DEVELOPMENT OF A DIGITAL THERAPEUTIC TARGETING ANXIETY SENSITIVITY TO REDUCE PTS-CUD IN WOMEN PRESENTING FOR EMERGENCY CARE AFTER SEXUAL ASSAULT

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SUMMARY OF CHANGES FROM PREVIOUS VERSION:

VERSION	DATE	REVISION SUMMARY
2.8	20.24.11.27	This version removed the blood sample collection, eSense, and trauma interviews during ED visit, which were not performed. We have also revised the aims of the study to assess feasibility, as opposed to efficacy, of the intervention. This change is reflected throughout the protocol.

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I ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ACTH	Adrenocorticotropic hormone
AE	Adverse Event
AR	Autoregressive
AS	Anxiety Sensitivity
AUDIT	Alcohol Use Disorder Identification Test
CBD	Cannabinol
CBM	Cognitive Bias Modification
CBT	Cognitive Behavioral Therapy
CEQ	Credibility/Expectancy Questionnaire
CFR	Code of Federal Regulations
CI	Confidence Interval
CIDI-SC	Composite International Diagnostic Interview Screening Scales
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CUD	Cannabis Use Disorder
DAST	Drug Abuse Screening Test
DCC	Data Coordinating Center
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition
DSMB	Data Safety Monitoring Board
EBP	Evidence-Based Practice
ED	Emergency Department
EDA	Electrodermal activity
EMA	Ecological Momentary Assessment

EMI	Ecological Momentary Intervention
FIML	Full Information Maximum Likelihood
FTND	Fagerstrom Test of Nicotine Dependence
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HPA	Hypothalamic-Pituitary-Axis
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
MCQ	Marijuana Cravings Questionnaire
MMM	Marijuana Motives Measure
MPS	Marijuana Problems Scale
N	Number (typically refers to subjects)
NC TraCS	North Carolina Translational and Clinical Sciences
NSI	New Safety Information
PANAS	Positive and Negative Affect Schedule
PCL-5	PTSD Checklist
PHI	Protected Health Information
PI	Principal Investigator
PROMIS	Patient-Reported Outcomes Measurement Information System
PTS	Posttraumatic Stress
PTSD	Posttraumatic Stress Disorder
QC	Quality Control
RA	Research Associate
RCT	Randomized Control Trial
REDCap	Research Electronic Data Capture *(database platform)*
RISE	RCT for Innovating Stress-related eHealth
SAE	Serious Adverse Event
SANE	Sexual Assault Nurse Examiner
SD	Standard Deviation
SE	Standard Error
SMS	Short Message Service
SNS	Sympathetic Nervous System
SoA	Schedule of Activities
SOP	Standard Operating Procedures
SSN	Social Security Number
SUD	Substance Use Disorder
TAAS	Treatment Acceptability/Adherence Scale
THC	Tetrahydrocannabinol
TUA	Treatment Utilization and Acceptability
UNC	University of North Carolina

US	United States
WHS	Women's Health Study *(observational study informing this RCT)*

2 PROTOCOL SUMMARY

2.1 SYNOPSIS

Title:	Development of a Digital Therapeutic Targeting Anxiety Sensitivity to Reduce PTS-CUD in Women Presenting for Emergency Care after Sexual Assault
Study Description:	The proposed research aims will test the hypotheses that a highly promising digital therapeutic targeting anxiety sensitivity (AS) will be acceptable to women sexual assault survivors, feasible to deliver, and that an RCT testing it will be feasible to recruit and retain participant for. If successful, this intervention (RISE Guide) could be provided at no cost to all women who present to US EDs for emergency care after sexual assault.
Objectives and Associated Outcome Measures:	**Aim 1**. Evaluate usability (TUA), acceptability (TAAS), and credibility (CEQ) of both interventions. • Treatment Acceptability/Adherence Scale (TAAS; 1 week) The TAAS is a 10-item measure of treatment acceptability (e.g., I would recommend this treatment to a friend) and adherence (e.g., I would be able to finish [this treatment]) that participants rate on a 7-point Likert scale. • Credibility/Expectancy Questionnaire (CEQ; 1 week) 6-item measure of treatment credibility and expectancy of treatment to improve symptoms. Items are rated on 9-to-11-point Likert scales. • Treatment Utilization and Acceptability (TUA; 7 week) 6 items created for the current study on a 5-point Likert scale, such as How often did you log in? How interested were you? and 4 open-ended questions; e.g., What did you like about RISE Guide?; What did you not like? **Aim 2**. Assess feasibility of conducting a randomized controlled trial to test the RISE Guide intervention. • **Recruitment.** Final sample size recruited and number of participants recruited per month will be used to evaluate the feasibility of recruiting the target sample (goal recruitment=2-4 participants per month). • **Retention.** Final proportion of participants who completed all follow-ups (1 week, 7-week, 6 months) will be used to evaluate feasibility of retaining the target sample (goal retention=75% or higher). • **Adverse Events.** We will examine whether adverse events occur throughout the study. • •
Study Population:	Women (natal and self-identifying) presenting for emergency care within 72 hours of sexual assault at one of our study sites (Section 6.8.1) may participate if they are English speakers, able to provide informed consent, have a smart phone with continuous service (1 year), and elevated AS (>17 on the ASI-3).[2,3]
Target Sample Size	In total, 150 eligible women will be enrolled. We anticipate that 37 of these 150 enrollees (i.e., 25%) will drop out or have incomplete longitudinal data.
Phase:	2
Description of Study Intervention:	RISE Guide is a mobile health intervention that is designed to mitigate PTS-CUD among survivors of sexual assault by acting upon anxiety sensitivity.
Study Duration:	The study will begin in July 2021 and data collection will end in June 2026.

Participant Duration:	12 months
Data Coordinator Center (DCC)	The University of North Carolina at Chapel Hill
Study Sites	Austin SAFE (Austin, TX) Tulsa Forensic Nurse Examiners (Tulsa, OK) Participant recruitment sites outside of UNC will sign reliance agreements with UNC's IRB prior to launching the study locally.

2.2 STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with Good Clinical Practice (GCP) and federal regulations.

The protocol, informed consent forms, recruitment materials, and all participant materials will be submitted to the UNC Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; the IRB will determine whether previously consented participants will need to reconsent via a newly-approved consent form.

2.3 COLLABORATIVE STUDY SITES

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2.5 SCHEMA

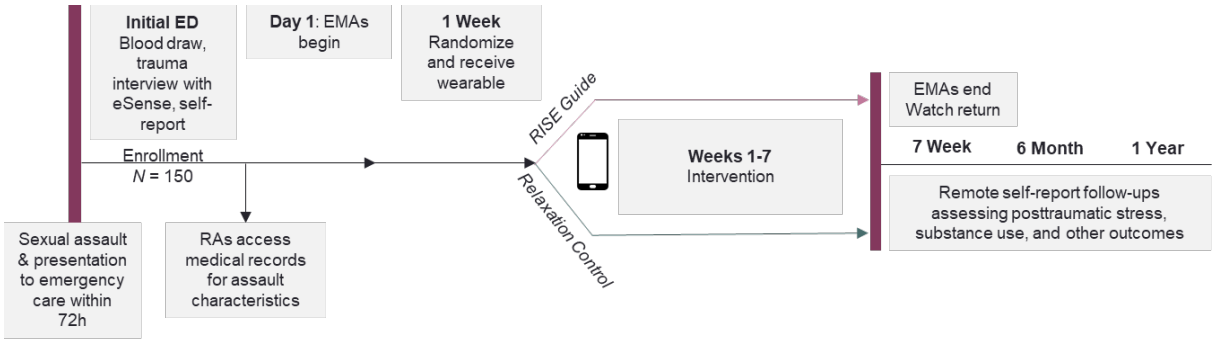


Figure 1 Study overview (See Figure 4 for detailed intervention timepoints)

2.6 SCHEDULE OF ACTIVITIES (SOA)

Table 1. Study Activities by Time Point

	0	*1-6*	*7-21*	*22-48*	*49-77*	*110-138*	*181-209*	*365-393**
Screening	✓							
Informed Consent	✓							
Self-Report Assessment	✓		✓		✓		✓	✓
EMA				✓				
Randomization			✓					
Empatica Wearable				✓				
Intervention								
• *Experimental: RISE Guide*				✓				
• *Control: Breathe2Relax*								

Contact information update	✓		✓		✓	✓	✓	✓

* Self-report assessments and contact information updates are only conducted at the 12-month (365-393 day) timepoint for participants who consented to this study prior to the timepoint's removal in version 2.4 of this protocol.

Note. EMA = ecological momentary assessment.

