Practice Experiences for School Reintegration: An Immersive Virtual Reality Program to Enhance Skill Development of Hospitalized Adolescents

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Master Protocol Document

Title	Practice Experiences for School Reintegration
Sub-Title	An Immersive Virtual Reality Program to Enhance Skill Development of Hospitalized Adolescents
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I have read, understood, and approved this version of the protocol. [electronic signatures accepted]

Principal Investigator: Marisa Marraccini Date: 7/16/25

Statistical Co-investigator: Leslie A. Brick Date: 7/16/25

Table of Version Changes

Previous Version No.	Affected Sections	Summary of the Changes to the Protocol	Reason for Changes
1.1	**1, 2.3, 3, 4, 4.5, 4.6, 4.7, 4.8, 5.5, 7, 9, 12.5, 13.1.1**	• Due to limited power, the exploratory aim was revised to remove exploration of possible impact and utility of the intervention and instead address assessment of candidate intermediary and outcome measures (addressed throughout and in statistical plan, section 9); • Clarification of what is considered success for Aims 1-2 (i.e., minimum recruitment rate, average completion times, average ratings, see 4.8) • Change in stopping rules for study discontinuation and closure based on DSMB recommendations (now using SUDS to assess safety instead of CSSRS; see 4.5 and 12.5) • Clarification of intervention design based on developed feedback and final prototype (see 4.6, 6) • Removal of stratification procedures for gender due to pilot nature of trial (see 4.7, 5.5) • Addition of missing measures collected (see Figure 2, Table 1, section 7) • Included list of IRB approved consent/assent documents (13.1.1) • Addition of Electronic Signatures	Meeting with statistician concerning power of analyses, sample size implications for stratification, and improving specificity of measures for Aims 1-2; Meeting with DSMB about improving assessment of safety; Final review to correct errors or add any missing information related to number formatting, acronyms, and specific information related to intervention components (Intro to CBT was previously missing) and procedures based on final prototype and meeting with hospital.
1.2	**4.8** **8.3** **12.1.1** **1** **4.6** **4.7** **6** **11.4**	• The specific primary outcomes and candidate exploratory outcomes were added to the statistical analysis section to ensure consistency across the document; • The appendices listing consent and assent documents were removed since clinicaltrials.gov requires final consent uploaded at the completion of the trial. • We have clarified that the worksheets are provided by the researchers to all participants and that participants receiving the intervention will also receive additional worksheets part of a workbook aligned to the intervention. • We have removed the virtual reality Intro to CBT module as we were unable to include this in the final intervention. • Based on previous DSMB review, we revised our safety protocol in 11.4 (these changes were made in version 1.2; however, we missed one instance in 11.4 and corrected it for 1.3): Previously, we indicated that intensity of suicidal thoughts would be	Finalization of clinicaltrials.gov submission and review provided by UNC office of clinical trials. Final development and selection of worksheets and intervention workbook. We were not able to include the Intro to CBT VR lesson due to limitations of the VR device and time constraints. Previous DSMB review of safety protocols

		monitored pre and post intervention completion; instead we will monitor using the SUDS scale (distress level) pre and post intervention.	
1.3	**TABLE OF ABBREVIATIONS** **4.7** **4.8** **7.1** **8.2** **12.1** **12.1.2**	• We removed a placeholder in the table of abbreviations that was part of the template • Relaxation was changed to Affect Regulation • The Authoritative School Climate Survey (ACS) and School Connectedness Scale (SCS) were removed from post-intervention assessment • Qualtrics was added as an additional option for obtaining parent permission virtually	The placeholder was removed for readability Relaxation was changed to Affect Regulation to ensure consistency of wording throughout the intervention ACS and SCS were only meant to be completed once during baseline given they measure perceptions on school and participants remain in hospital throughout baseline Both Qualtrics and REDCap are approved data collection tools in the study IRB
1.4	**4.8** **7.1**	• We amended timepoints for when medical records will be collected • Admission and discharge date were added to information collected from medical record	Medical records will be collected during baseline and again at 3-months to ensure consistency and accuracy Admission and discharge date were added to consider length of hospitalization as a covariate and to facilitate follow-up appointments
1.5	**4** **4.7** **7** **7.4**	• We corrected an error in which the protocol stated the 3-month follow-up assessments were anchored to discharge, but they are anchored to school re-entry. • We have allowed post-intervention assessments to be completed following discharge as needed.	The full protocol anchors follow-up appointments to school re-entry (not discharge) and this was inconsistent with the other aspects of the protocol. Hospital discharge can occur very last minute, and it is not always possible for us to complete post-intervention assessments prior to discharge. Although we will

			continue to prioritize completing assessments prior to discharge, we are revising the protocol to allow to complete assessments following discharge as needed.
1.6	**4.5** **11.5** **7**	• We identified an error in study suspension procedures (a 3-point increase pre/post VR on the 0-10 distress scale was meant to signal concern, and the protocol mistakenly reports this as a 30% increase when it is actually a 300% increase. • The abbreviated feedback form completed by adolescent participants was moved to the correct place in the table	This was a percentage calculation error, as a 30% increase would be a much too small threshold and a 300% increase is considered appropriate. Approval for this correction was confirmed by the DSMB on 01/23/2024. The abbreviated feedback form completed by adolescent participants was mistakenly placed with the clinician feedback
1.7	**5.1**	• We noted that hospital professionals can be recruited from one of two hospitals and that 1-2 UNC hospitals will be used for patient recruitment	We are adding a new site to the trial (UNC Youth Behavioral Health)
1.8	**12.9**	• Reporting procedures for protocol deviations corrected.	Reporting procedures for protocol deviations were clarified to align with policies and procedures of funding agency and institutional review board.
1.9	**1, 5.2**	• Eligibility for adolescent patients participating with a hospital professional (not part of the randomized trial) was clarified and revised	Hospital professional participants have been supporting decisions around appropriateness of intervention and many patients without expected return to school have been considered appropriate; given the open trial does not follow outcomes, but rather, aims to inform implementation, we have revised eligibility criteria for these patients. Note that the randomized trial eligibility remains the same.

1.10	**4.8**	• Amended Table 2 to correct occasions of retention rates measurements • Corrected minor typos throughout	Correcting information for readability and clarity, including addressing errors in tables.

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Statement of Compliance

This study will be conducted as specified in the protocol and in accordance with the *International Conference on Harmonization Guidelines for Good Clinical Practice* (ICH E6) and the *Code of Federal Regulations on the Protection of Human Subjects* (45 CFR Part 46).

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the *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 into the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

If required by the IRB, the master protocol document, informed consent form(s), recruitment materials, and all participant materials will be submitted to the *Scientific Review Committee* (SRC) prior to IRB review (research.unc.edu/clinical-trials/src).

The statistical analysis plans will be consistent with guidance in CONSORT Statement [1] or STROBE Statement [2], ICMJE recommendations [3], the 2016 and 2019 statements of the American Statistical Association [4,5], and recommendations in Nature [6,7].*

All personnel involved in the conduct of this study have completed human subjects protection training.

* [1] www.consort-statement.org
[2] www.strobe-statement.org
[3] www.icmje.org
[4] Wasserstein RL, et al. (2016), The ASA's Statement on p-Values, ***The American Statistician***, 70:2, 129-133
[5] Wasserstein RL, et al. (2019), Moving to a World Beyond p < 0.05, ***The American Statistician***, 73:sup1, 1-19
[6] Amrhein, et al. (2019) Scientists rise up against statistical significance, ***Nature*** 567, 305-307
[7] Editorial (2019) It's time to talk about ditching statistical significance: Looking beyond a much used and abused measure would make science harder, but better. ***Nature*** 567, 283-283.

Table of Abbreviations

AE / SAE	Adverse Event / Serious Adverse Event
ASCS	Authoritative School Climate Survey
ATQ	Automatic Thoughts Questionnaire
BHS	Beck Hopelessness Scale
CASI	Child Anxiety Sensitivity Index
CBT	Cognitive Behavioral Therapy
CBTSQ	Cognitive-Behavior Therapy Skills Questionnaire
CFR	U.S. Code of Federal Regulations (www.eCFR.gov)
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences (cioms.ch)
CoC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials (www.consort-statement.org)
CRF	Case Report Form
CRO	Contract Research Organization
CSCC	UNC Collaborative Studies Coordinating Center (sites.cscc.unc.edu/cscc)
CSSRS	Columbia Suicide Severity Rating Scale
CT.gov	ClinicalTrials.gov website
CTAS	Cognitive Therapy Awareness Scale
DCC	Data Coordinating Center
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
eCTD	Electronic Common Technical Document
ESE	Emotional Self-Efficacy Measure
FDA	U.S. Food and Drug Administration (www.fda.gov)
GCP	Good Clinical Practice
HIPAA	U.S. Health Insurance Portability and Accountability Act (www.hhs.gov/hipaa)
ICF	Informed Consent Form
ICH	International Council for Harmonization (www.ich.org)
ICMJE	International Committee of Medical Journal Editors (www.icmje.org)
IDE	Investigational Device Exemption
IDS	UNC Investigational Drug Services (uncids.web.unc.edu)
IND	Investigational New Drug Application
IRB	Institutional Review Board
MAR	Missing at Random Criterion
MCAR	Missing Completely at Random Criterion
MNAR	Missing Not at Random Criterion
MICE	Multiple Imputation by Chained Equations
MSSQ	Motion Sickness Susceptibility Questionnaire
MOP	Manual of Procedures
MOST	Multiphasic Optimization Strategy
MPD	Master Protocol Document
N	Number of Enrolled Participants
NDA	New Drug Application
OCT	UNC Office of Clinical Trials (research.unc.edu/clinical-trials)
OHRP	Office for Human Research Protections
PCTS	Performance of Cognitive Therapy Strategies
PHI	Protected Health Information
PI	Principal Investigator

PRC	UNC Oncology Protocol Review Committee (UNClineberger.org/protocol review)
PrESR	Practice Experiences for School Reintegration
PROMIS	Patient-Reported Outcomes Measurement Information System -Pediatric Self Report
QA	Quality Assurance
RCT	Randomized Controlled Trial
REDCap	Research Electronic Data Capture system
SCS	School Connectedness Scale
SD	Standard Deviation
SE	Standard Error
SITB	Self-Injurious Thoughts and Behaviors Interview
SoCT	Skills of Cognitive Therapy
SOP	Standard Operating Procedures
SRC	UNC Scientific Review Committee (research.unc.edu/clinical-trials/src)
SSQ	Simulator Sickness Questionnaire
STROBE	Strengthening Reporting of Observational Studies in Epidemiology (www.strobe-statement.org)
SUDS	Subjective Units of Distress Scale
TraCS	N.C. Translational and Clinical Sciences Institute (tracs.unc.edu)
UNC	The University of North Carolina
UNCH	UNC Hospitals
VR	Virtual Reality

1. Protocol Synopsis

Title	Practice Experiences for School Reintegration: An Immersive Virtual Reality Program to Enhance Skill Development of Hospitalized Adolescents
Study Description	This study is developing and refining a novel Virtual Reality (VR) supplement for inpatient treatment: the Practice Experiences for School Reintegration (PrESR) program. The PrESR will provide immersive school experiences for inpatient adolescents (with suicidal-related admissions) to practice skills in real-world settings with the guidance of a trained clinician within the confines of a hospital. This pilot study follows a Multiphasic Optimization Strategy (MOST) to conduct a pilot optimization trial of the PrESR to inform the feasibility of training clinicians, the ability to recruit adolescent inpatient participants, and management of experimental conditions. This study is not powered to test hypotheses; however, in addition to assessing feasibility and acceptability, this pilot trial will assess candidate intermediary and outcome measures.
Specific Aims **(objectives)**	Aims for the pilot optimization component of the MOST preparation phase are: **Aim 1.** Conduct a pilot optimization trial of the PrESR to *examine* feasibility and acceptability of identifying, enrolling, and retaining participants at the hospital.

