PROTOCOL TITLE: **A Novel Cognitive Reappraisal Intervention for Suicide Prevention**

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IRB Protocol #: **1603017115**

ClinicalTrials.gov Identifier: **NCT03026127**

Current Version: **8/6/2018**

Prior Version Dates:
Initial 11/30/2016
Renewal 9/6/2017

BACKGROUND

Drawing upon recent advances in affective neuroscience, we developed a novel psychosocial intervention called "Cognitive Reappraisal Intervention for Suicide Prevention (CRISP)." CRISP aims to improve cognitive reappraisal (i.e. modifying the appraisal of a situation to alter its emotional significance) (target), and reduce suicide risk (outcome). Our conceptual framework (model) views suicidal ideation and behavior as failed attempts to regulate negative emotions. Thus, by improving cognitive reappraisal, a well-documented and effective emotion regulation strategy, we expect to reduce suicide risk. Our theory is supported by studies showing that unsuccessful attempts to regulate negative emotions and decreased cognitive reappraisal are associated with increased suicidal ideation and behavior. Further, our pilot data suggest that CRISP improves cognitive reappraisal and reduces suicide risk in middle-aged and older adults after discharge from a hospitalization caused by increased suicide risk. We assembled a team with complementary expertise required by this study. Dr. Kiosses (Cornell) is the developer of CRISP, Dr. Gross (Stanford) is a leading investigator on emotion regulation, and Dr. Hajcak (Stony Brook) is an expert on ERPs. The study is aligned with: a) the National Institute of Mental Health's (NIMH) "Strategic Plan for Research", b) "A Prioritized Research Agenda for Suicide Prevention: An Action Plan to Save Lives", developed by the National Action Alliance for Suicide Prevention, and c) the NIMH Research Domain Criteria (RDoC) initiative.

STUDY DESIGN

The goal of this two phase (R61 and R33) project is to refine and test a novel emotion-regulation based psychosocial intervention designed to reduce suicide risk in middle-aged and older adults (50-90 years old) who have been discharged after a suicide-related hospitalization (i.e. for suicidal ideation or suicide attempt). Suicide rates in this group are alarmingly high, and reducing suicide rates in at-risk populations is a major NIMH priority. The R61/R33 mechanism is a new mechanism that funds the first two years (R61) and depending on the results, the NIMH may fund the following two years (R33). Therefore, the funding of the R33 depends on the R61. We were advised to use one protocol by NIMH as we will have one clinicaltrials.com. Not only will the funding depend on the R61 results, but also the R33 study design will depend on the results from the R61 phase: for example, we don¿t know the exact duration of the CRISP intervention (6 or 12 weeks) that we will be using for the R33 phase, because we are testing these two durations in the R61 phase; and we don¿t know what ERP task will be the best one to use for the R33 phase. As seen in the grant, there is a committee that will decide together with the NIMH PO about those choices. Therefore, we do not have the R33 consent form, as we don't know the exact design decisions for the R33 phase. However, we are planning to submit an amendment with all the R33 IFCs as soon as we get funded for the R33 phase. The aims are described in the document attached. R61 SPECIFIC AIMS: The goals of this proof-of-concept phase are to optimize CRISP (Cognitive Reappraisal Intervention for Suicide Prevention) and test its engagement with cognitive reappraisal (target). Certified social workers will administer 12 weekly sessions of CRISP to 40 middle-aged and older adults (50-90 years old) after a suicide-related hospitalization. Research assistants will conduct

