a brief presentation describing the program, arranged by project staff with school staff assistance. This presentation emphasizes the content (health topics relevant to middle schoolers, such as sex) and approach (gaming), both of which are of interest to adolescents in this age group. The presentations are conducted in groups (e.g., homerooms), and project staff members distribute flyers that depict engaging images of the intervention with "consent to contact" forms for parents to sign and return if interested in participation. Homeroom staff will provide reminders, and project staff will be present at schools on a regular basis to serve as reminders to students as well. Recruitment for the Advisory Boards and Acceptability Trial is often enhanced by adolescents' interest in providing their opinions to advise on the development of a product, leading to a short recruitment period. Recruitment for the RCT is staggered over time, and anecdotal evidence suggests that positive word of mouth about the program (from those classes that receive the presentation and thus participate first) enhances recruitment during this phase.

Our previous studies have also demonstrated that having an identified school staff member who serves as a "project champion" and liaison to our study team is key to successful recruitment, thus we will identify such a "champion" at each school during the startup period of iTRAC-SRP. The participating schools are familiar with this model; we will reimburse schools for staff time and school space used by the project, which eases the burden of recruitment procedures and enhances the likelihood of success.

Another strategy for recruitment that avoids relying on adolescents to transport paperwork is the use of email communication with parents. Principals at participating schools send regular updates to parents and have included an introduction to our projects with a link to a REDCap page for parents to electronically complete the consent to contact form that allows project staff to contact them with details about the project.

Finally, project staff recruit at school events attended by parents (open houses, awards nights, school plays, sporting events, etc.). Again, having a presence at events where some families have previously participated in the project and spontaneously refer other parents to the project table has proven beneficial to recruitment.

Recruitment is also enhanced by the respect for participants that is a core component of the training received by research assistants responsible for interactions related to recruitment. Families are encouraged to take time to discuss the project and to ask questions at all phases, including when deciding whether to schedule a consent appointment. Respect for families' time is conveyed by the reimbursement schedule that compensates both adolescents and parents separately for the time invested in completing assessment procedures for the project. Respect for school procedures and personnel has also fostered positive, ongoing relationships between our research lab and the local school districts; these supportive relationships enhance collaborative problem solving around recruitment when issues arise.

Health Education Professionals Panel (HEPP) Recruitment: Health teachers and other school health professionals (e.g., nurses, counselors) will be recruited (n=8) for the HEPP to advise on the adaptation of the TRAC intervention during Phase 1. School staff directly involved in health of middle school students at each participating school, in addition to school health personnel who are members of the Rhode Island Department of Health (RIDOH) school nurses listserv and representatives of the Planned Parenthood Federation of America, will be invited to participate in the panel meetings during Phase 1. Staff will be contacted through the RIDHO listserv or through their publicly available organization or school district email accounts, a strategy that has been successful in our current research.

Intervention Retention: After families are enrolled in the project, retention to completion of the intervention will be critical to assessing its efficacy. The pilot trial showed excellent retention to the intervention, with 88% of adolescents randomized to the intervention condition completing all 4 sessions of the intervention. For the group-based format of TRAC, average attendance was 75%.

Several strategies will be used to engage and retain participants in iTRAC-SRP.

1) iTRAC was designed with intervention retention in mind by emphasizing an interactive gaming approach to the intervention that is appealing to adolescents and encourages participants to complete the program.

2) "Badges" are awarded for completing activities in the program. Used in the pilot with success, these badges are given names that reflect the construct of the game but are also engaging (e.g., "Emotion Commotion," "Truth Sleuth"). They mark progress through the program, and a tally of badges earned is noted in the upper corner of the game. Other in-program reinforcers will be employed in the complete program, such as virtual prizes (e.g., dressing up their character in the game) that enhance connection and individualize experience with the program.

3) Retention to the intervention is enhanced by the health content of iTRAC-SRP, especially the topics of relationships and sexual health. These topics are of interest to early adolescents, who anecdotally complain that information received in health class regarding sex and relationships is inadequate. In addition, the program teaches strategies for managing emotions that often interfere with relationships for early adolescents, thus creating interest in learning more through continued participation in the intervention.