	Aim 2: Conduct a pilot optimization trial of the PrESR to *examine* feasibility and acceptability of implementing assessment protocols (including motion sickness screening), fidelity of the intervention delivery (including applying the PrESR to existing hospital Cognitive Behavioral Therapy (CBT) protocols), candidate intermediary variables (i.e., threat habitation, cognition), and candidate outcomes (psychological distress, self-efficacy, suicidal thoughts and behaviors, and rehospitalization). **Exploratory Aim:** Because this study is a treatment development study, an exploratory aim is to calculate descriptive statistics for candidate proximal outcome variables to inform power for a future study that examines efficacy of the intervention.
Target Population	This study recruits a prospective sample of youth hospitalized for suicide-related crises. Based on hospitalization data, adolescents are expected to be 65% female, 15% Hispanic or Latino, 65% Caucasian and 30% minority across all aims. **Adolescent Inclusion Criteria:** 1) current hospitalization for suicidal thoughts and behaviors, 2) ages 13-18; 3) expected return to school following discharge, 4) ability to speak, read, and understand English sufficiently to complete study procedures, 5) consent of a parent/legal guardian (in English or Spanish), and 6) adolescent assent. **Adolescent Exclusion Criteria:** 1) evidence of active psychosis; 2) evidence of intellectual disability; 3) Cybersickness (≥50th percentile as measured on the Motion Sickness Susceptibility Questionnaire). **Hospital Professional Inclusion Criteria**: A clinician at the treatment site(s) who delivers treatment (potentially including CBT) to hospitalized adolescents. Hospitalized adolescent patients working with hospital professionals have the same eligibility criteria as listed as above, with the exception of inclusion criteria #3 (“expected return to school following discharge”) and may be included irrespective of school status.
Numbers of Enrollees	<u>Adolescent Participants</u> Target sample size is N = 48 enrolled adolescents. Recruitment will continue until N = 48 individuals have completed all aspects of the protocol and have complete data or until the study end date. We anticipate 20% of attrition; however, the purpose of this study is to explore feasibility and acceptability of intervention and study protocols, with true estimates of attrition unknown (attrition rate is considered to be an estimand of the study). Up to 1,000 individuals will be recruited and screened.

	Hospital Professional Participants Target sample size is N=5, with a minimum of 2 considered adequate. Up to 12 individuals will be recruited.
Interventions	The PrESR VR supplement will focus on increasing acquisition and utilization of critical cognitive-behavioral skills for treating adolescents with suicidal thoughts and behaviors. All participants will receive treatment as usual during inpatient and all adolescents will receive research-related worksheets instructing them on target cognitive behavioral skills (introduction to cognitive behavioral therapy, cognitive restructuring, problem solving, and affect regulation) aligning to worksheets used as part of typical hospital protocol. Adolescents receiving the intervention will practice skills using the PrESR, which will provide clinical guidance and feedback. Following a similar format to other therapeutic VR programs, a research clinician will observe adolescents wearing standard headsets as they learn and practice coping strategies in immersive experiences designed to mimic real life (school) stressors. At the end of the program, the adolescent and research clinician will develop a safety plan designed to address the return to school, based on these *in vivo* sessions and, when possible, in collaboration with the school. CBT skills provided through worksheets will follow a standard format across participants, with VR enhanced CBT skills based on randomization to intervention component.
Outcome Measures	**For Aim 1.** Feasibility and acceptability of identifying, enrolling, and retaining participants at the hospital will be assessed with: (1) rates of recruitment (proportion of >50th percentile as measured on the Motion Sickness Susceptibility Questionnaire); (2) rates of retention (and reasons participants cite for withdrawing from the study). **For Aim 2.** Feasibility and acceptability of implementing assessment protocols (including motion sickness screening) and intervention delivery (including applying the PrESR to existing hospital CBT protocols) will be assessed in four ways: (1) time to complete assessments; (2) time to complete the intervention; (3) ability of research staff to deliver intervention with fidelity; (4) adolescent participant feedback about the intervention (exit interview and feedback form); and (5) professional feedback about the intervention (focus group interviews or one-on-one interviews, feedback questionnaire). **Exploratory Aim:** Because this study is a treatment development study, candidate proximal outcomes of psychological distress (as measured by the Child Anxiety Sensitivity Index [CASI]; Beck Hopelessness Scale [BHS]; Emotional Distress-Anxiety/Depression - Pediatric Short Form [PROMIS]) and self-efficacy (as measured by the Emotional Self-Efficacy Measure [ESE]) will be collected to provide an assessment of candidate proximal outcome variables.
Statistical Analysis Plans for Each Aim	Feasibility and Acceptability

	The feasibility of the intervention for Aims 1 and 2 will be assessed via rates of recruitment and retention, ability of staff to deliver the intervention with fidelity, time involved in completing assessments, time involved in the intervention, and participant/staff feedback about the intervention. Acceptability is assessed qualitatively via interviews, and quantitatively via feedback forms. As such, feasibility and acceptability data are descriptive and qualitative and do not require null hypothesis significance testing analyses. **Exploratory Aim:** Assessment of Candidate Proximal Outcomes The pilot optimization trial was designed to use a balanced 2x2x2 full factorial to examine each component (VR enhanced cognitive restructuring, problem-solving, and affect regulation) across treatment level (standard vs. standard + PRESR). All participants will receive standard treatment, as well as researcher provided worksheets addressing introduction to cognitive behavioral therapy, cognitive restructuring, problem-solving, and affect regulation aligned to standard procedures, but the experimental conditions will vary according to VR enhancement of each skill. With this design, primary focus will be on calculating key statistics (means, standard deviations [SDs], correlations) and distributional properties of candidate proximal outcome variables based on condition of skill use (n=24 per group for each of the skills assessed) to provide an assessment of these variables.
Study Duration	2 years
Participation Duration	4-6 months, depending on participant discharge date and school re-entry date
Enrollment Duration	24 months

2. Introduction

2.1 Background Information

Rates of suicide and suicide-related thoughts and behaviors increased among adolescents over the decade prior to COVID-19. Based on data collected as part of the national Youth Risk Behavior Survey (YRBS), 13.8% of adolescents reported seriously considering attempting suicide in 2009, compared to 18.8% in 2019; 6.3% reported having attempted suicide in 2009, compared to 8.9% in 2019 (CDC, 2019). Since the onset of COVID-19, there has been a significant increase in concerns for depression and suicide-related risk within pediatric primary care settings for adolescent girls (Mayne et al., 2021). Moreover, rates of hospitalization for a suspected suicide attempt were significantly higher in the winter of 2021 compared to the previous year (Yard et al., 2021). More generally, suicidal thoughts and behaviors are a primary reason for psychiatric hospitalization for nearly 50% of hospitalized adolescents (Peterson et al., 1996; Tossone et al., 2014). Therefore, this intervention targets adolescents hospitalized for suicide-related crises.

Although the effectiveness of psychiatric hospitalization for individuals in crisis is highly debated (Jobes, 2017; Jobes et al., 2008), it remains standard practice for most individuals at high-risk for making a suicide attempt (Kidd et al., 2014). Inpatient treatment appears most effective when it involves cognitive behavioral therapy (CBT) based problem-solving skills (Blanz & Schmidt, 2000; Frazier et al., 2016; Green et al., 2007). CBT is well suited for

acute treatment of adolescents in crisis because it is an evidence-based, transdiagnostic intervention for reducing self-harm behaviors, appropriate for the multidetermined risk of suicide (Alavi et al., 2013; Esposito-Smythers et al., 2011; Ghahramanlou-Holloway et al., 2015; Ougrin et al., 2015). Unfortunately, a key mechanism of CBT skill learning is practicing skills in real life (Kazantzis et al., 2000; Stanley et al., 2009), something that is not typically possible during hospitalization.

Following discharge, youth are at increased risk for subsequent suicide attempts or re-hospitalization and require ongoing treatment (Brent et al., 1993; Chung et al., 2017; Goldston et al., 1999, 2001; Horwitz et al., 2015; James et al., 2010; Stensland et al., 2012; Wolff et al., 2017). Multiple studies underscore the importance of immediate, intensive interventions focused on relapse prevention, followed-up with close monitoring of adolescents after discharge (Goldston et al., 1998, 1999, 2001, 2009; Kelley et al., 1996; Prinstein et al., 2008). Yet, post-hospital treatment utilization remains low, with many adolescents receiving inadequate or *no* ongoing treatment (Brown & Jager-Hyman, 2014; James et al., 2010; Spirito et al., 2010). Many adolescents return to school at high-risk for making a suicide attempt without ongoing treatment in place (Brown & Jager-Hyman, 2014; Daniel et al., 2009). Moreover, adolescents report distinct concerns about returning to school following hospitalization, including ongoing management of symptoms, social stressors, and academic concerns (M. Marraccini & PIttleman, 2022; Preyde et al., 2018).

Immersive Virtual Reality (VR) is a novel way to enhance treatments applicable to lived settings. VR integrates computer graphics, body tracing, and sensory inputs to simulate life-like experiences (Lewis et al., 2018). By facilitating human-computer interactions, VR-based applications provide systematic training and practice in settings that mirror the real-world (Hubal & Parsons, 2017). Decades of research and development support the VR as a novel tool for training and practice conditions to promote skill development (Hubal, 2008; Hubal & Parsons, 2017). Increasing the ecological validity of assessments, virtual school environments can measure attention and cognition (Parsons, 2015; Rizzo et al., 2009) and students' tendency towards risky behavior (Hubal et al., 2015; Hubal & Parsons, 2017). Evidence supporting VR therapeutically demonstrates that VR exposure therapy has comparable effects to lived exposure therapy for real-life anxiety reduction (Carl et al., 2019; Morina et al., 2015).

In order to enhance clinical treatment of adolescents with suicide-related risk, this study is conducting a pilot optimization trial of a novel intervention to supplement inpatient treatment, the Practice Experiences for School Reintegration (PrESR) program. During its development, we have sought feedback from school professionals, hospital clinicians, and adolescents previously hospitalized for a suicide-related crises. Difficult school scenarios are based on this expert feedback, and also built from our previous work identifying adolescent, parent, school professional, and hospital professional perceptions of school-related influences of suicide-related risk (M. E. Marraccini, Pittleman, et al., 2022).

2.2 Scientific Rationale

This pilot optimization trial will be used to prepare for a fully powered optimization trial and RCT by investigating acceptability and feasibility of study procedures, assessment protocols, intervention delivery, candidate intermediary variables, and candidate outcomes with the PrESR intervention with a sample of 48 hospitalized adolescents randomized to VR conditions (using a balanced 2x2x2 full factorial).

The inclusion criteria are based on the target population (i.e., adolescents hospitalized for suicide-related risk), with specific exclusions (i.e., active psychosis, intellectual disability) based on expert feedback during model development (unpublished data collected from earlier phases of the study).

The specific skills taught, and length of virtual experiences were selected based on previous research (Blanz & Schmidt, 2000; Frazier et al., 2016; Green et al., 2007) and expert feedback during the development phase (Marraccini et al., 2024).
The approach of adding the research intervention to usual care ensures that no youth will receive less than what is typically considered to be the standard of care in these facilities.