3 INTRODUCTION

3.1 STUDY RATIONALE

3.1.1 SEXUAL ASSAULT IS COMMON AND RESULTS IN HIGH RISK FOR CANNABIS USE DISORDER (CUD).[4–6]

Approximately 683,000 women are sexually assaulted in the United States each year (more than one woman per minute).[7] Sexual assault and other traumas are among the most potent risk factors for CUD, a public health problem affecting >14 million Americans during their lifetimes and contributing to the $200 billion annual cost of substance use disorders (SUDs) in the United States.[8,9] CUD is often under-diagnosed and under-treated,[10,11] difficult to treat, and often chronic.[12] Over half of those with CUD have survived a sexual assault, and 1 in 5 sexual assault survivors report a SUD,[4] underscoring the critical need for CUD preventions to reduce the public health burden of CUD in this population.

3.1.2 POSTTRAUMATIC STRESS (PTS) IS COMMON AFTER SEXUAL ASSAULT[13,14] AND HEIGHTENS CUD RISK.[15,16]

Sexual assault results in higher incidence of PTS than any other trauma[14] (>50% of 706 women in our emergency care-based observational cohort study had clinically significant PTS at 1 year). Sexual assault survivors with PTS have 2-to-4 times higher risk of CUD compared to survivors without PTS,[17,18] and 26 times the risk of SUD compared to women without assault history.[7] Sexual assault survivors often use substances – such as cannabis – to cope with PTS[5,19–22] (the "self-medication hypothesis").[23] Cannabis is often perceived as an anxiolytic,[24] though it can have anxiogenic effects, depending on tetrahydrocannabinol (THC) and cannabinol (CBD) concentrations.[25] Sexual assault survivors commonly use cannabis to cope with PTS,[26–33] consistent with evidence that stress is a core motivator[34] and antecedent of cannabis use.[2,3,35]

3.1.3 COMORBID PTS-CUD IS MARKEDLY IMPAIRING AND DIFFICULT TO TREAT.[36]

Cannabis is often perceived as harmless[37,38] or even helpful for PTS.[24] Cannabis may provide subjective short-term relief, but, long-term, cannabis use leads to increased PTS[39–41] and worse PTS treatment outcomes,[42] and higher rates of depression,[43] violence,[40] suicidal behavior,[44] and SUD.[45]Those with PTS-CUD have worse treatment outcomes than those with either PTS or CUD alone. Even after completing state-of-the-art treatments,[46–48] half have residual clinically significant symptoms.[17,48] The severity and chronicity of PTS-CUD underscores the importance of developing preventive interventions that could prevent or dampen the pathogenic processes leading to PTS-CUD development.

3.1.4 GIVEN THE CHRONIC AND INTRACTABLE NATURE OF PTS-CUD, SECONDARY PREVENTION FOR CUD PROVIDED AFTER SEXUAL ASSAULT COULD REDUCE THE PUBLIC HEALTH BURDEN OF CUD.

One theory-driven and efficacious prevention approach is to identify mechanistic and transdiagnostic risk factors that can be targeted with cognitive behavioral therapy (CBT).[49] Delivering such CBT interventions via smartphone has tremendous potential due to its scalability: a smartphone-based intervention could be offered at the time of ED care to the ~100,000 women presenting to US EDs[6] after sexual assault annually. These women typically receive preventive interventions for pregnancy and sexually transmitted infections,[50] but not for PTS or SUD, which are even more common sequelae.[4,13]

3.1.5 ANXIETY SENSITIVITY (AS) IS A RISK FACTOR FOR PTS AND CUD.

AS, or fear of anxious arousal, is a cognitive-affective risk factor that is trait-like but malleable via intervention.[51,52] AS comprises three domains of fears about the consequences of anxious arousal: cognitive (e.g., uncontrollable thoughts indicate one is going "crazy"), physical (e.g., racing heart indicates a heart attack), and social (e.g., blushing will lead to negative evaluation from others).[52] AS is a transdiagnostic risk factor, with cross-sectional,[53] longitudinal,[54] and prospective[55–58] associations with PTS, including among sexual assault survivors.[59] Our pilot data of 52 women presenting to the ED after sexual assault indicate that elevated AS prospectively predicts increased PTS, anxiety, and depression.[60] AS is also associated with increased substance use,[61–65] cravings,[61,66–69] and SUD.[70–72] These data are consistent with the self-medication hypothesis and with evidence that AS promotes substance use to cope with anxious arousal,[73–76] including among women sexual assault survivors with PTS.[68,77,78] AS is specifically associated with cannabis use,[31,79] including increased use,[80,81] maladaptive motives,[82–84] barriers to cessation,[64,85,86] and withdrawal,[87] and may play a key role in mediating relations between PTS and SUD.[88]

3.1.6 BIOBEHAVIORAL MODEL OF THE ROLE OF AS IN PTS-CUD.

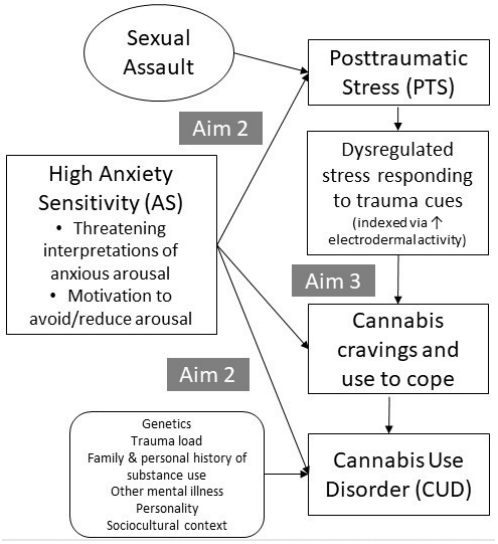


Figure 2 Simplified heuristic model of role of AS in PTS-CUD.

As depicted in Figure 2, individuals with high AS are at risk for PTS after trauma.[55,56,89,90] In addition to distress in response to trauma cues, individuals with PTS experience heightened/dysregulated stress reactivity, including increased sympathetic nervous system (SNS) activation[91,92] measured via electrodermal activity (EDA).[91,93] This heightened threat response continues at the neurobiological level, with dysregulated hypothalamic-pituitary-axis (HPA) activity assessed via increased adrenocorticotropic hormone (ACTH)[94] and cortisol secretion,[95] continuing SNS activation. Interestingly, increased peritraumatic EDA response to trauma cues may also be a predictive biomarker of PTS development.[96] Distress[97] and SNS activation in response to trauma cues results in physiologic changes, such as increased heart rate, blood pressure and perspiration,[I] which are aversive to those with high AS. AS is a common phenotype among individuals with PTS[98] in which interoceptive sensations are interpreted as threatening (e.g., signs one is having a heart attack or "going crazy"), and to be avoided. These fears may motivate increased avoidance behaviors, such as using cannabis to cope with distress or dampen arousal.[75] As noted above, consistent with this hypothesis, stress is often an antecedent and motivator of cannabis use,[2,35] particularly among those with PTS.[99,100] In turn, cannabis use is negatively reinforcing, providing rapid relief from distress,[34] and likely leading to a cycle in which individuals continue cannabis use to cope, exacerbating PTS,[41] further sensitizing stress responding,[101] and increasing reliance on cannabis use to cope, increasing risk for PTS-CUD.[102] In the long term, those with high AS report increased withdrawal symptoms during

cannabis cessation attempts,[87] potentially motivating relapse and interfering with treatment.[103,104] This model is particularly applicable to women, who are more likely to have affective comorbidities with CUD and use cannabis to cope with distress.[105] Behaviorally, this model also likely applies to other substances that actually do or are expected to dampen arousal.[65]

3.1.7 MEASURES OF EDA WOULD ENABLE TESTING OF THIS MODEL.

As noted above, EDA is a useful measure of SNS reactivity to trauma cues (e.g., trauma interviews[91]) and may be a biomarker of PTS development[96] and treatment response.[106] Consistent with the theoretical role of stress in cannabis use, a meta-analysis of craving paradigms found that increased EDA is linked with cravings in response to cannabis cues.[107] In contrast with other psychophysiological assessments, EDA can be assessed portably, inexpensively, and feasibly in clinical settings, including EDs[91]. Importantly, as described below, unlike other biomarkers, EDA can also be assessed in the natural environment to assess physiological antecedents of substance use.

