STUDY PROTOCOL

Written Exposure Therapy to Reduce PTSD Symptoms in Survivors of Acute Cardiovascular Events: A Pilot Randomized Trial

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1. Study Purpose and Rationale

The overall purpose of this project is to determine the feasibility of conducting a randomized clinical trial that compares written exposure therapy with usual care (attention control) among patients at risk for cardiovascular disease (CVD) event-induced PTSD. Experiencing a life threatening cardiovascular event, such as a stroke, transient ischemic attack (TIA), acute coronary syndrome (ACS), and cardiac arrest, has been found to be associated with PTSD symptoms in 12-30% of individuals.[1-3] Patients with elevated PTSD symptoms are at risk for lower medication adherence, increased readmissions and recurrent cardiovascular events, and worsened quality of life.[4,5] Despite these risks, these patients are not systematically screened or treated to prevent PTSD symptoms.

A growing number of studies has been evaluating early interventions after trauma to prevent PTSD.[6,7] While there is no gold-standard intervention, psychological interventions grounded in trauma-focused cognitive behavioral therapy (CBT) have shown promise in some populations. For example, compared to a supportive counseling control condition, CBT has been found to reduce PTSD symptom severity and incidence in individuals with acute stress disorder (ASD), an early manifestation of posttraumatic stress, detected within the first month of a traumatic event.[6,7] Preliminary research suggests that an exposure-based CBT intervention delivered in the immediate aftermath of trauma for individuals meeting Criterion A of DSM-IV PTSD may also hold promise for PTSD prevention.[8] Acute cardiovascular events such as stroke, ACS, and cardiac arrest as the source of trauma are inherently different from other forms of stressors that commonly lead to PTSD. As opposed to an external and past traumatic threat (e.g., combat, physical/emotional abuse), these events can represent an internal and ongoing somatic threat.[9] Accordingly, treatments for preventing PTSD such as the trauma-focused CBT interventions discussed above need to be formally evaluated in this distinct patient population before generalizing the findings from other patient populations. In particular, the willingness to engage in therapies to prevent or reduce PTSD symptoms may differ in this patient population. Few of these patients are actively seeking treatment. Many may not be aware of potential psychological symptoms that can onset after these events or perceive their psychological symptoms to be problematic. Hence, the acceptability of interventions is particularly relevant in this patient population. Risk for recurrent cardiovascular events is especially high in the initial weeks after acute cardiovascular events, and existing epidemiologic data suggest that PTSD symptoms increase this risk.[10] Thus, intervening early to prevent PTSD symptoms prior to waiting the full one or more months to make a PTSD diagnosis may provide new opportunities for offsetting CVD risk.

Written exposure therapy represents a promising intervention to prevent PTSD after cardiovascular events. Written exposure therapy is a brief exposure-based therapy, founded on the principles of Pennebaker and Beale's written disclosure procedure.[11] The treatment protocol consists of 5 sessions, each comprising 30 minutes of writing. In each session, participants are instructed to write about their memory of the traumatic event with particular attention to the felt emotions and the meaning of the event.[12] The initial session also incorporates psychoeducation and review of the rationale for the intervention by a study clinician. Sessions end with therapists' discussing how the writing session went. The rationale behind this exposure therapy is that there is a significant habituation of emotional reactivity to reminders of the traumatic event over repeated writing sessions. Consistent with this rationale, research suggests that these exposure writing sessions are associated with greater initial emotional and physiological reactivity and greater habituation of these responses over time compared to a control writing condition.[13-15] A recent study showed that this brief psychotherapy approach was non-inferior to a more

extensive trauma-focused CBT approach (cognitive processing therapy) for reducing PTSD symptoms in US Veterans with PTSD.[12] Further, written exposure therapy has been effective at lowering PTSD symptoms in patients with motor vehicle accident-induced PTSD.[16]

In contrast with more standard CBT interventions, written exposure therapy was designed to create a more acceptable exposure-based treatment option for PTSD that is easily disseminated and implemented. Like the promising trauma-focused CBT interventions for PTSD prevention, it is also exposure-based. In light of these qualities, written exposure therapy thus may be ideally suited for reducing PTSD symptoms in non-treatment seeking survivors of acute cardiovascular events. Key differences between written exposure therapy and other CBT approaches to treating PTSD include a lower number of sessions (5 vs. ~12-15) and no homework requirement, resulting in higher treatment completion compared to a more rigorous exposure-based therapy approach.[12] Other advantages of written exposure therapy are that it requires a lower level of training from clinicians and less clinician time, which could facilitate dissemination.

Targeting patients at increased risk of PTSD may be a more efficient approach to targeting PTSD preventive interventions, and initial research supports this notion.[6] For patients with cardiovascular event-induced PTSD, several key predictors of PTSD symptoms at 1-month after the index event have been observed in our samples. Most notably and consistent with the broader research on PTSD triggered by more external traumatic events, both elevated threat perceptions at the time of ED presentation and elevated early PTSD symptoms as measured by the ASD scale (ASDS) within days after the cardiac event have been associated with increased PTSD risk. Accordingly, we will screen patients for elevations in threat perceptions and ASD symptoms to determine eligibility, similar to what has been done in other early PTSD intervention work.