3. Specific Aims

The larger study involves several aspects of preparation of the MOST phase, specifically involving developing, refining, and pilot testing the intervention. Aims for the pilot optimization component of the MOST preparation phase addressed in this protocol are:

3.1 Aim 1

Conduct a pilot optimization trial of the PrESR to *examine* feasibility and acceptability of identifying, enrolling, and retaining participants at the hospital.

3.2 Aim 2

Conduct a pilot optimization trial of the PrESR to *examine* feasibility and acceptability of implementing assessment protocols (including motion sickness screening), fidelity of the intervention delivery (including applying the PrESR to existing hospital CBT protocols), measuring candidate intermediary variables (i.e., threat habitation, cognition), and measuring candidate outcomes (psychological distress, self-efficacy, suicidal thoughts and behaviors, and rehospitalization).

3.3 Exploratory Aim

Because this study is a treatment development study, an exploratory aim is to calculate descriptive statistics for candidate outcome variables to inform power for a future study that examines efficacy of the intervention.

4 Study Design

This Stage I Behavioral Intervention Development study follows a **multiphasic optimization (MOST)** research design to prepare for a subsequent fully powered optimization trial and RCT; this clinical trial is considered to be a pilot optimization component of the MOST framework. MOST is a comprehensive framework for optimizing and evaluating multi-component behavioral interventions. MOST has three phases: **preparation**, **optimization**, and **evaluation** (Collins & Kugler, 2018), with the optimization trial typically following a factorial design.

For the present study, a prospective sample of adolescents (N= 48) hospitalized for suicidal thoughts and behaviors will be randomly selected into one of 8 experimental conditions (N=5-6 per group) adhering to the "intent to treat" principle.

Adolescents will be invited to participate based on pre-screening of medical records to identify eligible participants. Prior to or immediately following consent/permission/assent procedures, adolescent participants will complete a motion sickness susceptibility questionnaire. Adolescents at risk for developing Cybersickness (Kidd et al., 2014), which is defined as 50th percentile as measured on the Motion Sickness Susceptibility Questionnaire (Golding, 1998), will be excluded from the study based on screen failure.

The intervention will be tested during the participant's index hospitalization, with data collection at baseline, over the 2-week period post-school re-entry, at 2-weeks post-school re-entry, and 3-months post-school re-entry (longitudinal). Participation is expected to take approximately 12 hours, and include consent/assent (30 min.), 3-7

intervention sessions (up to 50 min. each), and assessment procedures at all time points (90 min. each; see Figure 1 in Marraccini et al., 2025).

As part of training in the new research intervention, research staff are being trained to provide validation of any difficulties and coping strategies reduce distress. In addition, participants are informed that participation in this study is voluntary and that they can withdraw without penalty. If participants become distressed when completing assessments, or are too distressed to complete assessments, research staff can discontinue or delay the assessments at that point.

Although the intervention for the pilot optimization trial will be implemented by a member of research staff, this study will also aim to recruit 2-5 clinicians to deliver the intervention to inform acceptability and feasibility of the intervention within their clinical workflow.

4.1 End-of-Study Definition

Participants are considered to have completed the study if they contribute data during hospitalization and then participate in the three-month follow-up assessment.

4.2 Discontinuation of Study Intervention/Experimental Manipulation

The study intervention or assessments may be discontinued if, in the judgment of direct care and clinical staff at the psychiatric facility, youths' clinical situation (e.g., their level of agitation) appears to be worsening as a result of continuing efforts to implement the intervention or conduct assessments. A participant may also be withdrawn if s/he is declining to complete the assessments for the study.

4.3 Participant Discontinuation/Withdrawal from the Study

Participation in this study is completely voluntary and participants (youth or guardians) are free to withdraw consent/assent at any time without penalty. The reason for participant discontinuation or withdrawal, if given, will be recorded. Participant discontinuation or withdrawal will be recorded on case report forms.

4.4 Lost to Follow-Up

A participant will be considered lost to follow-up if he or she fails to complete the follow-up assessment(s) and study staff are unable to contact the participant after at least three attempts. Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant, including, at a minimum, three phone calls to the respective participant's family whose contact information will be obtained during consent/assent.

4.5 Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending, or terminating party to the funding agency, regulatory authorities, and any youth and family already in the follow-up phase of the study. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor/funding agency and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

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

1. Determination of unexpected, significant, or unacceptable risk to participants: If 10 Serious Adverse Events occur in 10 subjects during baseline procedures or if 10 number of subjects have a 300% increase in distress (as measured by SUDS captured before and immediately following a practice experience in PrESR, averaged across practice sessions), the study will be suspended
2. Insufficient compliance of study staff to the protocol (i.e., significant protocol violations)
3. Data that are not sufficiently complete and/or evaluable

The study may resume once concerns about safety, protocol compliance, and data quality are addressed and satisfy the funding agency, sponsor, IRB, or other relevant regulatory or oversight bodies (DSMB).

4.6 Intervention Design

The PrESR intervention will focus on increasing acquisition and utilization of critical cognitive-behavioral skills for treating adolescents with suicidal thoughts and behaviors. Inpatient clinicians will provide standard treatment and adolescents will receive researcher provided worksheets instructing them on target cognitive behavioral skills (introduction to cognitive behavioral therapy, cognitive restructuring, problem solving, and affect regulation) aligning to worksheets used as part of typical hospital protocol. Adolescents will practice skills using the PrESR with clinical guidance and feedback. Sessions begin with an overview of the skill to be practiced, followed by a brief immersive experience using virtual reality designed to mimic difficult school experiences in which adolescents are able to practice the learned skill. Participants receiving the intervention will also be provided with a workbook used during sessions that align to their lessons and practices in PrESR.

Following a similar format to other therapeutic VR programs, research clinicians will observe adolescents wearing standard headsets as they practice coping strategies. At the end of the program, the adolescent and clinician will develop a safety plan designed to address the return to school, based on these *in vivo* sessions and, if possible, in collaboration with the school. Selection of individual VR scenarios and number of lessons delivered to teach each CBT skill is determined based on the needs of individual patients, with the goal of providing at least two practice opportunities per skill. Note that although participants are randomized based on skill components (affect regulation, cognitive restructuring, problem solving), all participants receiving at least one component of the intervention will also collaborate on a safety plan.

This specific sequence was selected to allow individuals to become habituated to anxiety or distress provoking situations, and to use coping skills accordingly. The conceptual model (shown in Figure 1 in Marraccini et al., 2025) posits two mechanisms for change that lead to skill mastery and application: (1) habituation to fear based on inhibitory learning; and (2) cognitive shifts in beliefs and appraisals. As adolescents begin to increase their tolerance to these difficult experiences and shift away from faulty thinking and towards acceptance, they are able to build and apply skills in low-risk settings initially (i.e., mixed reality settings during hospitalization) and extend them into higher risk settings (i.e., in school post-discharge).

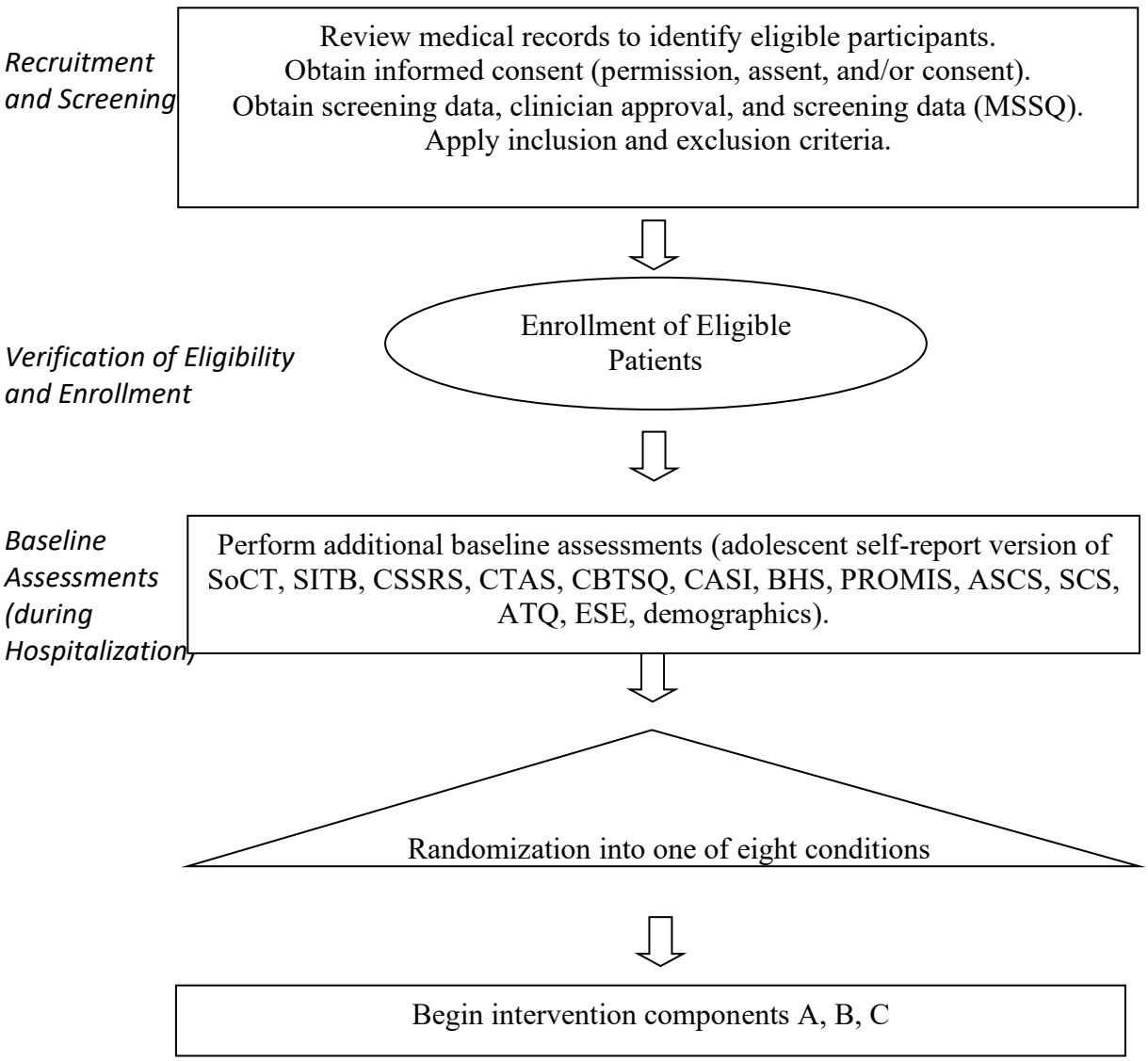
Inhibitory learning with exposure increases fear tolerance by building new (secondary) non-threat based associations (i.e., school experiences and skill use) with the original threat-based associations (i.e., school experiences and psychological distress) remaining intact (Kidd et al., 2014). Because habituation is understood as dynamic throughout exposure, in that it can deescalate and escalate in accordance with the intensity of exposure (Jobes, 2017), it will be measured with a Subjective Units of Distress Scale (SUDS) provided by researchers before, between, and following VR sessions to measure self-reported levels of distress. Note, however, that the PrESR differs from classic exposure therapy in that it is active, as opposed to passive. Where habituation during exposure discourages the use of skills such as cognitive restructuring, relaxation techniques, and distraction, because they are posited to interfere with habituation (Jobes, 2017), the PrESR proposes to enhance skill development through applied practice in *in vivo* like experiences. Thus, in addition to tolerance of fear, improvements in outcomes are also expected to be mediated by changes in cognition. Cognitive shifts in thinking are accomplished via the PrESR by providing data to challenge faulty thinking and appraisals, reciprocally reinforced by and reinforcing increased fear tolerance.