3.1.8 BRIEF CBT INTERVENTIONS ARE EFFECTIVE IN REDUCING AS, PTS, AND SUD.

AS is malleable with brief, computerized CBT interventions.[108,109] Existing evidence suggests AS interventions reduce *chronic* PTS and related symptoms (e.g., anxiety, depression) by up to 35%,[110,111] including among sexual assault survivors. These interventions provide psychoeducation regarding the adaptive nature of stress, challenge distorted cognitions related to AS, and encourage interoceptive exposures to decrease AS. In >5 RCTs, these strategies targeting AS reduced PTS, anxiety, and depression.[108,109,112–114] In addition, prior research indicates that such interventions are acceptable to recipients.[115] Brief AS interventions also reduce opioid use,[116] drinking,[117–119] and heroin cravings,[120] improve smoking cessation outcomes[120,121] and abstinence rates in SUD patients,[122] and may prevent cannabis use.[123,124] Despite these exciting data, no preventive studies targeting AS have been conducted in adults. The early aftermath of trauma may be an ideal time to initiate such interventions, as the early posttraumatic period is characterized by a high burden of PTS and is a key period of CUD development.[125]

3.1.9 ECOLOGICAL MOMENTARY ASSESSMENT (EMA) IS AN EXCELLENT APPROACH TO UNDERSTANDING PTS-CUD.

EMA, the repeated sampling of current experiences in real time, in the natural environment,[126] provides valid assessment of cannabis use not captured by retrospective questionnaires,[127] as well as of dynamic factors that change over short periods of time such as PTS. EMAs can be performed in the context of traditional longitudinal assessments, allowing for measurement of both dynamic short-term and longer-term processes. Even more exciting, ecological momentary intervention (EMI) leverages data from EMA (e.g., symptom severity or profile) to provide personalized interventions in the moment (often via SMS). EMI boosts efficacy of CBT interventions,[128] which may be critical for learning during the stressful acute post-trauma period. EMI is also useful for CUD interventions to target in-the-moment stress or cravings, reducing drinking,[129] smoking,[130] and cannabis use.[131]

3.1.10 THIS STUDY EMPLOYS CURRENT TECHNOLOGIES TOWARDS TRAUMA RECOVERY.

Previous work to prevent PTS-CUD after sexual assault has been promising, but limited by then-current technology (ED video), limited dissemination, and lack of mechanistic investigations of efficacy.[132–134] This study will use techniques to maximize efficacy (Cognitive bias modification [CBM-I], EMI), investigate biobehavioral mechanisms of prevention, and our research network allows for a promising dissemination avenue.

3.1.11 THIS STUDY ADDRESSES GAPS IN TRAUMA RECOVERY LITERATURE.

Biobehavioral mechanisms underlying targeting AS to prevent PTS-CUD have been neglected in prior research. Targeting AS likely reduces substance use and cravings in response to stress assessed via physiological indicators, but this has not been tested in the extant literature. This mechanistic work is critical to understanding how AS contributes to PTS-CUD and refine prevention strategies.[135,136] EMAs complemented by wearables assessing EDA could reveal temporal associations and treatment mechanisms of targeting AS to reduce cannabis cravings/use in response to physiological reactivity to trauma cues.

4 SAFETY MONITORING AND MANAGEMENT

4.1 RISK/BENEFIT ASSESSMENT

4.1.1 KNOWN POTENTIAL RISKS

4.1.1.1 DISTRESS

Participants may experience distress after revealing personal information during study activities, particularly when asked about mental health symptoms including PTS. Notably, among participants in the Women's Health Study, 83-85% denied that participating in the study upset them more than expected. Regardless of levels of distress, the vast majority of participants felt that their contributions to the study were worth it (93-95%) despite any inconvenience they may have experienced. The researchers will remain vigilant in preventing and responding to participant distress by training site RAs to attend to and manage participant distress as needed and continually evaluating participants' self-reported research experience, but do not expect substantial stress reactions to be common among participants. All research associates will have extensive prior experience working with sexual assault survivors and will receive training on human subjects protection prior to beginning work on the study. The research associate on call for the study will approach the potential participant independently at a time deemed appropriate by the care team. To decrease the risk of the participant continuing with an assessment despite the assessment being too emotionally difficult for them, participants are told that they may stop the study at any time, and that they will be paid the full amount for the assessment regardless of how many questions they answer or whether they decide to stop the assessment entirely. This practice was enacted during the Women's Health Study (WHS), in which 85-94% of participants reported feeling that they could stop their assessments at any time and 74-85% felt free to skip parts of the study. Research associates will be trained to alert Dr. Short (PI), a clinical psychologist, if they suspect that a participant is in distress. Dr. Short will assess the situation and take any necessary steps to ensure the participant's safety, including supervising site RAs, calling the participants to debrief and manage acute distress, and suggesting referrals. Attending to participants' distress in the moment during ED visits will also be possible in-person as all sites are emergency care facilities with trained providers, including site RAs, who can manage acute distress or make referrals to more intensive services as needed. All participant ecological momentary assessments and follow-up surveys are available via self-report questionnaire. The follow-up assessments never include details of or questions regarding the assault experience itself, decreasing risk of increased distress. This design increases privacy and anonymity and encourages candid participant feedback regarding study participation. The Lead Research Coordinator will pull and review data from self-report questionnaires (e.g., research experiences, qualitative data) every two weeks to determine whether any particular participant appears to be at high risk, in which case these participants will be called by the PI to assess distress levels and facilitate referrals, if appropriate. In our experience from WHS, however, this is rare, occurring in less than 1% of participants. Telephone interviews will only be performed if the survivors are unable to use the above method and wish to complete the follow-up assessment via telephone. We believe that this methodology balances our goals of providing as much anonymity as possible while adjusting for participants experiencing limitations in internet connectivity.

4.1.1.2 LOSS OF PRIVACY/CONFIDENTIALITY

Maintenance of privacy and confidentiality is of paramount importance for any study, and all possible strategies will be used to minimize any risk for breach of confidentiality, including intensive training of research staff in good clinical research practices, HIPAA, and the strategies listed in detail below.

4.1.1.3 SIDE EFFECTS/ADVERSE EVENTS

Side effects and adverse events are expected to be rare in the delivery of these previously used and efficacious cognitive behavioral strategies to reduce PTS-CUD. However, they will be monitored and responded to appropriately as discussed in Section 8.2.

4.1.2 KNOWN POTENTIAL BENEFITS

4.1.2.1 BENEFITS TO SOCIETY

This study will inform initial acceptability and efficacy of a brief, smartphone-based, cognitive behavioral intervention for women sexual assault survivors. Currently there is no standard preventative intervention for sexual assault survivors to mitigate the development of PTS and related symptoms such as CUD. This study will help us to understand whether it is feasible for women to receive a link to a smartphone-based intervention on their phone (representing an easily scalable intervention), whether and to what extent women engage with the intervention, as well as women's perceptions of acceptability of the intervention, and will provide an initial estimate of efficacy of the intervention in reducing AS, and, in turn, PTS and CUD. Developing early interventions to prevent chronic PTS-CUD among high-risk sexual assault survivors identified at the time of emergency care is important, because most survivors do not seek or receive further care after initial emergency department evaluation, and because once chronic PTS develops, it is difficult to treat and extremely costly. Of note, as we gain more knowledge with this population, we believe that we will also be able to include more of the women at high risk of PTS-CUD (e.g., adolescents, those living with assailants) beyond those eligible for the current study.

4.1.2.2 BENEFITS TO INDIVIDUAL PARTICIPANTS

Participants may benefit from increased insight by providing self-report information via clinical outcome assessments, as well as during EMA and wrist wearables when they trigger stress measurements. Although not guaranteed, a potential direct benefit anticipated for participants receiving the active RISE Guide intervention is a decrease in AS, and, in turn, potentially PTS, SUD, depression, and anxiety. While this is not guaranteed, it is hypothesized to occur given the intervention is based on evidence-based cognitive behavioral principles and an intervention previously found to be efficacious. Further, we selected a relaxation control condition leveraging diaphragm breathing, as this practice can result in improvement in clinical symptoms such as PTS, though typically not a strongly as evidence-based practices (EBPs) such as CBT. However, regardless of condition, there is theoretical and empirical rationale to believe receiving one of these interventions would lead to better outcomes than receiving no preventive intervention at all.

5 SPECIFIC AIMS

- **Hypothesis 1.** Treatment acceptability (CEQ, TAAS) for RISE Guide is greater than or equal to treatment acceptability for a relaxation control, and similar to previously identified norms for the Credibility/Expectancy Questionnaire and the Treatment Adherence/Acceptability Scale.
    - *Aim 1*. Evaluate usability, acceptability (TAAS), and credibility (CEQ) of both interventions.
- **Aim 2.** Assess feasibility of conducting a randomized controlled trial to test the RISE Guide intervention.
    - **Recruitment.** Final sample size recruited and number of participants recruited per month will be used to evaluate the feasibility of recruiting the target sample (goal recruitment=2-4 participants per month).
    - **Retention.** Final proportion of participants who completed all follow-ups (1 week, 7-week, 6 months) will be used to evaluate feasibility of retaining the target sample (goal retention=75% or higher).
    - **Adverse Events.** We will examine whether adverse events occur throughout the study.

6 STUDY DESIGN

6.1 OVERALL DESIGN

6.1.1 PARTICIPANTS

Women (natal and self-identifying) presenting for emergency care within 72 hours of sexual assault to one of our sites (Section 6.8.1) and who meet eligibility criteria (Sections 6.5 and 6.6). As we are interested in incident substance use post-assault, women will not be required to be cannabis or other substance users at the time of assault. However, our pilot data suggest >50% of sexual assault survivors with high AS use cannabis, thus we expect our final sample will include high rates of CUD without this inclusion criterion.