4) Adolescents complete the interventions in locations convenient, familiar, and comfortable for them. As in the pilot, sessions will be held immediately after school at the school (e.g., library or classroom; all schools have procedures allowing project staff to use their facilities after hours). This makes attendance for students feasible and convenient. Accommodations can be made for students who have after school commitments, though these are rarely daily events at this developmental stage. Alternative locations can include the local library (all

local libraries have rooms that can be reserved for privacy of assessment or intervention procedures), adolescents' homes (staff travel in pairs to ensure safety), and the research office.

5) Providing families with flexibility in timing of appointments is maintained as a priority by project staff. Several days each week will be offered for program completion right after school. This flexibility is an advantage over group-administered interventions, which are restricted to a specific time and can lead to missed content when participants miss group. Mobile formats allow participants to receive 100% of the content at their own pace.

6) Reminders will be sent via text messages to parents (and adolescents who have phones and permission to receive texts from research staff) regarding scheduled appointments to complete intervention sessions.

7) Snacks will be provided. Work from our previous trials has shown that hunger can lead adolescents to leave school at the end of the day; providing snacks reinforces attendance and focus.

Follow-up Retention: Retaining participants for follow-ups is critical to assessing efficacy. The PI has demonstrated strong retention to study completion with challenging populations in other studies (e.g., middle schoolers with mental health symptoms: 85% at 30-month follow-up (R01 NR011906); dyads of adolescent boys and their parents: 88% at 9-month follow-up (2014-MU-CX-0002). Similarly, the pilot study of iTRAC retained 94% of adolescents for the final assessment (3-months). We will facilitate retention over the proposed 6-month follow-up using successful procedures from our own studies and the literature.

1) Seventh graders attend 8th grade in the same middle schools, which facilitates tracking.

2) Compensation to families conveys respect for participant time and effort. Adolescents will receive $50 for completing assessment procedures at each time point (baseline, post-intervention/2-month, and 6-month follow-up) to convey the importance and value of completing the project. Parents will receive $30 for each of their assessments (baseline and 6-month follow-up) which involve less time than adolescent assessments.

3) The informed consent process is an opportunity to educate participants about the importance of data collection to research studies. To motivate collaboration, families will be educated during the consent process as to why completing the intervention (if randomized to iTRAC-SRP) and follow-up assessments is important to the research and problem solve any anticipated barriers to participation.

4) Each school will have a dedicated research assistant who will assume primary responsibility for recruitment and tracking of participants at that school. In this way, participants have a primary project contact who will conduct project activities with the family over time to develop rapport with families. This encourages familiarity and comfort with the project and, in turn, retention.

5) Follow-ups will be conducted at locations convenient to families (see Intervention Retention, item 4). The vast majority of adolescents prefer to complete study activities at school. However, alternative locations can include the local library, adolescent's home, or the research office. All assessment procedures can be completed in any of these locations, due to the portability of study devices.

6) Parent assessments will be brief (15-20 minutes) and follow-ups can be completed by email or phone.

7) To limit barriers to families of diverse cultural backgrounds, all parent materials (consents, questionnaires) will be available in Spanish, and at least one Spanish-speaking RA will be a part of the staff.

8) Other mailings, such as holiday cards are sent to enhance recall and familiarity with the project.

9) Standard assessment procedures include research assistants providing appointment reminders by phone/text and providing scheduled appointments in writing. Standard lab procedure also includes inquiring about anticipated moves or phone number changes, to avoid challenges in reaching families for follow-ups. In the unusual circumstance in which a family moves out of the range in which a research assistant can conduct an in-person assessment, the questionnaire portion of the battery can be emailed to adolescents via REDCap.

10) Families complete locator forms that provide contacts who can help staff locate the family if their contact information changes. These forms are completed at each assessment point and include a check box and signature procedure for parents to permit schools to provide updated contact information as well.