assessments at study entry (hospital admission), at discharge, and at 6 and 12 weeks post-discharge. Our aims are: 1. CRISP optimization: We will select the optimized CRISP dosage (6 or 12-week version) that improves cognitive reappraisal. 2. Initial demonstration of target engagement: Participants receiving the optimized CRISP dosage will show an improvement in cognitive reappraisal (from discharge to end of treatment) as assessed by electrocortical measures (i.e. late positive potential, LPP) during a standard pictured-based and our novel idiographic cognitive reappraisal paradigm. Go: If we meet Milestone 1 ("Feasibility and acceptability of CRISP") & 2 ("Target Engagement"). No-Go: If we fail to meet either Milestone 1 or 2. An experts committee will modify CRISP based on R61 results. While the research assistants may be aware of the study aims, we will take every reasonable effort to ensure they are not aware of the study hypotheses and Go/No-Go criteria in testing these hypotheses. Since this R61 phase is not a randomized controlled trial, but a pilot study to evaluate the effect of CRISP on cognitive reappraisal, we want to eliminate bias when the research assistants collect the data. However, we understand that we may not be able to always fully control it. The external investigators from Stanford University, University of Rochester Medical Center, and University of Stony Brook will serve as consultants and will only be involved in the protocol design and Dr. Hajcak from Stony Brook will also be involved in the statistical analyses of de-identified data. As they are not receiving funds or engaging in the actual research, no IRB is needed from these institutions, which has been confirmed. Please see attachments for continuation of NTRP study design regarding audio tapes.

R61 SPECIFIC AIMS: The goals of this proof-of-concept phase are to optimize CRISP (Cognitive Reappraisal Intervention for Suicide Prevention) and test its engagement with cognitive reappraisal (target). Certified social workers will administer 12 weekly sessions of CRISP to 40 middle-aged and older adults (50-90 years old) after a suicide-related hospitalization. Research assistants, unaware of the study aims, will conduct assessments at study entry (hospital admission), at discharge, and at 6 and 12 weeks post-discharge. Our aims are: 1. CRISP optimization: We will select the optimized CRISP dosage (6 or 12-week version) that improves cognitive reappraisal. 2. Initial demonstration of target engagement: Participants receiving the optimized CRISP dosage will show an improvement in cognitive reappraisal (from discharge to end of treatment) as assessed by electrocortical measures (i.e. late positive potential, LPP) and self-reported affect during our a standard pictured-based and our novel idiographic cognitive reappraisal paradigm. Go: If we meet Milestone 1 ("Feasibility and acceptability of CRISP") & 2 ("Target Engagement"). No-Go: If we fail to meet either Milestone 1 or 2. An experts committee will modify CRISP based on R61 results. R33 SPECIFIC AIMS: The R33 phase aims to provide further evidence of target engagement of the optimized CRISP in a larger sample, evaluate the relationship of cognitive reappraisal with suicide risk as measured with Columbia Suicide Severity Rating Scale-C-SSRS, and estimate implementation parameters for a large-scale clinical trial. A different sample of 75 middle-aged and older adults (using the same inclusion/exclusion criteria as for the R61 phase) will be randomized (2 to 1) to CRISP (N=60) or to Supportive Therapy (ST, a control treatment not designed to improve emotion regulation) (N=30). Assessments will be conducted on admission, at discharge, and at 6, 12, and 24 weeks post-discharge. Primary Aims: 1. CRISP participants will show an

improvement in cognitive reappraisal from discharge to the end of treatment. 2. Improvement in cognitive reappraisal in CRISP participants will be associated with reduced suicide risk over 24 weeks.

R33 Secondary Aim: Assessment of feasibility and acceptability of ST. Exploratory Analyses: 1. Obtain preliminary estimates of treatment effects (CRISP vs. ST) on cognitive reappraisal and on suicide risk over 24 weeks. 2. Does the relationship of cognitive reappraisal with suicide risk in CRISP participants differ by demographic variables (age, gender), discharge clinical characteristics (e.g., depression, executive functioning), types of pharmacotherapy (e.g. antidepressants, mood stabilizers) and frequency of utilization of cognitive reappraisal techniques (e.g. MindMe tablet app)?