6.1.2 PROCEDURE OVERVIEW

Women presenting for emergency care within 72 hours of sexual assault will be enrolled. As in Dr. McLean's recent large-scale observational study (UNC IRB 13-3193), women will be approached during their initial ED visit. In the 7 weeks after assault, women will complete EMAs to assess PTS, cannabis cravings and use, and wear a wrist wearable to assess EDA. Consistent with Dr. McLean's observational study, women will complete self-report remote follow-up evaluations 1 week, 7 weeks and, 6 months after assault via online surveys (REDCap).[137]

6.1.3 EMERGENCY DEPARTMENT (ED) VISIT

Providers will page the site research associate (RA), who will approach potentially eligible patients and describe the study. Alternatively, the providing Sexual Assault Nurse Examiner may be the site research associate. Interested and eligible participants will provide written informed consent and complete the assessments described below. Assault characteristics and past and prescribed medications will be abstracted from the medical record. EMAs will begin the day after the ED visit.

6.1.4 STUDY CONFIRMATION

Women who complete their one-week follow-up survey will be randomized and sent a wrist wearable.

The research coordinator will use REDCap, a secure survey platform, to randomize confirmed participants to the active or control condition. EMAs (for all participants), EMIs (for active participants) and RISE Guide (for active participants) will be delivered via Qualtrics, a smartphone-accessible, secure survey website that saves users' progress and automatically sends SMS reminders on a predetermined schedule based on progress The research coordinator will email the participant instructions for bookmarking her personalized Qualtrics link to her phone, allowing it to appear as an icon (similar to an app) so the participant can click the link and return to it as desired. Qualtrics will automatically send EMAs/EMIs via SMS and provide access and SMS reminders to complete their assigned interventions.

6.1.5 MECHANISM ASSESSMENTS

EMAs during the first 7 weeks after assault will assess PTS and cannabis cravings/use. EMAs will be distributed to participants via SMS a total of 4 times per day. Participants will be asked to complete $\geq$ 2 EMAs/day, as we have found providing additional opportunities to complete EMAs increases compliance rates. Three of the four EMAs will be signal contingent (i.e., occurring at random intervals throughout the day). The 4th will be interval contingent, occurring at the end of the day and assessing 1) total cannabis use quantity for that day and 2) whether the participant engaged in any strenuous physical activity, and when the activity occurred (to

exclude these time periods from physiological data analysis). EMAs are delivered weeks 0-7 for the control, and weeks 0-1 for the active condition, who receive EMAs with EMIs weeks 1-7

Figure 3 Empatica E4 wristband

Participants who complete the 1-week survey will be randomized and receive a wrist wearable (***Empatica E4, worn 6 weeks post-assault;*** Figure 3) via mail. This wearable continuously assesses physiologic measures (i.e., EDA), and allows users to press a button to mark occurrences. Participants will be asked to mark occurrences when they experience internal or external trauma reminders (e.g., intrusive memories or external cues). Participants will receive a brief introduction to the wrist wearable in the ED and further instructions at 1 week. Consistent with prior research,[143] data will be analyzed in 40-min blocks (20 min pre- and post-event triggers) and compared to random 40-min blocks in which triggers did not occur.

EDA will be assessed at 4 Hz from 2 wrist wearable sensors. Data (in MicroSiemens) will be analyzed using Ledalab,[144] a validated software package. Processed and cleaned data will be output for every 500 ms in the 40-min block. To quantify anxious reactivity, peak EDA will be identified from these data and subtracted from average EDA in the corresponding "baseline" interval. *Wearable and EMA data will provide a naturalistic assessment of PTS and cannabis cravings/use, and whether the intervention impacts these variables.* The E4 has been rated as acceptable and positive by substance users, from whom EDA data from the E4 has been successfully used to detect stress and cravings in the natural environment.[143]

Self-report. The ASI-3[52] will be completed at ED visit, 1 and 7 weeks, and 6 months to measure AS. We expect that individuals will go from above the clinical cut-off of the ASI (17) to below. There is no specific expected magnitude in AS change, as this will depend on individuals' initial levels of AS. It is expected that those in the control group may also have reductions in ASI, but to a lesser degree than those in the active group. The Marijuana Problems Scale (MPS) measures problems related to cannabis use (CUD symptoms). The Marijuana Motives Measure (MMM) includes a coping subscale to be used as an outcome measure. This measures using cannabis to cope with distress, which is a risk factor for CUD. The CIDI-SC measures the quantity/frequency of cannabis use regardless of whether or not this use is problematic, and is also a secondary outcome measure. Finally, the Marijuana Cravings Questionnaire (MCQ) measures state cravings to use cannabis. The total and emotionality subdomains (measuring cravings to use cannabis to cope with emotions) will be used as secondary outcomes.

6.1.6 SELF-REPORT ASSESSMENTS

Clinical assessments (Table 2) will occur remotely via REDCap, a reliable and valid method of data collection.[137] Treatment acceptability will be measured at 1 week via the Credibility/Expectance Questionnaire (CEQ),[145] Treatment Acceptability/ Adherence Scale (TAAS),[146] and 7 weeks with a study-specific measure with open-ended questions. PTS, CUD and secondary outcomes will be assessed at 6 months, allowing for temporal mediation tests. Demographic information will be collected on the one-week survey. Current medication use will be collected at one and seven weeks, and six months.

Table 2. Select Measures by Domain and Time Point

Domain	Measure	ED	EMA	1-wk	7-wk	6-mo	12-mo*
Anxiety	Patient-Reported Outcomes Measurement Information System (PROMIS) - Short Form 8a[147]			X	X	X	
Pre-SA Anxiety	Patient-Reported Outcomes Measurement Information System (PROMIS) - Short Form 8a[147], Retrospective			X			
Anxiety sensitivity	Anxiety Sensitivity Index-3 (ASI-3)[52]	X		X	X	X	
Depression	PROMIS - Short Form 8b[147]			X	X	X	
Pre-SA Depression	PROMIS - Short Form 8b[147], Retrospective			X			
Posttraumatic Stress	PTSD Checklist (PCL-5)[148], adapted for assault as index trauma and Ecological Momentary Assessment (EMA) when relevant	X	X	X	X	X	
Stress Reactivity	Empatica E4 (6 weeks post-assault), Positive and Negative Affect Schedule (PANAS)[138]	X	X				
Substance Use	Composite International Diagnostic Interview Screening Scales (CIDI-SC), daily use and quantity[149]	X	X	X	X	X	
Problematic Cannabis & Substance Use	Cannabis: Marijuana Problems Scale (MPS),[150] Marijuana Motives Measure (MMM),[151] Marijuana Craving Questionnaire (MCQ)[139]; Other: Alcohol Use Disorder Identification Test (AUDIT)[152], Drug Abuse Screening Test (DAST),[153] Fagerstrom Test for Nicotine Dependence (FTND)[154]		X	X	X	X	
Treatment Credibility / Acceptability	Credibility/Expectancy Questionnaire (CEQ),[145] Treatment Acceptability/Adherence Scale (TAAS),[146] study specific measure of usability			X	X		

* Self-report assessments and contact information updates are only conducted at the 12-month (365-393 day) timepoint for participants who consented to this study prior to the timepoint's removal in version 2.4 of this protocol.

6.1.7 3.5 MONTH CONTACT UPDATE

At 3.5 months (~14 weeks), participants will be sent a request to either confirm or update their contact information via REDCap. Participants will be allowed from 12-16 weeks to complete this update. Those who do will be compensated $10 for their time.

6.1.8 EXPERIMENTAL CONDITIONS

6.1.8.1 RISE GUIDE

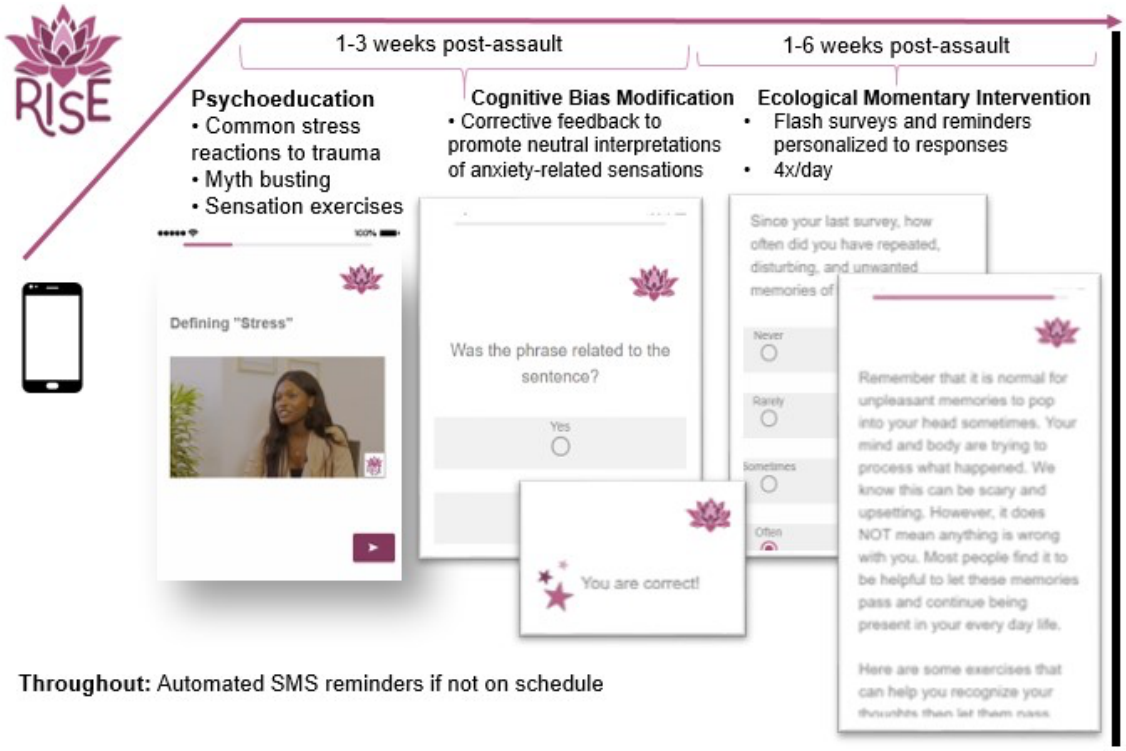


Figure 4 Overview of RISE Guide.