HUMAN SUBJECTS RESEARCH

This study is nonexempt research involving human subjects. Rhode Island Hospital (FWA#00001230) will provide the oversight IRB for the study. Approval for the project and for consent forms will be obtained from the Rhode Island Hospital Institutional Review Board.

PROTECTION OF HUMAN SUBJECTS

1. RISKS TO THE SUBJECTS

a. ***Human Subjects Involvement and Characteristics***

In Phase 1, two Adolescent Advisory Boards (AABs) composed of 8 members each will be convened in Rhode Island. A Health Education Professionals Panel (HEPP) of 8 school professionals will also be formed to advise on the translation.
In Phase 2, sixteen participants will take part in the Acceptability Testing Phase to complete the intervention and assessment to test procedures for the RCT. One hundred twenty adolescents (ages 12-14) and their parents will be recruited from public middle schools in Rhode Island for the Randomized Controlled Trial Phase.

For both phases, Inclusion criteria: enrolled at a participating school, in the 7th grade, between the ages of 12 and 14 years, and has a parent/legal guardian who speaks English or Spanish to provide consent. Exclusion criteria: unable to read English at a 4th grade level, has a sibling who has participated in the project, or has observable cognitive or developmental delays that would preclude participation. In the RCT, eligible adolescents will be randomized to participation in a web-based, tablet-delivered emotion regulation intervention (iTRAC-SRP) or a waitlist control until the goal of 120 participants is reached. Adolescents will be recruited from four schools in the Cranston School District: Hope Highlands Middle School, Bain Middle School, Western Hills Middle School, and Park View Middle School. (See **Resources** for more information on sites).

Students will be introduced via a brief description of the program emphasizing the content (sexual and emotional health) and approach (gaming), both of which are of interest to this age group. The introductions will be conducted by project staff in small groups (e.g., homerooms), who will distribute flyers with "consent to contact" forms for parents to sign and return. Principals will introduce the project via emails sent to all parents with school announcements. A REDCap link to the consent to contact form is attached for parents to complete electronically, to avoid students having to remember to return the form. Project staff will also recruit at school events attended by parents (open houses, sporting events, etc.).

Once permission to contact the family has been received, school staff involvement ends (to avoid perceived pressure to participate). Trained research staff will contact parents to arrange an individual meeting to describe the project activities they are being asked to complete and obtain parental consent. Participants will be compensated for their time and effort. Staff will separately explain the project to adolescents and obtain assent away from their parent's presence.

These procedures will be used for both Phase 1 and Phase 2. Fewer homerooms will need to be approached for the Translation and Acceptability stages, as fewer participants are needed.

A Health Education Professionals Panel of school personnel key to student health will also be formed to advise on the adaptation of the intervention to digital format. Identified from throughout the school system, this will include individuals with involvement in student health and risk behaviors (e.g., health teachers, administrators, school counselors, school nurses). Once each pool of professionals from Cranston Public Schools is identified, individuals within each profession will be chosen at random, to ensure a mix of perspectives are represented in the HEPP. They will be contacted using their publicly available school email addresses and offered participation. Additionally, members of the Rhode Island Department of Health (RIDOH) school nurses listserv, as well

as representatives from the Planned Parenthood Federation of America, will be contacted and encouraged to outreach study staff if interested in participating.

Adolescent participation for all activities will require parent consent and adolescent assent. Adolescents and their parents will be agreeing to let us use adolescent feedback as data for program adaptation and development in the Translation and Acceptability Testing stages. In the RCT stage, adolescents and their parents will be agreeing to the adolescent's participation in an 8-module tablet-delivered health intervention and completion of computerized questionnaires at three points (baseline, 2-, and 6-month follow-ups). Similarly, parents will provide responses to questionnaires. They will be agreeing to let their responses, collapsed with those of other participants, be used for reporting scientific results. Adolescents and their parents will be assured that they are free to withdraw from the study at any time.