These initial increases in fear tolerance and positive changes in cognitions are expected to lead to both reduced psychological distress and increased emotional self-efficacy in school, which ultimately will reduce rates of re-hospitalization and subsequent suicidal thoughts and behaviors.

4.7 Experimental Design

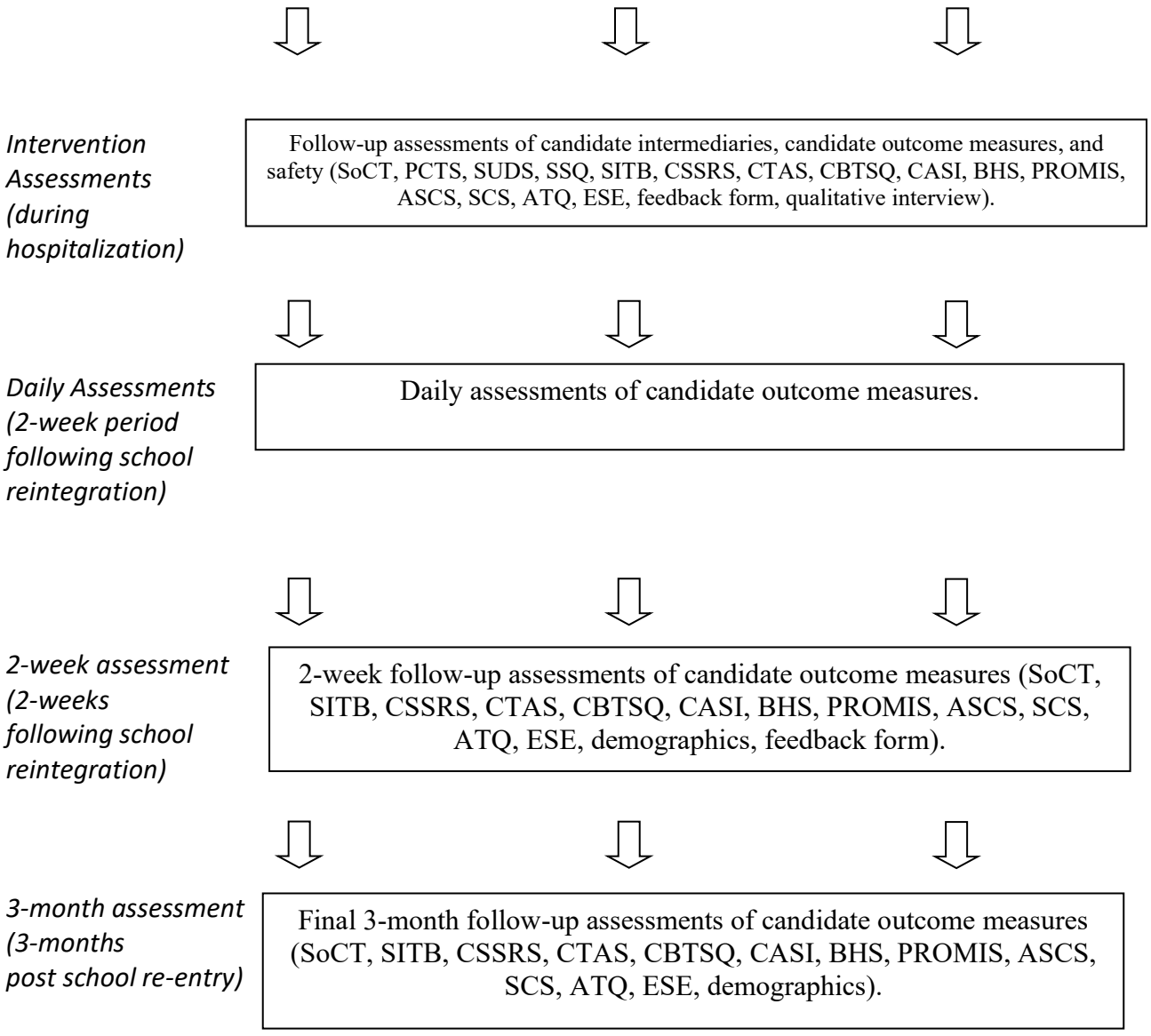
A prospective sample of adolescents (N= 48) hospitalized for suicidal thoughts and behaviors will be recruited from a psychiatric inpatient unit. An even number of participants will be assigned into one of eight conditions (see Table shown in Figure 2) in block sizes of 8, 16, or 24 to ensure equal assignment and avoid selection bias. As described in previous sections, treatment conditions are informed by a MOST framework, with conditions varying based on participation in the PrESR for specific skills or enhanced treatment as usual (i.e., provision of worksheets teaching CBT skills). Because this is a pilot trial, randomization will not be stratified; however, because gender identity may be an important stratification variable in a future, fully powered trial, we will collect information related to gender identity to inform stratification procedures in the future. A biostatistician with no other study responsibilities will set up randomization tables for use in REDCap (a secure web-based service for building and managing online surveys and databases), and other research staff will not have access to the tables. Participants will be randomized following the baseline assessment using the randomize feature in REDCap. This ensures allocation concealment.

Figure 2. Randomized MOST pilot trial of PrESR.



2^3 Factorial Experimental Design for Optimization Trial

Exp. Condition	A. Cognitive Restructuring	B. Problem-Solving	C. Affect Regulation	*n*
1	Yes	Yes	Yes	4-6
2	Yes	Yes	Yes + PrESR	4-6
3	Yes	Yes + PrESR	Yes	4-6
4	Yes	Yes + PrESR	Yes + PrESR	4-6
5	Yes + PrESR	Yes	Yes	4-6
6	Yes + PrESR	Yes	Yes + PrESR	4-6
7	Yes + PrESR	Yes + PrESR	Yes	4-6
8	Yes + PrESR	Yes + PrESR	Yes + PrESR	4-6



4.8 Measurement Design

Feasibility and acceptability

For Aim 1 (examine feasibility and acceptability of identifying, enrolling, and retaining participants at the hospital), the following measures will be administered/collected:

1. Proportion of patients in the target population who agree to participate
   a) Rate of Recruitment, with a minimum of 80% considered adequate
   b) [Time Frame: Baseline]
2. Proportion of patients in the target population excluded due to motion sickness screening
   a) Rate of recruitment related to motion sickness, with participant scores greater or equal than 50th percentile on motion sickness susceptibility questionnaire excluded
   b) [Time Frame: Baseline]
3. Proportion of participants who complete all study procedures, including reasons participants cite for withdrawing from the study.

a) Rate of Retention
b) [Time Frame: up to 3-months following school re-entry]

For Aim 2 (examine feasibility and acceptability of implementing assessment protocols [including motion sickness screening], fidelity of the intervention delivery [including applying the PrESR to existing hospital CBT protocols], candidate intermediary variables (i.e., threat habitation, cognition), and candidate proximal and distal outcomes [psychological distress, self-efficacy, suicidal thoughts and behaviors, and rehospitalization]), the following measures will be administered/collected:

4. Average number of hours to complete assessments at each time point
   a) Time to complete assessments, assessments are expected to last less than 4 hours, with average completion time less than 2 hours considered adequate
   b) [Time Frame: up to 3-months following school re-entry]
5. Average number of minutes to complete each intervention session
   a) Time to complete intervention sessions, each session is expected to last less than 60 minutes, with average time to compete a session below 50 minutes considered adequate
   b) [Time Frame: Baseline]
6. Average proportion of components of intervention fidelity checklist completed
   a) Fidelity of intervention delivery
   b) [Time Frame: Baseline]
7. Adolescents' Mean Acceptability Scores (feedback form)
   a) Percent of adolescents with average acceptability Score less than or equal to 2), with ratings averaging to 2 (or "agree") on a five-point scale from 1 (strongly agree) to 5 (strongly disagree) related to acceptability considered adequate.
   b) [Time Frame: Baseline]
8. Professionals' Mean Acceptability Scores (feedback form)
   a) Percent of professionals with average acceptability score less than or equal to 2), with ratings averaging to 2 (or "agree") on a five-point scale from 1 (strongly agree) to 5 (strongly disagree) related to acceptability considered adequate.
   b) [Time Frame: Baseline]
9. Adolescents' Perceptions of Acceptability (audio recorded exit interviews)
   a) Qualitative feedback based on transcribed interviews.
   b) [Time Frame: Baseline]
10. Professionals' Perceptions of Acceptability (audio recorded exit interviews)
    a) Qualitative feedback based on transcribed interviews.
    b) [Time Frame: Baseline]

Exploratory Aim: Assessment of Candidate Proximal Outcomes
As a treatment development study, this project is not powered to test hypotheses regarding efficacy. To demonstrate the potential viability of the approach, we will use this data to obtain precise enough estimate of these statistics in order to make reasonable guesses as to how to design the fully powered and definitive trial. Additionally, feasibility and acceptability of collecting other outcomes of interest (mechanisms and distal outcomes) require the following measures to be collected/administered (outcome measures are shown in Table 1):

Exploratory Intermediary Variables: *Threat habituation*: Subjective Units of Distress Scale (SUDS)**;** ***Cognition*:** Automatic Thoughts Questionnaire (ATQ-30);

Exploratory Candidate Proximal Primary Outcomes: *Psychological distress:* Child Anxiety Sensitivity Index (CASI); Beck Hopelessness Scale (BHS); Emotional Distress-Anxiety/Depression - Pediatric Short Form (PROMIS). ***Self-efficacy:*** *Emotional Self-Efficacy (ESE) measure.*

Exploratory Candidate Distal Primary Outcomes: ***Suicidal thoughts and behaviors:*** Self-Injurious Thoughts and Behaviors Interview (SITB); Columbia Suicide Severity Rating Scale (CSSRS). ***Rehospitalization:*** *Medical Record Review.*

Additional Exploratory Candidate Secondary Outcomes: ***Skill use and understanding:*** Performance of Cognitive Therapy Strategies (PCTS) assessment; Cognitive-Behavior Therapy Skills Questionnaire (CBTSQ); Cognitive Therapy Awareness Scale (CTAS); Skills of Cognitive Therapy (SoCT); Daily diary of difficult school experiences, suicidal thoughts and behaviors, skill use, and safety plan use for 2-weeks post school re-entry period. ***School experiences***: Authoritative School Climate Survey (ASCS); School Connectedness Scale (SCS).

Assessment of Service Use Following Release: With consent/assent of parents and adolescents, we will obtain adolescents' treatment records. Records will be used to verify the number, duration, and frequency of contacts with mental health providers.