The total number of subjects for the R61 and R33 phases are: 40 for the R61 and 90 for the R33 phase. DATA ANALYSIS: R61 Phase: Preliminary Analyses: For each variable, we will examine the distribution, outliers and abnormal values using graphical methods, e.g., the box-plot. If distribution assumptions are violated, we will use transformations or bootstrapping. Primary Aims: 1. CRISP optimization: We will select the optimized CRISP dosage (6 or 12-week version) that improves cognitive reappraisal. We will consider improvement in LPP and self-report measures from discharge to the end of treatment (6 vs. 12-week) as our target engagement outcomes. We will test the two dosage with an intent-to-treat (ITT) principle and perform t-tests or linear regression (with covariates) to test the between-group difference. If distributional assumptions are violated, their non-parametric counterpart or bootstrapping will be used. Dosage Optimization Decision: The decision will be made by the Experts Committee after taking into account both quantitative findings (a statistical comparison of target engagement between the two dosages; the effect sizes of each dosage at end of treatment) as well as qualitative factors including feedback from patients and therapists. Aim 2. Initial demonstration of target engagement: Participants receiving the optimized CRISP dosage will show an improvement in cognitive reappraisal (from discharge to end of treatment) as assessed by electrocortical measures (i.e. late positive potential, LPP) during a standard pictured-based and our novel idiographic cognitive reappraisal paradigm. We will obtain the standardized effect size for both measures of improvement in cognitive reappraisal. R33 Phase: Preliminary Analyses: For each variable, we will examine the distribution, outliers, and abnormal values using graphical methods, e.g., the box-plot. If distribution assumptions are violated, we will use transformations or bootstrapping. Primary Aims: Aim 1. CRISP participants will show an improvement in cognitive reappraisal from discharge to the end of treatment. The analytic plan will be similar to R61 Aim 2, but conducted in a larger sample. Aim 2. Improvement in cognitive reappraisal in CRISP participants will be associated with reduced suicide risk over 24 weeks. We will first use a generalized mixed effects regression model to analyze C-SSRS as a dependent variable over multiple assessment points and with improvement in cognitive reappraisal measures considered as an independent variable. We will test several distributions and corresponding link functions (e.g. Poisson distribution, normal distribution or binomial (Low vs High suicide risk, based on C-SSRS scores)) in this generalized linear mixed model. We will chose the best fitting model using Bayesian Information Criterion. Secondly, we will perform a survival analysis in CRISP participants to model time to event in a Cox proportional hazard model. The time to event will be based

on C-SSRS [Event=active suicide ideation with any methods (C-SSRS greater or equal to 3); or suicide-related hospitalization; or an attempt (actual, interrupted, or aborted)]. In two separate models, we will include the two measures of improvement of cognitive reappraisal from discharge to end of treatment (LPP and self-report affect) as dependent variable. We will test violations of proportional hazard assumptions using Schoenfeld's residual and by graphical techniques. We will focus on magnitude of effect following McGough and Faraone[98] rather than significance testing. Secondary Aim: Assessment of feasibility and acceptability of ST. Feasibility of ST: At least 80% of ST participants will either complete ST or discontinue treatment because of an adverse outcome. Acceptability of ST: We will obtain an average Treatment Satisfaction score ≥ 3 (out of 4) at the end of ST. ....

INCLUSION AND EXCLUSION CRITERIA

Inclusion Criteria:

1. Age: 50 years and older. 2. Diagnosis (based on SCID-5 Clinical Trials Version to assess DSM-5 diagnoses): Any DSM-5 depression or anxiety diagnosis, including major depressive disorder, bipolar depression, depressive disorder Not Elsewhere Classified, anxiety disorder Not Elsewhere Classified, adjustment disorder with anxiety and depressed mood (but without any of the diagnoses shown under Exclusion criteria). 3. Recent hospitalization for suicidal ideation or suicide attempt; at hospital admission, Columbia Suicide Severity Rating Scale greater or equal to 3, "Active Suicide Ideation with any methods or a suicide attempt". 4. Patients with any degree of suicidal ideation at discharge (Columbia Suicide Severity Rating great or equal to 0) will be included. 5. We will also include patients on psychotropics and on after-care community psychotherapy.

Exclusion Criteria:

1. History or current diagnosis of Psychotic Disorders; Current Diagnosis of Bipolar I or Bipolar II, with current episode hypomanic, manic or mixed; Diagnosis of Dementia. 2. Cognitive Impairment: We will exclude participants with Mini Mental State Exam less than 24. 3. Acute or severe medical illness (i.e., delirium; decompensated cardiac, liver or kidney failure; major surgery; stroke or myocardial infarction during the three months prior to entry). 4. Aphasia, sensory problems, and/or inability to speak English.