For all phases, once permission to contact the family has been received, trained research staff will contact parents to introduce and describe the program and what it involves for parents and teens. At the conclusion of this conversation, parents will be asked whether they would be interested in meeting to learn more about the program. Research staff will then arrange an individual meeting at a location convenient to them (e.g., the research office, the school, home, etc.) to describe the project in detail, obtain parental consent, and (for the RCT Phase) complete measures, for which they will be compensated for their time and effort. Separate meetings for adolescents will be arranged (typically at the school) to explain the project and obtain assent away from their parent's presence. Adolescents will be reassured that they do not have to participate in the program despite their parent's consent. They will be told that if they do not wish to participate, the research staff will not disclose to parents the reason that the student is considered ineligible, in order to protect their privacy and avoid coercion to participate. These methods have been successful in recruiting and consenting eligible adolescents in our previous projects.

b. ***Sources of Materials***

Participants in the Translation Stage (Phase 1) will provide feedback through discussions (AAB focus groups). Study staff will take notes on feedback provided by the Adolescent Advisory Boards. Data collected during this stage will include de-identified written notes taken by the research team during the meetings. During focus groups, discussions will be audiorecorded.

Participants in the Acceptability Testing Stage (Phase 2) will complete brief questionnaires assessing acceptability and usability after each module and participate in interviews about their experience with the digital modules (e.g., learning process, etc.). These discussions will be audiorecorded as well. They will also complete self-report questionnaires and computerized tasks to test assessment procedures for the RCT.

Participants in the Randomized Trial (Phase 2) will complete audio computer-assisted self-interviews (ACASI) on laptops at baseline, 2-, and 6-months after baseline. Adolescents will complete several questionnaires assessing demographic information, sexual attitudes and cognitions, risk behaviors, and emotional functioning. Parents will complete a locator form to assist in retention and tracking, as well as measures of demographic information and their adolescent's emotion regulation. Teens will also complete performance measures related to emotion regulation (Behavioral Indicator of Resilience to Distress; Diagnostic Analysis of Nonverbal Accuracy-2).

c. ***Potential Risks***

The risks in this study are considered minimal. During the Translation phase, participation requires only attendance at Advisory Board meetings where opinions will be shared, though participants will be advised that they may decline to answer any questions at any time. During Acceptability Testing, participation requires completion of the web-based program across several sessions, and completion of measures and interviews that assess the acceptability and clarity of the web-based program. Similarly, during the RCT, participation requires completion of measures as described above and participation in the finalized web-based program.

Some adolescents and parents may feel uncomfortable with the topics regarding sexual health. Families are notified of this content during the informed consent process. These topics will be discussed sensitively and openly, in a developmentally appropriate way during all phases of the project. Moderators during feedback

sessions will be trained to help participants with topics of sex and sexuality. In addition, they will heavily encourage confidentiality and respect.

With respect to use of the ACASI for data collection, the computer-assisted format is expected to reduce participants' discomfort answering questions about sensitive topics such as sexuality because the computer assessment format will prevent others from becoming aware of adolescents' answers. However, it will also be emphasized to participants that they may skip anxiety-provoking questions on any survey and that they can terminate their participation at any time during the course of data collection or interventions. If at any point during data collection or during the intervention, a parent or adolescent wishes to discontinue participation, they will be allowed to withdraw from the study without negative consequences.

While not directly assessed during the intervention or assessment procedures, if a subject discloses an abusive experience to project staff, parents will be notified and the matter resolved in accordance with standard hospital clinical practice (see **Protection Against Risks**). A similar protocol (described below) will be followed if adolescents disclose suicidal or homicidal ideation during the study.