Table 1. Candidate Outcome Measures

Instrument or Measurement Name	Time Frame	Brief Description	Scoring
Motion Sickness Susceptibility Questionnaire	Pre-enrollment	A measure used to evaluate motion sickness in various forms of transport	**Range**: Eligibility Score: □ 50%
Self-Injurious Thoughts and Behaviors Interview	Hospitalization, 2-Week Visit, 3 Month Visit	A structured interview that assesses the presence, frequency (number of episodes) and severity of a range of self-injurious thoughts and behaviors	**Range:** 0-4 **Frequencies**
Columbia Suicide Severity Rating Scale	Hospitalization, 2-Week Visit, 3 Month Visit	A measure used to identify and assess individual risk for suicide	**Range:** 0-5 **Frequencies**
Cognitive Therapy Awareness Scale	Hospitalization, 2-Week Visit, 3 Month Visit	40 true-false questions about basic CBT concepts and methods	**True/False**
Cognitive-Behavior Therapy Skills Questionnaire	Hospitalization, 2-Week Visit, 3 Month Visit	16 item self-report measure to assess frequency of behavioral activation and cognitive restructuring	**Range:** 5-point scale (I don't do this to I always do this)
Child Anxiety Sensitivity Index	Hospitalization, 2-Week Visit, 3 Month Visit	18 item self-report measure to assess how responsive children are to various symptoms of anxiety	**Range:** 3-point scale (None, Some, A Lot)
Beck Hopelessness Scale	Hospitalization, 2-Week Visit, 3 Month Visit	20 item self-report measure that measures three major aspects of hopelessness: feelings about the future, loss of motivation, and expectation	**True/False**

Emotional Distress-Anxiety/Depression - Pediatric Short Form (PROMIS)	Hospitalization, 2-Week Visit, 3 Month Visit	8 item self-report measure that assesses fear, anxious misery, hyperarousal, somatic symptoms related to arousal, negative mood, views of self, social cognition, as well as decreased positive affect and engagement	**Range:** 5-point scale (Never to Always)
Authoritative School Climate Survey	Hospitalization, 2-Week Visit, 3 Month Visit	Survey to assess school climate and bullying in school settings	**Range:** Variable by component (e.g., 1-4; 1-3) **Frequencies**
School Connectedness Scale	Hospitalization, 2-Week Visit, 3 Month Visit	54 item survey that reflects students' belief that peers and adults in the school support, value, and care about their individual well-being as well as their academic progress	**Range:** 5-point scale (Not at all true to Completely true)
Automatic Thoughts Questionnaire	Hospitalization, 2-Week Visit, 3 Month Visit	30 item questionnaire that measures the frequency of occurrence of automatic negative thoughts associated with depression	**Range:** 5-point scale (Not at all to All the time)
Emotional Self-Efficacy Measure	Hospitalization, 2-Week Visit, 3 Month Visit	7 item measure focused on the measurement of self-beliefs in relation to the management of emotions	**Range:** 5-point scale (Not at all to Very well)
Skills of Cognitive Therapy Strategies	Hospitalization, 2-Week Visit, 3 Month Visit	8 item self-report measure that assess understanding and use of basic cognitive therapy skills	**Range:** 1-5 (Never to Always or When needed)
Skills of Cognitive Therapy Strategies	Hospitalization	8 item self-report measure that assesses understanding and use of basic cognitive therapy skills	**Range: Multiple Choice (Correct/Incorrect)**
Performance of Cognitive Therapy Strategies	Hospitalization	15 item measure completed by a clinician to assess mastery and independent use of material covered in cognitive therapy	**Range:** 0-6
Subjective Units Distress Scale	Hospitalization	Tool for measuring the intensity of your feelings and other internal experiences	**Range:** 0-10
Simulator Sickness Questionnaire	Hospitalization	16 item questionnaire that assesses sickness levels before and after immersion in VR	**Range:** 4-point scale (None to Severe)
Daily diary of events, skill use, distress	Over 2 Weeks		**Range:** Variable by skill (e.g., affect regulation, cognitive restructuring, problem solving)

Across aims, variables of interest are show in in Table 2.

Table 2. Variables of interest: Their occasions of evaluation, their uses for the aims, their roles in the study

Variables within Domains	Scale[1]	Occasions[2]	Aims	Main Roles[3]
Identifiers				
Participant's unique ID	nominal	all	all	identifier
Experimental Condition (1-8)	nominal	E	all	identifier
Feasibility and Acceptability Measures				
Rates of recruitment	proportion	0	1	Feasibility and Acceptability
Rates of retention	Proportion	1, 2, 3, 4	1	Feasibility and Acceptability
Time to complete assessments	minutes	All	2	Feasibility and Acceptability
Assessment of intervention fidelity	Checklist	1	2	Feasibility and Acceptability
Adolescent exit interview and feedback form	Open text/response and ordinal	1	2	Feasibility and Acceptability
Professional exit interview and feedback form	Open text/response and ordinal	1	2	Feasibility and Acceptability
Adolescent retrospective feedback form	Open text/response and ordinal	3	2	Feasibility and Acceptability
Medical Records				
Reason for hospitalization	categorical	1, 4	all	Identifier primary outcome
Admission Date	date	1, 4	all	covariate uses
Discharge Date	date	1, 4	all	covariate uses
Diagnosis	categorical	1, 4	all	Exploratory primary outcome screening
Age	decimal yrs	1, 4	all	covariate uses
Sex	categorical	1, 4	all	covariate uses
Stressors	Open text	1, 4	all	covariate uses screening
Medications	Open text	1, 4	all	covariate uses screening
Treatment	Open text	1, 4	all	covariate uses
Researcher Observation				
Skills of Cognitive Therapy Strategies	Ordinal	1	All	Exploratory candidate intermediary outcome
Performance of Cognitive Therapy Strategies	Ordinal	1	all	Exploratory candidate intermediary outcome
Patient-Reported Outcomes				
Self-report demographic information	Ordinal	1,3,4	all	Covariate
Cognitive Therapy Awareness Scale	Score	1, 3,4	all	Exploratory candidate secondary
Cognitive-Behavior Therapy Skills Questionnaire	Ordinal	1, 3,4	all	Exploratory candidate secondary
Skills of Cognitive Therapy	Ordinal	1, 3,4	all	Exploratory candidate secondary

Child Anxiety Sensitivity Index	Ordinal	1, 3,4	all	Exploratory candidate primary
Beck Hopelessness Scale	Ordinal	1, 3,4	all	Exploratory candidate primary
Emotional Distress-Anxiety/Depression - Pediatric Short Form (PROMIS)	Ordinal	1, 3,4	all	Exploratory candidate primary
Authoritative School Climate Survey	Ordinal	1, 3,4	all	Exploratory uses
School Connectedness Scale	Ordinal	1, 3,4	all	Exploratory uses
Subjective Units Distress Scale (SUDS)	Ordinal 0-10	1	All	Exploratory candidate intermediary
Automatic Thoughts Questionnaire	Ordinal	1, 3,4	all	Exploratory candidate intermediary
Emotional Self-Efficacy Measure	Ordinal	1, 3,4	all	Exploratory candidate primary
Daily diary of events, skill use, distress	Multi-dim	2	All	Exploratory candidate secondary
Clinical Interviews				
Self-Injurious Thoughts and Behaviors	continuous	1, 3,4	all	Exploratory candidate primary
Columbia Severity for Suicide Rating Scale	continuous	1, 3,4	all	Exploratory candidate primary
Safety Monitoring				
AEs and SAEs documentation	events	1, 3,4	all	safety monitoring
Simulation Sickness Questionnaire	Ordinal	1	all	safety monitoring
Motion sickness susceptibility questionnaire	Ordinal	0	N/A	safety monitoring

Feasibility and acceptability

[1] Units of measurement or the scale.

[2] Occasions of evaluation or retrieval: **O** = screening, **1** = hospitalization, **2** = over 2 weeks, **3** = 2-week visit, **4** = 3 month visit **E** = experimental condition

[3]Main roles include: **Feasibility and acceptability** (the estimates of interest), **Study Identifiers**, **Safety Monitoring**, and **Measures that are integrated as part of the protocol in order to inform feasibility and acceptability of study protocols** (Primary Outcomes, Secondary Outcomes, Intermediaries)

5. Study Participants

5.1 Numbers of Participants

5.1.1 Number to be screened: n ≤ 1000 adolescents; n ≤ 12 hospital professionals.

Adolescent Participants

Initial screening will be based on medical chart records of patients hospitalized for a suicide-related billing code during hospitalization, and some may not be eligible for enrollment based on additional exclusion criteria.

Hospital Professional Participants

Hospital professional participants working on the adolescent inpatient unit at UNC Hospital and/or UNC Youth Behavioral Health will be invited to pilot the PrESR.

5.1.2 Number to be enrolled: N = 48 adolescents; N = 2-5 hospital professionals (maximum of 12).

Recruitment will continue until N = 48 adolescent individuals have completed all aspects of the protocol and have complete data or the study end date. We anticipate approximately 20% attrition, with N = 35 a conservative lower limit. We also anticipate that more adolescents will be consented into the study and excluded due to screening procedures following consent (see exclusion criteria).

The pilot optimization trial will occur at 1-2 UNC Hospitals, well-known as a leading center for psychiatric care. UNC is well positioned to integrate the PrESR into their program given their clinical care's emphasis on school readiness and use of CBT and skill-building tailored to individual needs.
As described previously, participants will be randomized to 1 of 8 conditions. As shown in Figure 2, between 4-6 participants will be enrolled one of the eight conditions.

5.2 Eligibility Criteria

Based on hospitalization data, adolescents are expected to be 65% female, 15% Hispanic or Latino, 65% Caucasian and 30% minority across all aims.
Hospital professionals anticipated to include 2-5 participants may include any professionals providing services to hospitalized youth using CBT in their treatment, including any of the following: hospital teacher, attending physician, occupational therapist, recreational therapist, psychologist, trainee, or fellow.

5.2.1. Inclusion Criteria

Adolescent Participants

To be eligible to participate in this study as an adolescent, an individual must meet all of the following criteria:

- Current hospitalization for suicidal thoughts and behaviors based on medical chart review
- Ages 13-18 based on medical chart review
- Expected return to school following discharge based on self-report*
- Approval of treating clinician
- Ability to speak, read, and understand English sufficiently to complete study procedures based on medical chart review and self-report
- Consent of a parent/legal guardian (in English or Spanish)
- Adolescent assent

*Adolescent patients receiving the intervention delivered by hospital professional participants may participate irrespective of school status (and do not need to be "expected to return to school following discharge")

Hospital Professional Participants

To be eligible to participate in this study as a hospital professional, an individual must serve in a clinical role providing treatment to adolescents on the UNC inpatient unit.

5.2.1. Exclusion Criteria

Exclusion criteria was selected to maintain participant safety.

Adolescent Exclusion Criteria

Any individual who meets one or more of the following criteria will be excluded from participation:

- Active psychosis based on medical chart review and/or clinician feedback
- Intellectual disability based on medical chart review, self-report and/or clinician feedback
- Risk for cybersickness based on score on Motion Sickness Susceptibility Questionnaire in combination with clinician feedback

Hospital Professional Exclusion Criteria
N/A

5.3 Enrollment/Selection Strategies

5.3.1. Prospective Recruitment

A prospective sample of hospitalized adolescents will be recruited during their hospital stay. The study will use effective recruitment protocols involving approval from the treating clinician, screening via chart review, and approach and consent completed by way of family phone communication.

The PI of the study has experience recruiting hospitalized adolescents with suicide-related risk in her role as a postdoctoral fellow on a federally funded grant and additional experience in recruiting adolescents with suicide-related risk following hospitalization on several research studies as PI.

Because this study focuses on adolescents, specific protections will be employed. Decisions regarding whether an adolescent will be invited to participate or not will be determined in collaboration with their attending physician. Adolescents will also be screened for risk of motion/cyber sickness.

We will take precautions to minimize coercion to participate. We will emphasize the voluntary nature of the study and remind participants that they may discontinue at any time. Members of the research team will be trained to be respectful towards participants' preferences regarding participation. We will present information verbally and in writing on the consent form to ensure participants are aware of the voluntary nature of the study. The informed consent procedure will include a careful explanation of study procedures, risks, benefits, and alternatives. We have selected compensation rates that we believe will not be excessive or coercive for adolescents. All participating children will complete assent procedures after or simultaneously to when consent is given by parents. Children can refuse to answer individual questions or withdraw from the study at any time.