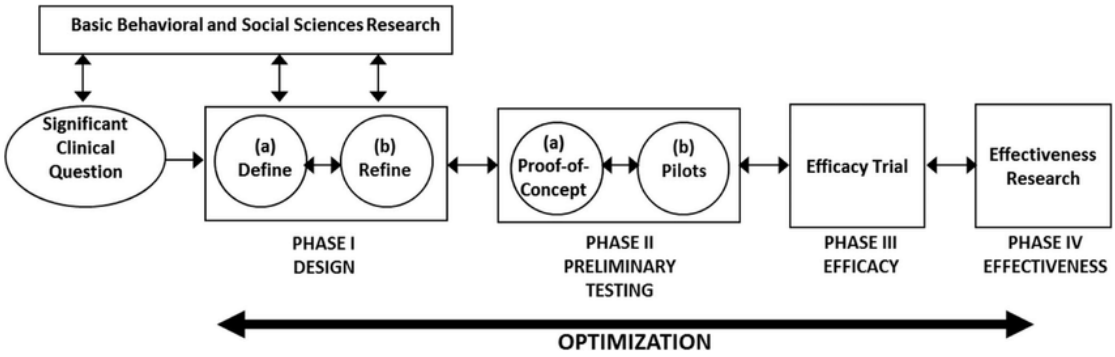
The RISE (RCT for Innovating Stress-related eHealth) Guide is based on CAST, an AS intervention effective in reducing AS, PTS, depression, and anxiety [108–111] but tailored for recent assault survivors with PTS and for delivery by smartphone via Qualtrics. Psychoeducation and CBT principles are delivered in an interactive, audio-visual format discussing the stress response, "myth busting" cognitive distortions related to stress, and exposure to feared sensations (Figure 4). For example, common reactions after trauma (e.g., intrusive memories) and how these can be catastrophically misinterpreted (e.g., I am going crazy or losing control) are discussed while providing corrective information (i.e., intrusive memories are normal, and, while distressing, not dangerous) and coping strategies (e.g., recognize thoughts and let them pass rather than attempting to suppress them), including those related to substance use (e.g., anxiety may seem like it will never go away without substance use, but substance use actually maintains anxiety in the long run). Participants will then complete a validated cognitive bias modification for interpretation biases related to AS (CBM-I), as combining these approaches enhances AS treatment efficacy.[114] Finally, intervention principles will be reinforced using EMI, in which surveys and personalized reminders are delivered (e.g., if a participant reports high re-experiencing, she will be reminded this is normal and linked to review relevant material). Further, if substance cravings or use are reported, EMIs will deliver coping tools (e.g., reminder anxiety is temporary and substance use exacerbates it in the long run) to boost efficacy.[155] RISE Guide is completed in approximately 45 minutes over 2 weeks, with EMI in the initial 6 weeks post-assault.

6.1.8.2 RELAXATION CONTROL

Breathe2Relax[156] is a mobile application that instructs users on diaphragmatic breathing, a coping tool in which slow breathing through the diaphragm reduces anxiety.[157,158] Participants in the control condition will download Breathe2Relax to their smartphones and receive SMS reminders to engage with the app. The control intervention is expected to reduce symptoms, but not as much as the CBT strategies taught in RISE Guide.[159,160]

6.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Overall, consistent with the ORBIT model of behavioral randomized controlled trials, the current study is considered to be Phase IIb. We have conducted an initial proof-of-concept, and now are at the stage of testing the feasibility of an RCT (termed a "pilot" RCT). The goal of the pilot RCT is to assess the feasibility of a further, larger efficacy trial (Phase III). Therefore, the design and outcomes are selected to be in line with a future, larger efficacy trial, but the current study will not test these outcomes. Instead, we will test whether the proposed RCT is feasible.



The following design questions refer to the ultimate larger RCT for which this is a pilot trial:

First, we selected a relatively narrow and homogeneous sample to maximize treatment effects. We will recruit those with high AS to ensure AS reduction is possible (in our pilot, nearly ¾ of women with high AS had clinically significant PTS in the 6 weeks post-assault), and exclude men as women are the vast majority (>90%) of survivors presenting to EDs.[6,161]

Second, women presenting to the ED after sexual assault often have a history of assault and PTS-SUD. Thus, prevention may serve as intervention for some. However, new traumas often cause symptom exacerbation,[125] preventive interventions may be even more effective among those with assault history,[162] and AS interventions are effective for chronic symptoms.[108,110,112]

Third, we selected an AS intervention vs. others (e.g., Resnick's video,[163] 1-session Prolonged Exposure,[7] Brief Behavioral Treatment for Insomnia[164]) because one transdiagnostic target (AS) can parsimoniously reduce symptoms of multiple disorders, level of engagement in out-of-session work does not impact AS treatment efficacy,[165] and digital therapeutics targeting AS are efficacious, scalable, and feasible for ED dissemination.

Fourth, we elected to initiate intervention 1 week after assault to allow between-group comparison of initial symptoms.

Fifth, we chose an active control because 1) AS interventions are effective vs. active controls,[108–110] 2) other secondary CBT preventions are effective compared to RCs after sexual assault,[166] and 3) ethically, this vulnerable group has a right to an intervention that provides some benefit.

6.3 END OF STUDY DEFINITION

A participant is considered to have completed the study if she has completed all phases of the study including the last survey shown in Section 2.6 Schedule of Activities (SoA).

The end of the study is defined as completion of the last visit or procedure shown in the SoA in the trial globally.

6.4 STUDY POPULATION

This study recruits female sexual assault survivors only, a historically understudied and underserved population. Female sexual assault survivors who present to a participating SANE program site for a forensic exam kit within 72 hours of the assault will be approached regarding participating in the study. Women from all races and ethnicities will be eligible for enrollment.

6.5 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

- Provision of signed and dated informed consent form
- Stated willingness to comply with all study procedures and availability for the duration of the study
- Women sexual assault survivors presenting for emergency care ≤72 hours post-assault at one of our study sites
- Able to speak, read, and write English
- 18+ years of age
- Able to provide informed consent
- Have a smartphone with continuous service ≥1 year
- Reports elevated AS (>17 on the ASI-3)

6.6 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

- Inability to provide informed consent (e.g., serious injury preventing the ability to hear, speak, or see to consent and participate, or other causes [e.g., diagnosed cognitive deficits, diagnosed dementia, asleep at time of screening])
- Prisoner
- Currently pregnant
- Lives with assailant and plans to continue to do so
- Admitted patient
- No mailing address
- Previously enrolled in this study
- No SANE examination

6.7 SCREEN FAILURES

Screen failures are defined as participants who do not meet eligibility criteria. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) because their phone is not with them in-clinic may be rescreened within 1 week of assault. Rescreened participants will be assigned the same participant number as for the initial screening. EMA data scheduled to occur between initial and secondary screening will be considered missing and follow-up surveys will remain scheduled based on the initial screening date (e.g., a participant's 7-week survey would take place 7 weeks after their initial screening).

6.8 STRATEGIES FOR RECRUITMENT AND RETENTION

6.8.1 DATA COORDINATING CENTER

The UNC Institute for Trauma Recovery will serve as the data coordinating center. UNC will send weekly email updates, and hold weekly site calls, annual in-person (or virtual if needed) conferences in Chapel Hill, NC, and quarterly teleconferences. These methods were used successfully in R01AR064700

6.8.2 RECRUITMENT SITES

Recruitment will be conducted at the two below Better Tomorrow Network sites. Additional sites may be added throughout the study; these sites will cede to UNC's Institutional Review Board (IRB), complete collaboration agreements with the UNC Institute for Trauma Recovery, receive a group-level training demonstrating proper enrollment procedures, complete one-on-one mock participant trainings (in which site research assistants "enroll" a member of the UNC research team in a non-production copy of the REDCap database), and receive a shipment of site start-up materials (a binder containing a current copy of the site standard operating procedures, a password-protected laptop or iPad and charger, and earbuds to distribute to participants). Site PIs will receive additional training entering patient screening results and managing site RA teams (further discussed in Section 10.1.6).