2. ADEQUACY OF PROTECTION AGAINST RISKS

a. ***Informed Consent and Assent***

Only research staff at Rhode Island Hospital will consent participants. Given that our study involves children, we have carefully designed our consent and assent procedures to meet HHS regulatory requirements for parental permission and child assent (45 CFR 46.408). Specifically, trained project staff will gather informed consent/assent from all participants in person. Parents will provide informed consent for their adolescent and their own participation in the project. Adolescents will provide assent for participation. Staff members will inform the parent of the research study procedures, discuss the inherent risks, explain the rules of confidentiality and obtain consent. Separate from parents, staff members will individually speak with each adolescent to describe the study procedures, review the inherent risks, discuss the rules of confidentiality and obtain assent. Research staff will be available to answer any questions about the study. All signed consent forms will be locked away securely and kept separate from any study data (see below). Participants will be provided with copies of the Informed Consent/Assent Forms.

b. ***Protection Against Risk***

As noted above, participation in all phases of the project is entirely voluntary and participants are free to withdraw from the project at any time, without negative consequences to their affiliation with the referring school.

Confidentiality. The study will maintain confidentiality of stored records according to the following guidelines:

- All records will be kept by assigned study numbers;
- RIH will maintain locked files of all gathered data and permit access only to authorized individuals. (The schools and any associated staff members will not have any access to these records.);
- Completed, signed consent forms will be stored in a separate, locked cabinet that holds no other study information;
- Data collected on laptops will be downloaded after each assessment onto a flash drive as separate password-protected files prior to transfer to RIH's secure servers; the flash drives will be stored in a locked cabinet at RIH;
- Audio files will be transferred from recording equipment to RIH encrypted servers and deleted from the original source. Any backup drives used will also be encrypted. Files will be deleted at the conclusion of the study;
- RIH will maintain a separate, secured digital file that holds the list linking study identification numbers to names. Only the Principal Investigator and the research assistants will have access to this list, which will be destroyed at the completion of the project;
- Notes and transcripts from focus groups will be deidentified and will be kept in locked cabinets;
- Conclusions and final results will be presented for aggregate data only, with no disclosure of specific cases;

- Collected information will not be released without the explicit consent of the participant, according to the Privacy Act;
- No personal identifying information will be released to NIH.
- All personal identifying information will be removed from data prior to sharing with Klein Buendel, Inc staff.

Backend user data during the Acceptability and RCT stages will be collected and stored via internet to Klein Buendel's server farm. KB's server farm has five Dell PowerEdge servers with two 3.2 Ghz Xeon processors, two with 32 gigabytes of RAM and two with 128 gigabytes, and three 1 Terabyte hard drives that operate off a hardware RAID5 system, connected to a local area network (LAN) running the Windows 2008 or 2012 operating system, and to the Internet through a 50 megabyte fiber connection. KB programmers monitor and maintain all programs and databases, working with data management staff. Sensitive information is protected by a hardware firewall (SonicWall TZ600) and each server has its own native Windows security software. All KB servers are connected via 1 Gigabit high-speed switched network, ensuring high-speed transfer between machines. All networked computers are protected from viruses by Sunbelt Vipre Business. A nightly backup of each computer provides protection against the loss of data.

Trauma-Informed Approach. Consistent with SAMHSA's Trauma-Informed Approach and guidelines published by CARDEA (Guide to Trauma Informed Sex Education) and the Responsible Sex Education Institute, iTRAC-SRP will be sensitive to the experiences of participants with a history of trauma. These focus on principles fundamental to a trauma-informed approach. While some recommendations apply to in-person, group-based education programs (collaboration and mutuality, peer support), many can be incorporated into technology-delivered platforms.