5.3.2. Screen Failures

We expect approximately 20% of consented individuals to be ineligible for the study following consent due to cybersickness. Accordingly, we will explain this exclusion criteria during the consent process. We do not expect individuals determined to be ineligible will be re-screened given the short-time frame available to complete study procedures during hospitalization.

5.4 Strategies for Retention

We will use effective strategies for retention used in previous studies, including collecting contact information from multiple members of the family (based on family preference to respect any privacy concerns related to eligibility for study) and providing study visit reminders. As needed, we will also develop protocols for follow-ups administered remotely in cases where transportation is difficult.

5.5 Matching and Stratification

Youth identifying as gender diverse at greater risk for suicide-related thoughts and behaviors compared to those identifying as cisgender (Marraccini, Ingram, et al., 2022). We will collect information about gender identity (cisgender boy, cisgender girl, or gender diverse [e.g., transgender or nonbinary]) based on participant self-report. Given the small sample size of this pilot study and the anticipated low frequencies of some gender groups, we will not stratify by gender identity but will focus our efforts on capturing information on the distribution of gender that will inform a stratification procedure for a future, fully powered trial that will have large enough recruitment to target a balanced design.

5.6 Randomization and Concealment

A biostatistician with no other study responsibilities will set up randomization tables for use in REDCap (a secure web-based service for building and managing online surveys and databases), and other research staff will not have access to the tables. Participants will be randomized following the baseline assessment using the randomize feature in REDCap. This ensures allocation concealment.

5.7 Blinding

We will **not** use blinding procedures in this study.

6 Treatment Design: Procedures

Description

As shown in Table 10.1, there are 8 intervention conditions with 4-6 participants per condition. Each condition is based on whether or not the participant receives the virtual reality supplement (PrESR) to learning three skills: affect regulation, cognitive restructuring, problem solving. All three skills will be provided by way of worksheets provided by researchers to all participants (irrespective of condition assignment). For each skill, if participants receive the supplemental intervention, participants will be guided to learn and practice the skill in a virtual reality session under the supervision of a trained researcher. Skills are introduced, and then participants engage in an immersive school scenario that involves several difficult social interactions and/or academic stressors, in which the participant can pause and practice using the target skill. At the close of each session, participants will complete a debrief with the onsite researcher. If participants receive any component of the intervention (conditions 2-8), they will also collaborate on a safety plan at the conclusion of the intervention.

Adherence Monitoring/Evaluations Researchers will be observing participants during sessions to monitor participation in treatment.

Concomitant Therapies Youth receiving the new intervention will receive usual care as part of their hospitalization stay and also complete worksheets provided by researchers to teach each of the three CBT skills (affect regulation, cognitive restructuring, problem solving). Families will be provided an authorization to release information, and, with permission, information from the assessments collected as part of the study will be shared with clinical staff and with the evaluating clinician so they can better address the needs of youth who have been suicidal. Concomitant therapies will be assessed at the 2-week and 3-month follow-up assessments based on medical record review.

7 Schedule of Activities and Procedures

7.1 Table of Events

Schedule of Activities

	Hospital Stay		**Post-Hospital Discharge**		
	Psychiatric Hospital Admission (Day 0)	Hospital Stay (Days 1-Discharge)[1]	Two-Week Assessments (Days 1-14 following **return to school**[2])	Two-Week Follow-Up Assessments (Day 15-35 following **return to school**)	Three-Month Follow-Up Assessments (Day 84-112 following **return to school**)
Pre-screening, Motion Sickness Susceptibility Questionnaire, and Consent/Assent	X				
Baseline assessments					
Self-Injurious Thoughts and Behaviors Interview		X			
Columbia Suicide Severity Rating Scale		X			
Cognitive Therapy Awareness Scale		X			

Cognitive-Behavior Therapy Skills Questionnaire		X			
Skills of Cognitive Therapy (self-report)		X			
Child Anxiety Sensitivity Index		X			
Beck Hopelessness Scale		X			
Emotional Distress-Anxiety/Depression - Pediatric Short Form (PROMIS)		X			
Authoritative School Climate Survey		X			
School Connectedness Scale		X			
Automatic Thoughts Questionnaire		X			
Emotional Self-Efficacy Measure		X			
Medical Record		X			
Interventions (Conditions 1-8)					
Intervention assessments and safety monitoring					
Subjective Units Distress Scale		X			
Simulator Sickness Questionnaire		X			
Post-intervention assessment					
Self-Injurious Thoughts and Behaviors Interview		X			
Columbia Suicide Severity Rating Scale		X			
Cognitive Therapy Awareness Scale		X			
Cognitive-Behavior Therapy Skills Questionnaire		X			
Skills of Cognitive Therapy (self-report)		X			
Skills of Cognitive Therapy (clinician-report)		X			
Performance of Cognitive Therapy Strategies		X			
Child Anxiety Sensitivity Index		X			
Beck Hopelessness Scale		X			
Emotional Distress-Anxiety/Depression - Pediatric Short Form (PROMIS)		X			

Automatic Thoughts Questionnaire		X			
Emotional Self-Efficacy Measure		X			
Exit interview and feedback forms		X			
Abbreviated feedback form				X	
At Home Assessments following return to school					
Daily diary of events, skill use, distress			X		
Follow-up assessment with youth					
Self-Injurious Thoughts and Behaviors Interview				X	X
Columbia Suicide Severity Rating Scale				X	X
Cognitive Therapy Awareness Scale				X	X
Cognitive-Behavior Therapy Skills Questionnaire				X	X
Skills of Cognitive Therapy (self-report)				X	X
Child Anxiety Sensitivity Index				X	X
Beck Hopelessness Scale				X	X
Emotional Distress-Anxiety/Depression - Pediatric Short Form (PROMIS)				X	X
Authoritative School Climate Survey				X	X
School Connectedness Scale				X	X
Automatic Thoughts Questionnaire				X	X
Emotional Self-Efficacy Measure				X	X
Medical Record					X
Exit interview and feedback forms for hospital professionals					
Feedback form		X			
Interviews		X			

1 Should adolescents be discharged from the hospital prior to completion of baseline procedures, the adolescent will be invited to complete post-intervention assessments as soon as possible following discharge.

2 There may be a gap between hospital discharge and return to school.

7.2 Screening

Screening will be conducted within 2 weeks of identification based on medical record review: Day 1 to Day 14. Screen assessments include: (1) review of medical record to confirm eligibility/exclusion; (2) approval from the treating clinician; (3) consent/assent of adolescent patient and parental permission (depending on age); (4) completion of motion sickness screening questionnaire.

7.3 Enrollment

Hospital Stay
Psychiatric Hospital Admission (Days 0 to 14):

- Verify inclusion/exclusion criteria
- Consent/assent
- Motion Sickness Screening Questionnaire

7.4 Study Visits

Hospital Stay
Hospital Stay (Days 1-discharge):

- Medical chart review
- Complete baseline self-report questionnaires
- Administer intervention and accompanying questionnaires/assessments/interviews (note that if participants are discharged prior to questionnaires/assessments/interviews, these will be conducted as soon as possible following discharge)
- Record adverse events as reported by participant or observed by staff/investigator

Post-Hospital Discharge and School Re-Entry
Two-Week Assessments following return to school (Days 1-14):

- Complete daily diary

Two-weeks following return to school (Days 15-35):

- Collect daily diary
- Complete follow-up assessments and self-report questionnaires

7.5 Final Visit

Post-Hospital Discharge
Three-months following return to school (Days 84-112):

- Complete follow-up assessments and self-report questionnaires
- Complete medical chart review

7.6 Phone Contacts

Participant and parent/guardian phone and email will be collected to support participant retention. Participants will be given scheduling and reminder calls and emails (depending on preference) prior to study visits.

Two-Week Assessments (Days 1-14):

- Reminder calls to complete daily diary (weekly, depending on participant preference)

Two-weeks following return to school (Days 15-35):

- Scheduling calls as needed, beginning day 1 of return to school (note that scheduling may occur during hospitalization, depending on participant availability)
- Reminder calls, 3-5 days ahead of appointment and 1 day ahead of appointment

Three-months following return to school (Days 84-112):

- Scheduling calls as needed, beginning day 70 of return to school
- Reminder calls, approximately 3-5 days ahead of appointment and 1 day ahead of appointment

7.8 Follow-Up Contact

Follow-up appointments will collect information as outlined in schedule of activities and medical records will be reviewed for subsequent hospitalizations/evidence of suicidal thoughts and behaviors.

7.9 Early Discontinuations

Data to be Collected

If a participant chooses to withdraw consent or chooses to discontinue the treatment that was being observed, or the investigator discontinues or modifies their treatment, the investigator will still collect medical records data for the duration of the study for follow-up purposes, even if the study intervention is discontinued.

Criteria for Intervention Discontinuation The study intervention or assessments may be discontinued if, in the judgment of direct care and clinical staff at the psychiatric facility, youths' clinical situation (e.g., their level of agitation) appears to be worsening because of continuing efforts to implement the intervention or conduct assessments. A participant may also be withdrawn if s/he is declining to complete the assessments for the study.

7.10 Enrollees May Drop Out

10 Participation in this study is completely voluntary and participants (youth or caregivers) are free to withdraw consent/assent at any time without penalty. The reason for participant discontinuation or withdrawal, if given, will be recorded. Participant discontinuation or withdrawal will be recorded on case report forms. Recruitment will continue until enrolled participants completing study procedures meet 48 participants or study end.

8 Statistical Analysis Plans

8.1 Strategies that Apply to all the Aims

The analysis plans will include outcome-dependent exploratory analyses to generate new hypotheses.

8.2 Sample Description

Key statistics (means, SDs, correlations) and distributional properties of main outcomes will be calculated for each condition. It is noted that while randomization involves 4-6 individuals per 8 conditions, calculation of descriptive statistics and distributional properties of main outcomes will be based on approximately n=24 given that half of the 48 participants receiving VR enhanced skills in each of the three components (A, B, and C; n=16-24 in each group); see Table 3 with highlighted rows showing 24 participants per intervention group for A, B, and C). Calculations will provide an assessment of candidate proximal outcome variables.

Table 3.