We do not expect these sites to launch simultaneously, as the steps required to launch a site (as explained in the previous paragraph) will vary in duration across sites.

6.8.2.1 AUSTIN SAFE

Site PI: Jenny Black
jblack@safeaustin.org
(512) 356-1530

Site Address: 1515 Grove Boulevard
Austin, TX 78741

Projected enrollment (based on WHS recruitment)**:** 70 women

6.8.2.2 TULSA FORENSIC NURSING SERVICES

Site PI: Kathy Bell, RN, MS
kbell@cityoftulsa.org
(918) 596-7608

Projected enrollment (based on WHS recruitment)**:** 80 women

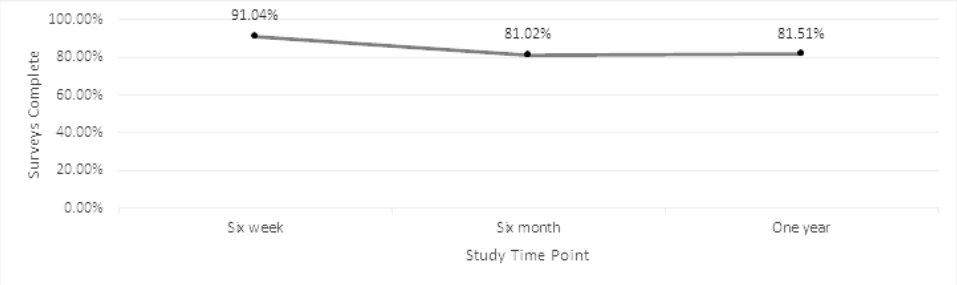
6.8.3 RECRUITMENT ESTIMATES

All sites are emergency care providers for women sexual assault survivors and provide SANE services. In Dr. McLean's prior sexual assault study, approximately 14 women per month were successfully recruited (10/month including only the sites at which we plan to launch this study), and 98% of these participants said they would be willing to participate in interventional studies.

6.8.4 RETENTION PLAN

For the prior sexual assault study, follow-up rates were >80% at all study time points (i.e., six-week, six-month, one-year) over one year post-assault (Figure 5).

Figure 5 Final follow-up rates for the Women's Health Study



To achieve these successful follow-up rates, a number of strategies have been tested and will be utilized in the current study, including: collecting several different methods of contact (e.g., phone, email, address, emergency contact), ensuring participant contact early in the follow-up window, continuous tracking of retention rates and adding countermeasures if rates drop below 80%, using SMS to contact participants for follow-ups, and allowing participants to complete follow-ups remotely via an online, encrypted database or via phone if preferred. We have also devised a plan for possible retention challenges and countermeasures to be deployed for this study (Table 3).

Table 3. Potential Retention Challenges and Strategies

Potential Challenge	Strategies to Address
Reduced follow-up rate	• Obtain multiple methods to contact. • Track follow-up rates for each follow-up method (i.e., treatment completion, standard questionnaire follow-ups, ecological momentary assessment, wearable wear) and implement countermeasures if rate is <80%. • Dedicate increased resources to achieving follow-up as patient nears end of window. • Confirm patient contact information at regular intervals. • Offer telephone follow-up. • Consider increasing compensation or adding bonuses for participation.
Reduced treatment adherence	• Ensure that participants' feedback about the treatment during Phase I is implemented as needed. • Track adherence rates and execute follow-up countermeasures if rate is <80%. Contact participants via various modes of contact. • Offer opportunity to complete intervention all at once via their laptop or at a study site.

Participants will also receive compensation for their time spent on and expertise provided to the current study as described in

Table 4. These compensation rates are consistent with other studies of recent trauma survivors.

Table 4. Participant Compensation by Activity

	Initial	One-Week	Time Intervention Completion	Ecological Momentary Assessment (EMA)	Wristband Wear	Seven-Week	3.5 Month Contact Check	Six-Month
Compensation	$40 *Participant ineligible after screener earn $20	$50	Active: $15/module (3 modules, $50 for entire intervention completion) Control: $50 for intervention completion (no modules)	$1/EMA	$15 for meeting $1/day of wear $5/data upload $5 upon return ($132 maximum)	$50	$10	$50

Potential participants who are deemed ineligible after going through the initial screening process will be compensated with a one-time payment of $20.

After 6 weeks of the wristband portion, if the participant does not return wristband after 3 attempts of contact, coordinator will reach out and notify participant that they will receive a bonus of $20 after they have mailed the wristband back.

7 STUDY INTERVENTION

7.1 STUDY INTERVENTION(S) ADMINISTRATION

7.1.1 STUDY INTERVENTION DESCRIPTION

Active Intervention. The RISE (RCT for Innovating Stress-related eHealth) Guide is based on CAST, an AS intervention effective in reducing AS, PTS, depression, and anxiety,[108–111] but tailored for recent sexual assault survivors with PTS and for delivery by smartphone via Qualtrics. Psychoeducation and CBT principles are delivered in an interactive, audio-visual format discussing the stress response, "myth busting" cognitive distortions related to stress, and exposure to feared sensations (Figure 4). For example, common reactions after trauma (e.g., intrusive memories) and how these can be catastrophically misinterpreted (e.g., I am going crazy or losing control) are discussed while providing corrective information (i.e., intrusive memories are normal, and, while distressing, not dangerous) and coping strategies (e.g., recognize thoughts and let them pass rather than attempting to suppress them), including those related to substance use (e.g., anxiety may seem like it will never go away without substance use, but substance use actually maintains anxiety in the long run). Participants will then complete a validated cognitive bias modification for interpretation biases related to AS (CBM-I), as combining these approaches enhances AS treatment efficacy.[114] Finally, intervention principles will be reinforced using EMI, in which surveys and personalized reminders are delivered (e.g., if a participant reports high re-experiencing, she will be reminded this is normal and linked to review relevant material). Further, if substance cravings or use are reported, EMIs will deliver coping tools (e.g., reminder anxiety is temporary and substance use exacerbates it in the long run) to boost efficacy.[155] RISE Guide is completed in ~45 minutes over 2 weeks, with EMI weeks 1-7 post-assault.

Control Intervention. Breathe2Relax[156] is a mobile application that instructs users on diaphragmatic breathing, a coping tool in which slow breathing through the diaphragm reduces anxiety.[157,158] Participants in the control condition will download Breathe2Relax to their smart phones and receive SMS reminders to engage with the app. The control intervention is expected to reduce symptoms, but not as much as the CBT strategies taught in RISE Guide.[159,160]

7.2 EFFORTS TO MINIMIZE BIAS

Randomization tables will be generated by the study Biostatistician and uploaded into the study REDCap database by the UNC Research Coordinator prior to launching data collection. Participants are randomized (1:1) to receive either the RISE Guide (experimental) condition or Breathe2Relax (control) condition after completing their 1-week survey. The list of assignments will be stored securely in REDCap.

Participants will *not* be masked to their study conditions, as branding is visible in both RISE Guide and Breathe2Relax. Moreover, the UNC Research Coordinator will not be masked to condition, as they will be responsible for tracking RISE Guide progress and managing participant payments. The Principal Investigator, Biostatistician, Site Principal Investigators, Site Research Associates, and anyone involved in data analysis will remain masked to condition until data analysis is complete; masking will be maintained through reduced data viewing privileges in REDCap.

7.3 STUDY INTERVENTION COMPLIANCE

The study database will track RISE Guide module progress and EMI/EMA completion in real time. Compliance is encouraged via reminders to engage with the intervention to participants and bonus compensation for timely module completion and significant EMI/EMA completion. Participants in both the experimental and

control conditions will complete the Treatment Acceptability/Adherence Scale (TAAS)[146] during their 1-week and 7-week follow-ups.

8 INTERVENTION DISCONTINUATION AND PARTICIPANT WITHDRAWAL

8.1 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request. The research team will ask participants to share their reason for leaving the study, though withdrawn participants may elect not to share their reason.

An investigator may discontinue or withdraw a participant from the study for the following reasons:

1. Significant study intervention non-compliance
2. If any clinical adverse event (AE) or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
3. If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

The reason for participant discontinuation or withdrawal from the study will be recorded in the study database. Subjects who sign the informed consent form and are randomized, receive the study intervention, and subsequently withdraw, or are withdrawn from the study, will not be replaced.

8.2 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.2.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

8.2.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of the investigator, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity, or substantial disruption of the ability to conduct normal life functions. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include expression of a suicidal or homicidal plan.

8.2.3 CLASSIFICATION OF AN ADVERSE EVENT

8.2.3.1 SEVERITY OF EVENT

The following guidelines will be used to describe severity of AE:

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.

- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.2.3.2 RELATIONSHIP TO STUDY INTERVENTION

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

- **Related** – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

8.2.3.3 EXPECTEDNESS

Drs. Samuel McLean and Nicole Short will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.2.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care.