Safety, both physical and emotional, is the foundation for a trauma-informed approach to sexual health education. iTRAC-SRP has advantages in creating a safe environment that may not exist in some group-based programs. The content is standardized and avoids shaming language ("you shouldn't have sex…"). Participants may proceed at their own pace, maintaining control throughout the program. In addition, other participants are not present to introduce content that may lead to strong emotions based on their personal experiences. In this way, technology-delivered sex education may be a more effective strategy than classroom-based learning where some students may have undesired responses. Trustworthiness and transparency will be achieved by alerting participants to upcoming sexual health content before it is presented (e.g, drawings of sexual anatomy). These activities are also used as practice with emotion regulation, as they are emotionally arousing for most adolescents regardless of trauma history because of the taboo around sexual health in US culture. Thus, coaching will be provided for use of ER skills to manage feelings while learning this important content. These skills are expected to increase the likelihood that participants will recall the information provided and will increase self-efficacy for ER strategy use. Empowerment and choice are facilitated through the teaching of emotion regulation skills as a way to manage emotions that might otherwise influence decisions in ways that adolescents do not intend. Other strategies for creating empowerment include reaffirming bodily autonomy during all sexual health content- that they have many choices over what happens to their body and when- and allowing participants to skip questions that they prefer not to answer during assessment procedures. Cultural, historical, and gender issues will be considered in all elements of the program, to avoid stereotypes and biases. The use of a space theme allows for use of non-human characters that are not easily associated with cultural stereotypes. Of particular importance in sex education programs is consideration of heteronormative language that may exclude youth who identify as LGBTQ. Inclusive language (e.g., "partner" vs. "boyfriend/girlfriend") creates a safe environment for all participants and reflects sensitivity to the traumas experienced by many who have historically had less power in our culture.

The sexual health content of TRAC has been used in a previous large trial without adverse events. Staff will be provided education to improve awareness of how trauma can affect youth, families, and communities to inform their day-to-day work with participants. Descriptions of violence or abuse that might be particularly sensitive for those with trauma histories are not a part of the original TRAC program. Adolescents consistently see sexual content in media and social media; the content of iTRAC-SRP will be developmentally appropriate and provide a context in which adolescents can interpret the information that they receive in other forums. People with trauma histories can lead full lives and develop healthy sexual identities; sexual health education is critical to this development. Respectful, affirming programs are key to this process and can be achieved through

technology. Those that incorporate emotion regulation skills may be particularly valuable to those with trauma histories as they navigate sexual content and experiences in their lives.

If a subject discloses an abusive experience, suicidal, or homicidal thoughts and/or behavior during any phase of the project, a trained research staff member will interview the subject immediately and the PI will be contacted. Next, the parent will be notified and the matter resolved in accordance with standard medical/psychiatric care as follows. Abuse is a reportable condition. In the majority of cases, a history of abuse has already been reported to the appropriate authorities. If not previously disclosed, the situation will be reported to authorities per state law and hospital standards. Suicidal or homicidal thoughts or behavior will be handled in the same fashion and the case will be reviewed immediately with one of the investigators. If the participant is in imminent danger, the participant will be taken by ambulance to the nearest hospital emergency room for immediate intensive psychiatric evaluation. Participants are informed of the limits to confidentiality, including these reportable conditions, during the consent process.

c. ***Vulnerable Subjects***

Our study is aimed at completing the development and testing the efficacy of a preventive intervention designed for middle schoolers. As such, this study necessitates the involvement of children. Importantly, this study presents ***no greater than minimal risk*** to children. Furthermore, as noted above, we have made numerous provisions for soliciting the assent of the children and the permission of their parents or guardians.

3. POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO THE SUBJECTS AND OTHERS

We hope that the emotion regulation training of the iTRAC intervention will be successful in reducing the rates of sexual onset and other health risks in our subject population. Waitlist control participants will be provided the opportunity to complete iTRAC-SRP after a 6-month delay. We believe that the clear examination of these questions outweighs the previously mentioned risks. Youth have an opportunity to learn emotion regulation strategies and consider safer sexual behavior to avoid future risks. The potential benefits to individual subjects outweigh potential risks, particularly in offering adolescents a chance to better understand the nature and consequences of their risk behaviors and to learn skills related to emotion regulation.

4. IMPORTANCE OF THE KNOWLEDGE TO BE GAINED

This study will provide an important sex education tool and elucidate the role of emotion regulation in improving sexual self-efficacy, a critical factor in healthy sexual activity during development, and delaying early sexual debut, which is associated with significantly greater future sexual risk, including more unwanted pregnancies, more sexually transmitted infections, greater number of sexual partners, greater frequency of intercourse, and less condom use. Even if an adolescent or parent does not directly benefit from the project, the information we gain may be used to improve the effectiveness of sexual health programs for other early adolescents.