DATA AND SAFETY MONITORING PLAN

The study will help this population who has suicide ideation to monitor their depression, their suicide ideation, and emotion regulation through weekly therapy sessions and research assessments. The therapy will have 12 weekly sessions during which the therapists will evaluate these. In addition, the research assessments will be conducted at admission, discharge, week 6,

and week 12 (end of treatment). If the patient has any suicide ideation, the research assistant will complete the Suicide Risk Assessment Protocol. The PI will be available 24 hours a day to speak with therapists, research assistants, and patients to ensure appropriate actions in case of suicide ideation. Participants will have Dr. Kiosses's cell number (in the informed consent) to call 24 hours a day and they will be asked to contact him if there is any increase in suicide ideation. The Suicide Risk Assessment (attached) has been approved by NIMH for determining an increase in suicidal ideation, is completed by the research assistant, and reviewed immediately by the PI or another psychologist, either in person or over the phone. Depending on the level of risk, the subject will be encouraged to speak to his/her own clinician; the PI or therapist may call the subject's clinician and/or family member; the subject may be referred for an evaluation by a psychiatrist present in the office at the time, or the subject may be escorted to the evaluation center at NYPH to possibly be hospitalized. Other urgent risks may necessitate calling 911 or having a family member bring the subject to a local emergency room for evaluation (if subject is being interviewed over the phone, for example). This protocol has been successfully used in other protocols at our Institute. This Suicide Risk Assessment will be administered to all subjects during the weekly phone meeting, and the action plan will be followed as stated, after being reviewed by the PI or another psychologist at the Institute: if there is a mild risk, it will be recommended that the subject speak to their clinician. If there is more than a mild risk of SI, the PI or on-call psychologist may speak with the subject over the phone and take appropriate clinical action. This may include calling 911 or having a family member or caregiver bring the subject to a local emergency room. A referral to an external mental health referral will be offered to subjects: a) who withdraw from the study in the event of personal distress, and b) after the subjects complete the 12 week treatment.

The study will use the adverse event grading guidelines provided by WCMC's Office of Research Integrity and Assurance. All adverse events will be reported to the WCMC IRB in the timeline indicated by the WCMC Human Research Protections Program Immediate Reporting Policy. Plan for Grading Adverse Events. Adverse event (AE): An adverse event (AE) is any adverse change from the participant¿s baseline condition, regardless of relationship to the study intervention which occur after informed consent is signed. Adverse events include but are not limited to: (1) worsening or change in nature, severity, or frequency of conditions or symptoms present at the start of the study; (2) participant deterioration due to primary illness; and (3) intercurrent illness. Following questioning and evaluation, all AEs, whether determined to be related or unrelated to the study psychosocial intervention by the Site Protocol Principal Investigator, must be documented in the participant¿s medical records, in accordance with the investigator¿s normal clinical practice. Each AE is evaluated for duration, severity, seriousness, and causal relationship to the study intervention. Serious Adverse Event (SAE): Any untoward medical occurrence that: results in death, is life-threatening, require inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect (NIH Guide-6/11/99). Note 1: Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other

situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the outcomes listed in the definition above. Note 2: Hospitalizations that fulfill one of the following conditions will not have to be reported as SAE: 1. Hospitalizations for social reasons and thus unrelated to a deterioration of the subject¿s condition or adverse event (e.g., deterioration of the living conditions related to environmental factors rather than to a deterioration of the disease, lack of transportation to the investigational site, respite care for the caregiver) 2. Hospitalizations for elective surgical interventions for which the date had already been determined prior to the study participation. Attribution of Adverse Events.

1. Definite: Adverse event(s) will clearly be related to the intervention and cannot be reasonably explained by an alternative explanation. 2. Probable: Adverse event(s) will likely be related to intervention. 3. Possible: Adverse event(s) may be related to the intervention. 4. Unlikely: Adverse event(s) will doubtfully be related to the intervention. 5. Unrelated: Adverse event(s) will clearly not be related to the intervention.

Adverse events will be reported to the WCMC IRB as per WCMC AE reporting policy. We will submit individual adverse events, as well as summary tables every six months to the DSMB, but we would respond to the DSMB recommendation if a higher frequency of reporting is desirable. This is a talk therapy study which does not involve medications or medical devices.

No interim analyses of the outcomes will be performed as that may affect the remaining part of the study.