All AEs not meeting the criteria for SAEs will be captured in the study REDCap database. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to RISE Guide (assessed only by Dr. Short), and time of resolution of the event. All AEs occurring while participating in the study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution (assurance of immediate safety and provision of referral to care).

Any medical or psychiatric condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, the study participant's symptoms will be recorded as an adverse event if their:

- anxiety severity doubles between assessments *and* falls above the cutoff for moderate anxiety (PROMIS Anxiety ≥ 17[167]),
- depression severity doubles between assessments *and* falls above the cutoff for moderate depression, (PROMIS Depression ≥ 23[167,168]),
- and/or PTS severity doubles between assessments *and* falls above the cutoff for probable PTSD (PCL-5 ≥ 31[169]).

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. Documentation of onset and duration of each episode will be maintained for AEs characterized as intermittent.

The research coordinator will record all reportable events that they learn of with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. Events will be followed for outcome information until resolution or stabilization (assurance of immediate safety and provision of referral to care).

8.2.5 ADVERSE EVENT REPORTING

Adverse events (AEs) will be tracked within the study's REDCap database. Serious adverse events (SAEs) and AEs that are unexpected or possibly related to participation in the research study will be submitted to IRB as New Safety Information (NSI) within 7 calendar days of the event being brought to our attention. The report of AEs or SAEs will include whether they were expected or unexpected, the severity of the event, a brief narrative summary of the event, a determination of whether a causal relationship existed between the study procedures and the event, whether the informed consent or study procedures should be changed as a result of the event, and whether all enrolled participants should be notified of the event.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

- **Hypothesis 1**: Treatment acceptability for RISE Guide is greater than or equal to treatment acceptability for a relaxation control.
- **Hypothesis 2**: A randomized controlled trial to test the RISE Guide intervention will be feasible.Sample Size Rationale

A balanced, site-stratified randomization scheme (1:1) will be used. We ensured adequate power (.80, α =.05) to test all hypotheses by ensuring power for the hypothesis in need of the greatest sample size (mediation effects of the intervention on clinical outcomes via changes in AS). Power analyses were conducted and sample sizes were chosen based on power as well as feasibility of this initial pilot study.

Statistical Analyses

9.1.1 AIM 1 (USABILITY, ACCEPTABILITY, AND CREDIBILITY)

To examine usability, credibility, and acceptability of RISE Guide, mean credibility/acceptability scores will be compared to norms to ascertain treatment credibility/acceptability.

Specifically, mean levels of the Credibility/Expectancy Questionnaire (CEQ)[197] to assess credibility and the Treatment Acceptability/Adherence Scale (TAAS)[211] will be examined to assess acceptability and adherence at 1 week will be compared to published CBT interventions, with the hypothesis that CEQ and TAAS total scores will exceed 30 and 40, respectively. Utilization and acceptability will also be examined via response from the 6 week measure designed for the current study (including 6 items on a 5-point Likert scale, such as *How often did you log in? How interested were you?* and 4 open-ended questions; e.g., *What did you like about RISE Guide?; What did you not like?*). Descriptive statistics will be analyzed to determine if any specific area needs improvement. Then, open-ended items will be evaluated by reading and noting important and common feedback, focusing on comments related to ease of use, comprehensibility, limitations, and suggestions for improvement. Scores will be compared to the Relaxation Control condition as well, but the primary Hypothesis is that mean scores will exceed the CEQ and TAAS cut-offs provided above.

9.1.2 AIM 2 (FEASIBILITY)

To assess feasibility of conducting a randomized controlled trial to test the RISE Guide intervention.

Recruitment. We will calculate the total number of participants recruited, and how many participants were recruited per month. The goal is that we will recruit 2-4 participants per month.

Retention. We will calculate the total number of participants completing each time point, with the goal of 75%+ retention rates.

Adverse Events. We will evaluate the total number of adverse events, including by condition.

will be used to assess whether RISE Guide attenuates associations between wrist wearable EDA reactivity to trauma cues (triggered on the E4 by participants) and EMA cannabis cravings/use. Hypothesis 3 will be assessed when75 and 150 participants have completed the study.

9.1.3 BASELINE DESCRIPTIVE STATISTICS

We will use SPSS Version 25[181] to analyze descriptive statistics and generate histograms. These will be reviewed and visually inspected for potential nonnormality and outliers. If needed, appropriate data transformations will be applied, or alternative data procedures (e.g., nonparametric, bootstrapping) will be used. Special attention will be paid to the distribution of cannabis use to determine if alternate analytic strategies are needed if rates are low.[182]

9.1.4 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual participant data will be listed by measure and time point.

10 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting the intervention. The following materials are submitted with this protocol:

- Adult consent form
- HIPAA authorization form
- Participant discharge flyer outlining study schedule and contact information for the study. Importantly, this flyer does *not* disclose anything about the assault.
- Planned email and text communications

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Full study consent is obtained at the time of presentation for care. Each consent is obtained by traditional in-person consent or by electronic teleconsent (detailed below). A potential participant must provide consent to participate. The RA will explain the study and answer any questions from the potential participant, emphasizing the voluntary nature of the study and the ability for the participant to cease or withdraw their participation at any time. A signed copy of the consent form will be given to the participant. Consent will be obtained via REDCap, and it will be documented and timestamped in the study tracking database prior to the initial assessment.

Teleconsent is used as a consent option, because it has been widely shown to be a safe and valid method of obtaining consent in medical settings,[189,190] and because it addresses barriers that prevent critically needed research in settings where it is very difficult to consistently physically provide trained research staff at the time and place necessary for consent. (In this study, and more generally in research, teleconsent also addresses inequities created by the fact that research staff are more difficult to hire/provide in socioeconomically disadvantaged and/or rural areas). Teleconsent facilitates the consent process and provides the same opportunity to make an informed and voluntary decision as a traditional consent. Importantly, the teleconsent platform used in this study complies with Health Insurance Portability and Accountability Act (HIPAA) requirements by (1) encrypting all transmitted data, (2) not storing patient information, (3) keeping an audit trail of the consent process, and (4) signing a business associate's agreement (BAA) with the user.

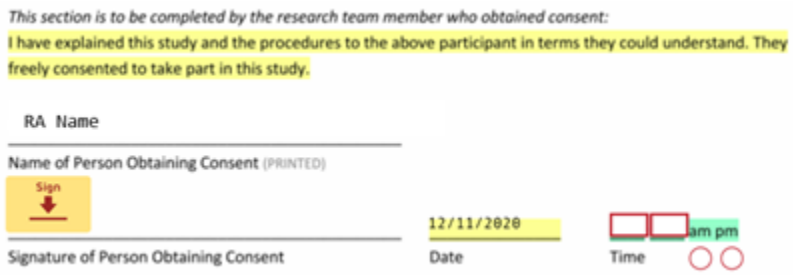
Teleconsent is obtained in the following manner. The SANE nurse approaches the potential participant at the time of her SANE exam to assess her willingness to speak to an RA about participation in an ongoing study via

laptop or tablet. If the potential participant is willing, an individual at the local site will notify the on-call teleconsent RA with an estimate for when the participant will be ready to speak. Alternatively, if patient requests, the SANE may schedule an appointment time in a secure communication platform, within 24 hours, to meet directly with the teleconsent team to complete informed consent and the remainder of the enrollment process.

Once ready, the SANE uses the study laptop or tablet to open Zoom and joins the teleconsent RA's HIPAA-enabled Zoom meeting room. If the patient chooses to meet with RA within 24 hours, the RA will send the patient a Zoom meeting invite and join the meeting room at the scheduled time. The RA introduces her/him/themself via live two-way video communication and describes her/his/their role as a research associate in an ongoing study testing an app-based intervention to aid recovery after sexual assault. Just as in person, if the potential participant is willing, the RA reviews the study consent and requirements for participation in real-time, and uses the online database to screen the potential participant for study eligibility. If eligible, the teleconsent RA opens DocuSign – a secure eConsent platform – and sends the consent, HIPAA authorization, and social security number collection forms to the participant's email inbox. Both the participant and the teleconsent RA will open and review the documents. Because both the RA and the participant will have the forms open, the participant can follow along on her screen while the RA explains each section. This allows teleconsent to be an interactive and engaging experience, similar to in-person consent, and facilitates a careful explanation and discussion of the consent document.

After reviewing the consent documents on the laptop or tablet, if the potential participant is willing to participate, the RA and participant both electronically sign the consent through DocuSign and enter their time of signature (the date of signature is automatically piped in by DocuSign). DocuSign only allows the participant and RA to sign and timestamp their respective sections (i.e. the RA cannot mistakenly sign on behalf of the participant, and vice-versa), protecting the integrity of the consent process.

Figure 6 Example of RA signature field.