5. HUMAN SUBJECTS PROTECTION EDUCATION

To meet mandatory training certification in Human Subjects Protection, the Office of Research Administration offers an online training program through CITI, Collaborative IRB Training Initiative. This online program offers both the initial certificate and a three-year re-certification program required by Lifespan. Drs. Houck, Hadley, and Barker have completed required training through CITI.

Klein Buendel, Inc. maintains compliance with mandatory training through the NIH Office of Extramural Research's training program. Ms. Berteletti and all required staff members have completed this training.

Collaborating Sites

This research involving human subjects will take place at both Rhode Island Hospital (FWA#00001230) and the participating school districts. School sites will be made aware by project staff of proper procedures for reporting any issues related to risks related to human subjects. Due to their limited role in the study (informing families about the availability of research and permitting use of their facilities for intervention) schools do not meet criteria for engagement in research according to OHRP guidance (dated October 16, 2008). Rhode Island Hospital will provide the oversight review board for the study for all activities occurring in Rhode Island. Western Institutional Review Board will provide oversight for any study activities taking place at Klein Buendel (FWA#00003715).

DATA AND SAFETY MONITORING PLAN

The nature of the population and setting warrants the development of a Data Safety and Monitoring Plan. The current study is considered to present minimal risk to participants given that subjects will provide data via questionnaires and performance measures as well as participate in a psychosocial intervention. In this plan, the Principal Investigator with input from colleagues (Hadley, Barker, Berteletti) will provide oversight of all recruitment and study procedures.

Specifically, the Principal Investigator will take primary responsibility for:

- Monitoring the safety of the participants

It is possible, though it has never happened, that adolescents in the schools may become aggressive with each other. Each school has identified personnel who are present during after school activities, and session moderators will have cell phones to contact any necessary assistance.

- Monitoring the safety of the researchers

It is possible, though unlikely, that the physical safety of the PI and facilitators could be threatened, either through direct implementation of the study (e.g., a participant becomes agitated and assaults a facilitator) or while in the school environment more generally (e.g., an adolescent uninvolved in the study assaults a facilitator at the school for the project). To help prevent and/or respond to such occurrences, school staff will be onsite for assistance. Such events are unlikely to occur, but in the case that they do, the event will be reported to the PI and school staff immediately. If any project staff is injured as a result of such an event, they will seek care, as warranted, by Rhode Island Hospital's Employee Health Services.

Home visits will be conducted in pairs, to ensure staff safety. Lab procedures include providing supervisors with time and location of all home appointments and texting a supervisor prior to entering the home as well as when the pair has left.

- Maintaining the confidentiality and integrity of the data

Data will be confidentially maintained under the stringent guidelines put forth in the aforementioned **Protection Against Risk** (see **Human Subjects Protection**). RIH will maintain locked files, stored off-site, and permit electronic access only to authorized individuals. ID numbers are used as identifiers throughout databases. The collaborating schools and any associated staff members will under no circumstances have any access to records.

- Receiving/eliciting reports of adverse events from research assistants (RAs) and school staff

The PI will receive these reports on an event-by-event basis. They will also be elicited in an open-ended manner through regular contact between the PI and school staff.

- Reporting adverse events to:

Co-investigators
School
The Rhode Island Hospital IRB
The Program Officer at NIH

The major adverse event that could occur as a result of study participation includes psychological distress from study procedures resulting in hospitalization. Project staff will be instructed to immediately contact the PIs when they first become aware of any event that could potentially be considered adverse. The PIs will immediately investigate the event and determine the appropriate manner in which to proceed. It is the responsibility of the PI to review serious adverse event reports, provide commentary, and provide oversight to ensure that reports are relayed to the co-investigators, Rhode Island Hospital IRB, and to the OHRP, as indicated. In the event of adverse events or unexpected problems posing risks to subjects, the PI is empowered to modify protocols and/or request interim data analyses.