Factorial Experimental Design for Optimization Trial

Exp. Condition	A. Cognitive Restructuring	B. Problem-Solving	C. Affect Regulation	*n*
1	Yes	Yes	Yes	4-6
2	Yes	Yes	Yes + PrESR	4-6
3	Yes	Yes + PrESR	Yes	4-6
4	Yes	Yes + PrESR	Yes + PrESR	4-6
5	Yes + PrESR	Yes	Yes	4-6

6	Yes + PrESR	Yes	Yes + PrESR	4-6
7	Yes + PrESR	Yes + PrESR	Yes	4-6
8	Yes + PrESR	Yes + PrESR	Yes + PrESR	4-6

8.3 Aim-Specific Plans

Feasibility and Acceptability

The estimands of interest for Aim 1 are the following primary outcomes:

1. Proportion of patients in the target population who agree to participate
   a) Rate of Recruitment, with a minimum of 80% considered adequate
   b) [Time Frame: Baseline]
2. Proportion of patients in the target population excluded due to motion sickness screening
   a) Rate of recruitment related to motion sickness, with participant scores greater or equal than 50th percentile on motion sickness susceptibility questionnaire excluded
   b) [Time Frame: Baseline]
3. Proportion of participants who complete all study procedures, including reasons participants cite for withdrawing from the study.
   a) Rate of Retention
   b) [Time Frame: up to 3-months following school re-entry]

The estimands of interest for Aim 2 are the following primary outcomes:

4. Average number of hours to complete assessments at each time point
   a) Time to complete assessments, assessments are expected to last less than 4 hours, with average completion time less than 2 hours considered adequate
   b) [Time Frame: up to 3-months following school re-entry]
5. Average number of minutes to complete each intervention session
   a) Time to complete intervention sessions, each session is expected to last less than 60 minutes, with average time to compete a session below 50 minutes considered adequate
   b) [Time Frame: Baseline]
6. Average proportion of components of intervention fidelity checklist completed
   a) Fidelity of intervention delivery
   b) [Time Frame: Baseline]
7. Adolescents' Mean Acceptability Scores (feedback form)
   a) Percent of adolescents with average acceptability Score less than or equal to 2), with ratings averaging to 2 (or “agree”) on a five-point scale from 1 (strongly agree) to 5 (strongly disagree) related to acceptability considered adequate.
   b) [Time Frame: Baseline]
8. Professionals' Mean Acceptability Scores (feedback form)
   a) Percent of professionals with average acceptability score less than or equal to 2), with ratings averaging to 2 (or “agree”) on a five-point scale from 1 (strongly agree) to 5 (strongly disagree) related to acceptability considered adequate.
   b) [Time Frame: Baseline]
9. Adolescents' Perceptions of Acceptability (audio recorded exit interviews)
   a) Qualitative feedback based on transcribed interviews.
   b) [Time Frame: Baseline]
10. Professionals' Perceptions of Acceptability (audio recorded exit interviews)
    a) Qualitative feedback based on transcribed interviews.
    b) [Time Frame: Baseline]

Aims 1 and 2 are assessed qualitatively via transcribed audio recorded interviews, and quantitatively via feedback forms, rates of recruitment, retention, time to complete assessments and intervention, and monitoring of intervention fidelity. As such, feasibility, safety, and acceptability data are descriptive and qualitative and do not require null hypothesis significance testing analyses.

Exploratory Aim: Assessment of Candidate Proximal Outcomes
As a treatment development study, this project is not designed to test treatment efficacy. To demonstrate the potential viability of the approach, we will examine this data to estimate key statistics of our exploratory outcome variables (e.g., frequencies, distributional properties, standard deviations) and their correlations with key intermediary variables. The goal is to gain information that will inform the design of a fully powered and definitive phase III trial.

The pilot optimization trial was designed to use a balanced 2x2x2 full factorial to examine each component (VR enhanced cognitive restructuring, problem-solving, and affect regulation) across treatment level (standard vs. standard + PRESR). All patients will receive standard treatment, and will receive worksheets about cognitive restructuring, problem-solving, and affect regulation aligned to standard procedures provided by researchers, but the experimental conditions will vary according to VR enhancement of each skill (involving a VR lesson and practice session). With this design, primary focus will be on the candidate proximal outcome variables based on skill condition. Specific analyses include exploring the distribution and degree of variability among variables, as well as preliminary indicators of change over time (e.g., via pre-post comparisons before and after the intervention using paired sample t-tests to gauge directionality; maintenance of change at 2-week and 3-month follow-up visits) in order to evaluate which candidate variables are most promising.

As shown in Table 1, candidate outcomes include:

Exploratory Intermediary Variables: *Threat habituation*: Subjective Units of Distress Scale (SUDS)**;** ***Cognition*:** Automatic Thoughts Questionnaire (ATQ-30);

Exploratory Candidate Proximal Primary Outcomes: *Psychological distress:* Child Anxiety Sensitivity Index (CASI); Beck Hopelessness Scale (BHS); Emotional Distress-Anxiety/Depression - Pediatric Short Form (PROMIS). ***Self-efficacy:*** *Emotional Self-Efficacy (ESE) measure.*

Exploratory Candidate Distal Primary Outcomes: *Suicidal thoughts and behaviors:* Self-Injurious Thoughts and Behaviors Interview (SITB); Columbia Suicide Severity Rating Scale (CSSRS). ***Rehospitalization:*** *Medical Record Review.*

Additional Exploratory Candidate Secondary Outcomes: *Skill use and understanding:* Performance of Cognitive Therapy Strategies (PCTS) assessment; Cognitive-Behavior Therapy Skills Questionnaire (CBTSQ); Cognitive Therapy Awareness Scale (CTAS); Skills of Cognitive Therapy (SoCT); Daily diary of difficult school experiences, suicidal thoughts and behaviors, skill use, and safety plan use for 2-weeks post school re-entry period. ***School experiences***: Authoritative School Climate Survey (ASCS); School Connectedness Scale (SCS).

Assessment of Service Use Following Release: With consent/assent of parents and adolescents, we will obtain adolescents' treatment records. Records will be used to verify the number, duration, and frequency of contacts with mental health providers.

8.4 Planned Interim Analyses

No interim analyses will be performed.

9 Sample Size Rationale

The focus of this pilot clinical trial is to develop tools, procedures, and knowledge to inform the design of a larger study and is not intended to assess efficacy. A sample size of 48 with anticipated attrition of 20% was selected to allow n=4-6 per condition in the 2x2x2 factorial design. A sample of n=4-6 per condition will allow the researchers to assess key estimates of feasibility and acceptability within each condition. Even though this pilot is not designed to test efficacy, the analytic plan for the exploratory aim will focus on estimation of key statistics (means, SDs, correlations) and distributional properties of candidate proximal outcomes that in preparation for the fully powered trial. Ultimately, completion of this pilot clinical trial will result in a proof-of-concept paper that outlines the utility, feasibility, and acceptability of the PrESR conceptual model and in preparation for the fully-powered optimization trial.

10 Data Capture and Database Management

10.1 Software for Data Capture

The study data will be entered into a REDCap database developed by the study personnel. REDCap is a data capture system provided by the NC TraCS Institute at UNC. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate (note, however, that REDCap is not currently 21CFRPart11 compliant). Study data will be entered directly from the source documents. Data may also be collected using paper questionnaires (e.g., during hospitalization, at home diaries) and entered directly into REDCap.

10.2 Responsibilities for Data Capture and Database Management

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, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs)) will be entered into REDCap, a HIPAA-compliant data capture system provided by the UNC TrACS Institute. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

Authorized representatives of the NIH, sponsor, and regulatory agencies are permitted to examine (and when permitted by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress, and data validity.

10.3 Study Records Retention

The study results will be retained in the participant's research record for three years after the study is completed or until the youth participant reaches the age of 21, whichever is longer.

11 Safety Monitoring and Management

11.1 Risk / Benefit Assessment

Potential Risks:

The primary risks associated with the study are: (1) distress in relation to answering questions about their experiences or physical (e.g., motion sickness) or psychological discomfort in relation to viewing/participating in stressful experiences that mimic real life stressors in the intervention; (2) coercion to participate in the study; and (3) loss of privacy or confidentiality. In the following sections we outline a number of ways we protect against risks.

Distress/Motion Sickness. Because the intervention provides an immersive experience that mimics real life stressors, it is possible that participants will feel distressed or uncomfortable during the intervention. Decisions regarding whether an adolescent will be invited to participate or not will be determined in collaboration with their attending physician. Additionally, adolescents at risk for developing cybersickness (50^{th} percentile as measured on the Motion Sickness Susceptibility Questionnaire) will be excluded from the study. Staff will be trained to provide validation and reduce stress during interactions, and to monitor physical safety during participation. Participants and staff will be taught how to end the intervention should they feel too stressed or agitated. Participants will be reminded that they may pause or end the intervention at any time. All equipment will be thoroughly cleaned before and after use.

Coercion: We will take precautions to minimize coercion to participate. We will emphasize the voluntary nature of the study and remind participants that they may discontinue at any time. Members of the research team will be trained to be respectful towards participants' preferences regarding participation. We will present information verbally and in writing on the consent form to ensure participants are aware of the voluntary nature of the study. The informed consent procedure will include a careful explanation of study procedures, risks, benefits, and alternatives. We have selected compensation rates that we believe will not be excessive or coercive for adolescents.

Confidentiality or loss of privacy. The information we are collecting is considered potentially sensitive and as such participants could experience distress or increased psychological risk if information is improperly handled or released inappropriately. Potential risk from breach of confidentiality will be minimized by strict adherence to the guidelines for research outlined by UNC and HIPAA. Study data will only be identified by numeric ID and any other records that do contain potentially identifying information will be stored separate from all other research data. All electronic data will be stored on a secure server. Data will only be stored on password-protected computers and electronic transmission of identifying data will not be permitted. Team members accessing data and identifying information will be trained on the management of sensitive clinical information. All data will be considered confidential, and only trained research staff will have access to data.

Potential Benefits:

It is possible that adolescents receiving the PrESR intervention may benefit; however, the efficacy of the PrESR for reducing psychological distress and preventing suicide-related thoughts and behaviors is unknown. Additional benefits may involve increased monitoring of suicidal-thoughts and behaviors as part of follow-up procedures.

11.2 Assessment of Safety

Safety will be assessed throughout the intervention by monitoring participant responses and documentation of adverse events.

Eligible participants will be recruited with permission of the treating clinician and screened for motion sickness using the following assessment protocols:

- Motion Sickness Susceptibility Questionnaire (MSSQ)

Participants will be taught how to complete a SUDS scale and reminded of the potential risks of the intervention prior to beginning each session. Participants and clinicians will be taught how to immediately pause or end the intervention as needed, and clinicians will be trained to monitor participant safety during the intervention (i.e., watching where their body is at all times, validating and supporting their experiences). The intervention will be administered at the psychiatric hospital, with trained clinical staff available to support patients as needed. Participants are a vulnerable population (adolescents with a recent suicide-related crises) and the intervention is designed to supplement treatment as usual. Accordingly, all participants will receive treatment as usual and if randomized to participate in one of the conditions of the intervention will not disrupt other necessary treatments or interventions.

11.3 Unanticipated Problems, Adverse Events, Serious Adverse Events

Unanticipated Problems:
This protocol uses the definition of Unanticipated Problems as defined by the Office for Human Research Protections (OHRP). An unanticipated problem is any incident, experience or outcome that meets all three OHRP criteria (1) unexpected (in severity, specificity, frequency, or nature), (2) related or possibly related to the research, and (3) suggests the research places participants or others at greater risk than previously known or recognized. Only a subset of adverse events will meet criteria for unanticipated problems.

Adverse Event (AE) Definitions: This protocol uses the definition of adverse event from 21 CFR 312.32 (a): any untoward medical occurrence associated with the use of an intervention in humans, ***whether or not considered intervention-related***.

Serious Adverse Events (SAE) Definition: A serious adverse event is an adverse event that results in death, is life-threatening, requires hospitalization, results in disability, is a congenital anomaly, or is a medically important event.

Grading the Severity of Adverse Events and Events of 'Special Interest': For adverse events (AEs), the following guidelines will be used to describe severity.

- **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".]

In this study, serious/severe adverse events include expected events such as suicide attempts, emergency department visits, and hospitalizations.

Relatedness Definition: All adverse events (AEs) will have their relationship to study procedures, including the intervention, assessed by an appropriately trained clinician based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Related** – The AE is known to occur with the study procedures, there is a reasonable possibility that the study procedures caused the AE, or there is a temporal relationship between the study procedures and the event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study procedures and the AE.

- **Not Related** – There is not a reasonable possibility that the study procedures caused the event, there is no temporal relationship between the study procedures and event onset, or an alternate etiology has been established.

Expectedness Definition:

A clinician with appropriate expertise in suicidal thoughts and behaviors and non-suicidal self-injury 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 procedures.

AE and SAE Assessment, Follow-up Procedures: 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.

All AEs, not otherwise precluded per the protocol, will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study procedures (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study will be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

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, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

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.