When the consent document is complete, DocuSign checks to ensure all data fields have been filled out. If required fields have not been completed, the document automatically scrolls to display the first missing field. When the document is completely filled out, a PDF file of the completed consent, HIPAA, and SSN documents is generated and emailed to the participant, and the RA saves a copy to the central, secure online study database.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

If participants in the active group exhibit, on average, clinically significant exacerbations in ASI scores (transition from scores <25 to ≥25), PCL-5 scores (12-point increase, scaled based on the 10-point cut-off used in PCL-IV[191]), or MPS scores (increase of 8 pts[192]), then the investigative team will review the findings to evaluate the safety of continuing with the trial. This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will

promptly inform the Institutional Review Board (IRB) and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to the study activity schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, substantial, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the IRB.

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators and their staff. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to participants' clinical information. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Principle Investigator.

All research activities will be conducted in as private a setting as possible.

Representatives of the Institutional Review Board (IRB) and regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information and research data will be securely stored in the study's REDCap database. At the end of the study, all records will continue to be kept in a secure location for 3 years prior to being destroyed.

The study data entry and study management systems used by clinical sites and by UNC Institute for Trauma Recovery research staff will be secured and password protected.

10.1.3.1 CERTIFICATE OF CONFIDENTIALITY

To further protect the privacy of study participants, the research team already obtained a Certificate of Confidentiality (COC; **CC-OD-20-266**) for the ongoing pilot study of the proposed intervention. A COC for this RCT will be requested prior to enrolling participants. This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

10.1.4 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management. These plans will be reviewed and approved by the data coordinating center at UNC.

The research coordinator will run quality control (QC) checks on the REDCap database each month. Any missing data or data anomalies will be communicated to the sites for clarification and resolution.

10.1.5 DATA HANDLING AND RECORD KEEPING

10.1.5.1 DATA COLLECTION AND DATA MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, and timeliness of the data reported.

Study data (including adverse events (AEs), study assessment data, and digital copies of sexual assault medical records) will be entered into the study REDCap database, which includes password protection and internal quality checks (such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate).

10.1.6 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol or International Conference on Harmonisation Good Clinical Practice (ICH GCP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with the following sections of the ICH GCP Consensus Guideline[193]:

- 4.5 Compliance with Protocol, sections *4.5.1*, *4.5.2*, and *4.5.3*
- 5.1 Quality Assurance and Quality Control, section *5.1.1*
- 5.20 Noncompliance, sections *5.20.1*, and *5.20.2*.

Protocol deviations may be initially identified by a site research associate (RA), site principal investigator (PI), or UNC-based research coordinator. Site personnel are trained to report any deviations from the study protocol to both the UNC PI and Coordinator immediately following enrollment (the only timepoint at which site personnel and participants interact). The Coordinator maintains a digital Protocol Deviation Log, uploads Notes to File to the study REDCap database, and receives guidance from the PI regarding whether deviations constitute New Safety Information (NSI); the Coordinator reports NSI to UNC's IRB within 7 calendar days of becoming aware of the deviation, per guidance from UNC's Office of Human Research Ethics.[194]

The reporting pathway for protocol deviations is illustrated in Figure 7:

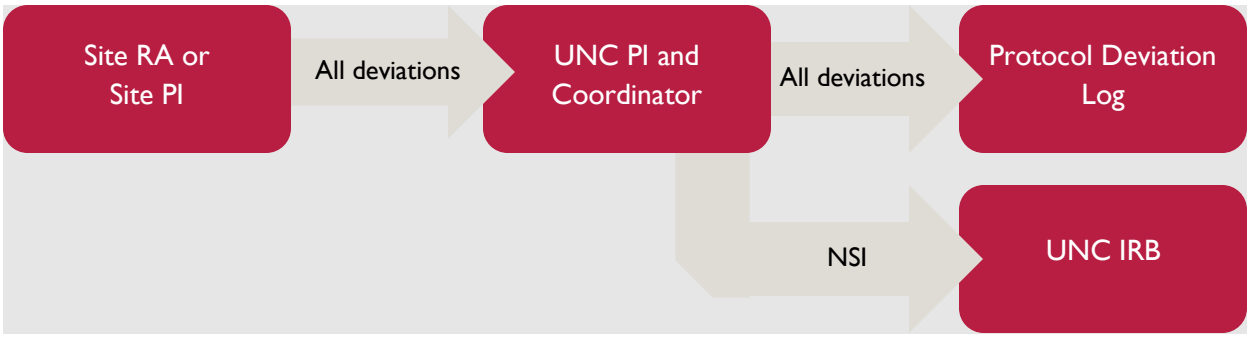


Figure 7 Protocol deviation reporting pathway.

10.1.7 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. All team members will disclose Conflicts of Interests via the UNC Activities, Interests, and Relationships (AIR) Management System.

11 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
1.0	04/13/2021	(Initial submission)	N/A
1.1	05/06/2021	Described risk of bruising post- blood draw. Created table of abbreviations	Per IRB stipulations Per scientific review requirements
2.0	07/02/2021	Clarified that pre-assault depression and anxiety are collected retrospectively at 1 week. Clarified that re-screening does not shift study timeline. Clarified that primary outcome is CUD, not general SUD. Clarified plan to use FIML to address missing data. Clarified plan to compare AS between active and control participants. Revised definition of AE to require doubling of symptom severity *and* score within or above moderate range. Revised AE reporting guidelines to clarify that all only AEs possibly related to research participation will be reported as NSI. All SAEs will still be reported as NSI. Added Xinming An as biostatistical support. Created sub-headings within "Study Rationale". Expanded Table of Contents to include 4 levels of headings. Expanded upon data monitoring plans to clarify that Lead Research Coordinator will review data every two weeks. Standardized font size and style throughout protocol. Rephrased "emergency care sites" to "study sites". Added number of sites, site names, site PIs, estimated enrollments by site, site onboarding plans, and site protocol deviation reporting pathway. Detailed data coordinating center role. Clarified references to ICH GCP Consensus Guidelines. Justified use of multiple measures for similar constructs. Explained role of DNA and RNA analysis in study. Explained that reasons for study drop-out will be collected, given that participants are willing to share. Rephrased "Endpoints" to "Outcomes" throughout. Removed plans to modify RISE Guide during study. Expanded upon interim analysis plans and rationale.	Per Scientific Review Committee feedback

		Clarified criteria for stopping in the study based on interim analysis results. Corrected interim analysis timeline to take place when 75 and 150 women complete study procedures. Clarified interim vs. safety monitoring. Clarified variables associated with specific constructs throughout protocol. Clarified that Aim 1 will assess active and control conditions. Organized outcomes by aim in Protocol Summary. Rephrased hypotheses to reference potential population-level impact and be testable. Changed heading "Sample Size Determination" to "Sample Size Rationale". Changed heading "Populations for Analyses" to "Cohorts for Analyses". Removed plans to test for demographic or clinical differences between control and active conditions, Added plans for sensitivity analyses. Rephrased "Exploratory Analyses" to "Secondary Analyses". Stated that all hypotheses yielding high *p*-values will be reported as inconclusive. Stated that *p*-values will be reported to four decimal places without dichotomization. Removed references to statistical significance. Stated that all statistical estimates of population parameters will be tabulated along with corresponding CIs. Added "Target Sample Size" to Protocol Summary. Clarified plans to recruit 150 women. Incorporated full details of sample size rationale. Clarified that power analyses suggested, and did not reveal, target recruitment numbers. Expanded upon randomization process. Added funding source to title page.
2.1	09/01/2021	Added Janhvi Rabadey as a Study Coordinator Added specific aim 2d: "Assess whether specific genetic variations predict RISE Guide treatment efficacy, as measured by AS (ASI-3) reductions 7 weeks post-assault". Clarified that the blood draw during the Initial wave is optional

2.2	2021/12/14	Added information regarding payments for participants during screener become ineligible. Table 4 updated to include one-time compensation of $20 for ineligible potentials after screener.	
2.3	11/28/2022	Removal of one year follow-up, providing payment for intervention completion, and collecting updated contact information at 3.5 months.	Increase follow-up rates.
2.4	2022.11.28	Due to logistical issues, the 1-year follow-up is being removed. Study participation will now end after the 6-month follow-up. Participants will receive compensation for completing the RISE (active) intervention and the Breathe2Relax (control) intervention ($50 for each condition). At 3.5 months post-assault, we will collect updated contact information from participants. They will be compensated $10 for updating their information.	
2.5	2023.12.13	Updated PI to Samuel McLean.	Dr. Nicole Short transitioned to a new role outside of UNC Chapel Hill.
2.6	2023.07.13	Add the University of Nevada at Las Vegas as a collaborative study site. Update Nicole Short's affiliation to the University of Nevada at Las Vegas	Dr. Nicole Short transitioned to a new role outside of UNC Chapel Hill.
2.7		Specify NCT number. Update degree for Kristen Witkemper. Remove April Soward as personnel. Clarify that contact information updates are conducted at the baseline, 1-week, 6-week, and 6-month timepoints. Clarify that 1-year contact information updates and surveys are still being conducted with participants who consented prior to the Protocol 2.4 update. Specify mailing addresses for all study sites. Update mailing addresses for UNC-based personnel.	

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