Department of Health and Human Services (DHHS) Required Education in the Protection of Human Research Participants

To meet mandatory training certification in Human Subjects Protection, the Office of Research Administration offers an online training program through CITI, Collaborative IRB Training Initiative. This online program offers both the initial certificate and a three-year re-certification program required by Lifespan. Drs. Houck, Barker, Hadley, and all research staff in their laboratory have completed required training. Klein Buendel, Inc. maintains compliance with mandatory training through the NIH Office of Extramural Research's training program. Ms. Berteletti and all required staff members have completed this training.

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STATISTICAL DESIGN AND POWER

Data preparation: Relevant tests of model assumptions will be evaluated with all analyses, and appropriate corrections for problems in distributions will be implemented. Because even small and statistically non-significant between condition differences in baseline characteristics can adversely affect treatment effect estimates, we will use inverse probability of treatment weights (IPTW) to adjust for potential imbalance between conditions[1,2]. Covariate balancing propensity scores[3] will be used to generate the weights and the model will include demographics and baseline measures of primary outcomes, secondary outcomes, exploratory outcomes, moderators, and mechanisms. The effectiveness of the IPTWs will be evaluated by looking at the average and largest effect sizes for between condition differences prior-to and following weighting. We will also examine the positivity or common support assumption required for IPTW by visually examining the overlap in propensity score distributions for each condition. This assumption is likely to hold in the context of a randomized trial.

Missing data: Based on previous projects, we expect 10% attrition by the end of the 6-month follow-up. We will use fully conditional multiple imputation (a.k.a., multiple imputation using chained equations [MICE][4]) to address bias introduced by missing data. MICE was selected because it can handle outcomes with different statistical distributions (i.e., binomial, Poisson, normal), it can be applied to a large number of variables, and it has solid performance in simulation studies[4]. This approach assumes data are missing at random (MAR).

Primary Outcome: The primary outcome of the RCT will be Self-efficacy for Sexual Risk Prevention at the 6-month follow-up. All participants who were randomized will be included in all analyses (i.e., intent-to-treat). This outcome will be assessed using an analysis of covariance with baseline included as a covariate.

Secondary Outcomes: Secondary outcomes include sexual health knowledge, abstinence attitudes, sexual behaviors, and condomless sex acts. Sexual health knowledge will be analyzed like the primary outcome. Sexual behaviors will be summed across the follow-up assessments. Multiple imputation will be used to address missing assessments and the summation will occur within each imputation to ensure that missing assessment are appropriately counted. These data are expected to be zero-altered and will thus be analyzed using generalized linear models with a negative binomial distribution and a log link function. Condomless sex acts will be analyzed like sexual behaviors.

Mechanisms: Measures of mechanisms include theoretically important emotional competencies (e.g., emotion regulation, emotion recognition, distress tolerance) that mediate risk as measured by self-report, performance measures, and parent report. These outcomes will be assessed at the 2-month and 6-month follow-ups using analysis of covariance like for the primary outcome.

Power and Sample Size: This trial was powered to the continuously scaled outcomes (self-efficacy, knowledge, and emotional competencies). With 120 participants, this study is powered at .80 to detect moderate effect sizes (standardized mean difference $d \geq .47$). The power analysis was run using the R package simstudy v0.2.1 and assumed a two tailed type-1 error rate of .05 and a correlation between baseline and the 6-month outcome of $r=.6$. Effect sizes from our previous work showed effect sizes ranging from .20 to .70.

Exploratory analyses of mediation and treatment modifiers: Mediation: Causal mediation will be used to evaluate whether treatment-related change in self-efficacy was attributable to change in mechanisms. Causal mediation was selected because the framework can handle mediators and outcomes with non-normal distributions such as a binary outcome[8]. Mediation analyses will be run for each of the hypothesized mechanisms. *Moderation:* To better understand who is benefiting most from the intervention we will use causal random forests, a non-parametric data-mining procedure[9]. Although this principled exploratory approach cannot definitively define subgroups, it has better statistical properties than looking at individual moderators and will help suggest subgroups that differ in terms of their response to the intervention. Power was not calculated for these exploratory analyses.

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