Designated study personnel will record events 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. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

Reporting and Documentation Procedures:

Any unanticipated problems or serious and unexpected adverse events will be promptly reported by the principal investigator or designated member of the research team to the IRB, DSMB and sponsor or appropriate government agency if appropriate.

Participant Notification of New Information:

Participants will be informed of new information related to the study or intervention that might influence their interest/willingness to participate in the study.

11.4 Safety Monitoring

The principal investigator will be responsible for the overall monitoring of the data and safety of study participants. The principal investigator has extensive experience in overseeing research conducted with adolescents hospitalized or previously hospitalized for suicide-related crises and is a trained school psychologist and licensed psychologist. A Data Safety & Monitoring Board (DSMB) will be utilized, (see Section 16.6). Screening and assessment of motion sickness will be monitored and documented. Additionally, self-report measures of distress based on SUDS scales will be collected throughout the intervention; simulation sickness will be measured prior to and following the initial virtual reality session; and distress level will be measured pre- and post-intervention completion.

11.5 Study Suspension / Early Termination of the Study

There is no interim analysis of the study so early termination is not expected; however, we are monitoring for safety as described elsewhere and we may stop based on an adverse event or accumulation of adverse events. If 10 Serious Adverse Events occur in 10 subjects during baseline procedures or if 10 number of subjects have a 300% increase in distress (as measured by SUDS captured before and immediately following a practice experience in PrESR, averaged across practice sessions), the study will be suspended

12 Regulatory, Ethical, and Study Oversight Specifications

12.1 Informed Consent Process

Assent and consent forms describing in detail the study intervention, study procedures, and risks will be given to the participant and caregiver. Consent and assent will be obtained in-person using paper forms, or virtually using electronic capture with a REDCap or Qualtrics interface. Offering in-person and virtual permission for parent(s)/guardian(s) is necessary given the constraints of parents with hospitalized youth (e.g., families that live farther away from the hospital or with rigid work schedules may be unable to visit their child during hospitalization).

12.1.1. Consent/Assent and Documents Provided to Participants

Consent and assent forms describing in detail the study intervention, study procedures, and risks are provided to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention. Parent permission will also be available in Spanish, but adolescent participants will need proficiency in English to complete the intervention (which is only available in English).

12.1.2. Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator or research assistant will explain the research study to the parent/guardian and participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants (and their parents, if applicable) will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants will be provided the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Permission and assent will be available in paper format and electronically via REDCap or Qualtrics in case parent(s)/guardian(s) are not available in-person. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records (either electronically or in paper format). The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

To ensure a standardized approach that ensures all elements of informed consent/assent are covered, we will develop a sample script for introducing the research study. Prior to the beginning of consent/assent procedures, we will role play administration of consent/assent with researchers providing consent and provide feedback.

There is no requirement about whether the consent or assent should be obtained first. However, to participate in the study, both assent and consent will be required.

In general, it should take no longer than 15 minutes to obtain consent/assent. However, as much time as needed will be allocated for answering any questions about the study.

Participants and parent(s)/guardian(s) will be advised that if they have any questions about the research study, they can contact the principal investigators (for whom the appropriate telephone number is provided). Participants will also be informed that if they have any questions regarding their rights as research subjects, they may contact the Institutional Review Board at University of North Carolina at Chapel Hill.

Youth who do not understand English will not be enrolled in the study. Permission procedures will be made available for parent(s)/guardian(s) speaking Spanish.

Participants will be notified that the UNC School of Medicine is not conducting this study. Participants will be apprised of the voluntariness of the research, and that the decision to participate or not will not have an impact on medical care or general conditions while in psychiatric care.

Participants will be apprised that confidentiality will be broken if youth (a) indicate plans to harm themselves, (b) indicate plans to harm someone else, and/or (c) disclose previously unreported abuse according to the state of North Carolina. This information will be immediately reported to the adolescent's treatment team or a caregiver during follow-up procedures.

During follow-up procedures, adolescents who were previously a minority age who have since turned majority age will be re-consented into the study.

12.2 Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, the investigator, funding agency, and regulatory authorities.
If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Examples of circumstances that may warrant termination or suspension of the study include:
1. Criteria established in the MPD for early termination of the study have been satisfied
2. Detection of an unexpected unacceptable level of risk to participants
3. In preparatory (pilot) studies, futility due to insufficient adherence to protocol requirements
4. Unexpected inability to recruit participants

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the regulatory oversight (e.g., DSMB, sponsor, IRB, FDA).

12.3 Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, the safety and oversight monitor(s), and the sponsor(s) and funding agency. This confidentiality is extended to the data being collected as part of this study. Data that could be used to identify a specific study participant will be held in strict confidence within the research team. No personally identifiable information from the study will be released to any unauthorized third party without prior written approval of the sponsor/funding agency.

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

Study data will be entered into REDCap databases so there are minimal hard copies of data, reducing possibilities for breach of confidentiality. In data sets, participants will be identified by number only, with the subject's name and linked study number kept in a locked separate file in the office of the PI.

Data gathered in the study will be protected in the following manner: participants will be identified by number only; data disks and study computers will be encrypted and kept in locked storage in locked rooms; data collected via paper at the psychiatric facilities will be entered into an encrypted REDCap Data Capture System maintained at UNC. The data set linking identifying information to subject numbers will be password protected/encrypted. Data bases with identifying information (e.g., contact information) will not include de-identified data from the study. Conversely, data bases with de-identified data will not include identifying information but will be assigned a subject code.

The study participant's contact information will be securely stored at UNC for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor/funding agency requirements.

Authorized representatives of the sponsor or funding agency, and representatives of the Institutional Review Board (IRB), and other 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).

We disclose the exceptions to confidentiality in this study in the informed consent/assent process. To further protect the privacy of study participants, the National Institute of Mental Health, has issued a Certificate of Confidentiality (CoC) to all researchers engaged in biomedical, behavioral, clinical, or other human subjects research funded wholly or in part by the federal government. Recipients of NIH funding for human subjects research are required to protect identifiable research information from forced disclosure per the terms of the NIH Policy (see https://humansubjects.nih.gov/coc/index). As set forth in 45 CFR Part 75.303(a) and NIHGPS Chapter 8.3, recipients conducting NIH-supported research covered by this Policy are required to establish and maintain effective internal controls (e.g., policies and procedures) that provide reasonable assurance that the award is managed in compliance with Federal statutes, regulations, and the terms and conditions of award. It is the NIH policy that investigators and others who have access to research records will not disclose identifying information except when the participant consents or in certain instances when federal, state, or local law or regulation requires disclosure. NIH expects investigators to inform research participants of the protections and the limits to protections provided by a Certificate issued by this Policy.

No reference to any individual participant will appear in reports, presentations, or publications that may arise from the study.

12.3.1. Certificate of Confidentiality

To further protect the privacy of study participants, a Certificate of Confidentiality will be issued by the National Institutes of Health (NIH). 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.

12.4 Future Use of Stored Specimens and Data

Data collected for this study will be analyzed and stored in a secure, encrypted location following UNC and IRB guidelines. Transcriptions of audio recordings from interviews completed during baseline will be redacted of identifying information.

12.5 Key Roles and Study Governance

[Provide the name and contact information of the Principal Investigator and the Medical Monitor.]

Principal Investigator
Marisa Marraccini, PhD, Assistant Professor
University of North Carolina at Chapel Hill
100 East Cameron Ave., Chapel Hill, NC 27599
919-843-5099
mmarracc@unc.edu

In addition to the study PI, a mentorship team part of the K23 award is available for consult and support to the PI in determining conduct, management, and oversight.

12.6 Safety Oversight

The principal investigator will be responsible for the overall monitoring of the data and safety of study participants.

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB). The DSMB includes experts in scientific disciplines needed to monitor the data and ensure patient safety during the conduct of this study, a psychologist or psychiatrist, a clinical trials or mental health services expert who will chair the committee, a statistician, and a public member (e.g., school professional). No DSMB members will be directly involved in other aspects of the project or have a stake in its outcome. DSMB members have no association with the project investigators, and no conflicts of interest with study outcomes. The DSMB will meet by teleconference or in person on a twice yearly basis (unless there are compelling reasons to meet more often) to assess safety and data of the study.

DSMB procedures conform with usual standards, including reviewing emerging trial data and maintaining confidentiality. The main responsibilities of the DSMB include, but are not limited to the following: (1) reviewing the research protocol, consent form(s) and plans for data and safety monitoring prior to the initiation of the study; (2) monitoring of the progress of the study, including data quality, timeliness, recruitment and retention of study participants, adverse events, serious adverse events (SAEs), reasons for participant withdrawal, adherence to the timeline of the study, protocol deviations, and factors that may affect the risks and benefits of the study such as emerging literature; and (3) making directives about the continuation, modification, or termination of the study, based on the balance of adverse events and beneficial outcomes. Throughout the study, notification of SAEs as well as any proposed investigator-initiated changes in the protocol will be submitted to the DSMB. Based on its review of the protocol, the DSMB will identify the data parameters and format of the information to be regularly reported. The DSMB may at any time request additional information from the Principal Investigators.

12.7 Clinical Monitoring Plan (CMP)

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonization Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

A. All SAEs and adverse events (AEs will only be reported to the DSMB annually) will be tabulated and submitted to the DSMB in the biannual DSMB data reports. Based on review of safety data, the DSMB will issue directives concerning the conduct of the study. Recommendation/directives made by the DSMB may include amending safety monitoring procedures, modifying the protocol or consent, terminating the study, or continuing the study as designed.

B. Independent audits will not be conducted.

12.8 Quality Assurance and Quality Control

Quality control (QC) procedures will be implemented as follows:

Informed consent --- Study staff will review both the documentation of the consenting process as well as a percentage of the completed consent documents. This review will evaluate compliance with GCP, accuracy, and completeness. Feedback will be provided to the study team to ensure proper consenting procedures are followed**.**

Electronic data --- When possible, data will be initially captured via a REDCap Electronic Data Capture system to minimize errors. Otherwise, paper data will be entered directly into REDCap. Electronic data will be reviewed regularly for errors, unusual patterns, and outliers that need to be checked.

Intervention Fidelity — Consistent delivery of the study interventions will be monitored throughout the intervention phase of the study using a fidelity checklist.

Protocol Deviations – The study team will review protocol deviations on an ongoing basis and will implement corrective actions when the quantity or nature of deviations are deemed to be at a level of concern.

Should independent monitoring become necessary, the PI will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor/funding agency, and inspection by local and regulatory authorities.

12.9 Protocol Deviations

This protocol defines a protocol deviation as any noncompliance with the clinical trial protocol, International Council on Harmonization Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) 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 will be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:
- Section 4.5 Compliance with Protocol, subsections 4.5.1, 4.5.2, and 4.5.3.
- Section 5.1 Quality Assurance and Quality Control, subsection 5.1.1.
- Section 5.20 Noncompliance, subsections 5.20.1, and 5.20.2.

It will be the responsibility of the site investigator to use continuous vigilance to identify and report deviations within **ten working days** of identification of the protocol deviation, or within **ten working days** of the scheduled protocol-required activity. All deviations will be addressed in study source documents, reported to the National Institute of Mental Health when requested or as required by NIMH policies. Protocol deviations will be sent to the reviewing Institutional Review Board (IRB) and/or documented per their policies. The site investigator will be responsible for knowing and adhering to the reviewing IRB requirements.

12.10 Publication and Data Sharing Policy

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial

will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers five years after the completion of the primary endpoint by contacting Dr. Marraccini at University of North Carolina at Chapel Hill.

12.11 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. The study leadership in conjunction with University of North Carolina at Chapel Hill and the National Institute of Mental Health have established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

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