To test our hypothesis that it is feasible to conduct a randomized trial of written exposure therapy, we propose to enroll 20 patients who are hospitalized for a CVD event, either ACS, stroke, TIA, or cardiac arrest. We will leverage the recruitment infrastructure of the REACH-Stroke, REACH-ACS, and REACH-Arrest studies (IRB protocols: IRB-AAAR8497) to identify possible participants for this trial, and to conduct baseline and 1-month follow-up assessments. Patients will first be screened for: 1) threat perceptions in the ED for ACS and stroke/TIA patients or upon hospitalization for cardiac arrest patients and 2) ASD symptoms within days of their enrollment in the study. Those with elevated threat perceptions and/or ASD symptoms will be randomized to 1) written exposure therapy (INT); *N*=10 or 2) usual care (CTR); *N*=10.

Specific Aim. To determine the feasibility of conducting a randomized trial of written exposure therapy in survivors of acute CVD events.

Feasibility Hypothesis 1. We can enroll and randomize 20 hospitalized CVD patients at NYP into randomized trial.

Feasibility Hypothesis 2. A majority of participants (>=7 of 10) assigned to the intervention will attend the majority (>=4 of 5) intervention visits.

Significance. Though prior studies suggest that written exposure therapy can reduce PTSD symptoms in those with diagnosed PTSD, this approach has never previously been used as an early intervention to prevent PTSD symptoms, particularly among patients whose PTSD is induced by acute CVD events. If our study demonstrates that this approach is feasible, we will use these data to support grant applications to fund a clinical trial sufficiently powered to test the effectiveness of this intervention at reducing PTSD symptoms after CVD events.

2. Study Design and Statistical Procedures

Design. We will conduct a feasibility randomized controlled trial that compares written exposure therapy with usual care as part of an early intervention to reduce PTSD symptoms in survivors of acute CVD events. Outcomes will be evaluated in a blinded manner. Key features of the intervention are outlined in **Table 1**. The flow of patients through the study is displayed in **Figure 1**.

Table 1. Key features of written exposure therapy intervention

Study population	Recent or currently hospitalized patients with CVD events and with increased risk for PTSD by virtue of having elevated PTSD symptoms due to elevated threat perceptions in response to the CVD event and high ASD symptoms in the acute aftermath of the CVD event
Intervention recipient	Survivor of acute coronary syndrome, stroke, TIA, or cardiac arrest at risk for PTSD
Intervention content	5 sessions of written exposure therapy
Delivery personnel	Member of the study team with prior experience in delivering psychotherapy and with specific training
Method of communication	In-person visits with study clinicians
Intensity	First session in hospital or at study office upon discharge, sessions 2-5 in hospital or at study office within 1 month of index hospitalization (~2 sessions/week); first session 60 minutes, subsequent sessions 40 minutes (30 minutes for writing and 10 minutes for discussion with study clinician)
Environment	In-hospital and office setting
Outcome measures	PTSD symptoms 1-month after hospitalization; satisfaction with intervention

Statistical Approach

All randomized participants will be analyzed according to the group to which they are assigned (i.e., intent-to-treat principle). All participants will be followed for 1 month.

Data Management. Data collected for this study will be entered into a Filemaker Pro database, leveraging the data infrastructure already in place for the REACH studies.

Sample Size Estimate. As this is a pilot study, our sample size was guided by the need to enroll enough participants to examine the feasibility of conducting a larger scale trial of our intervention. In particular, we wanted to ensure that we were capable of recruiting, retaining, and assessing participants as well as implementing the desired intervention. Based on this goal, we estimated we needed to randomize 20 participants (10 per group) into the study. We felt that it was essential to include a randomization arm as this will give more realistic estimates of

patients' willingness to participate in a randomized experiment of this intervention being delivered in a novel context (for prevention and for those with CVD-event PTSD)—information that will be helpful for planning the larger study.

Although some have used pilot studies to estimates effect sizes on primary outcomes, we and other leaders in our field[17] are of the strong opinion that there is too much imprecision in these estimates in small pilot studies, and hence, do not provide power calculations for the effect of our intervention on key outcomes. In the larger study, we will power the study to have sufficient power to detect a meaningful reduction in PTSD symptoms at 1-month.

Analyses. We will use descriptive statistics to describe our participants and their outcomes; to determine the number of participants needed-to-screen and consent; the proportion who complete 1-month follow-up without loss-to-follow-up; the proportion who adhere to the WET intervention, and the proportion who were satisfied with the intervention. We will use qualitative methods to describe the writing samples produced by participants in the WET intervention.

3. Study Procedures

Setting. Participants will be recruited from inpatient units of Milstein Hospital of New York-Presbyterian Hospital (NYP). NYP is located in the Washington Heights neighborhood of New York City, a predominantly Hispanic community with a large number of individuals from low-income and racial/ethnic minority groups.

Study Population. Participants will include patients hospitalized for CVD event, enrolled into the REACH cohort studies, and identified to be at increased risk of PTSD at 1 month after discharge.

Screening. Patients who have consented to be in the REACH-Stroke, REACH-ACS, or REACH-Arrest studies and agree to be approached about further research opportunities will be screened for eligibility through chart review after they complete the baseline interviews. Patients must have elevated scores on ED threat perceptions and/or ASDS (ED threat score >=12 or ASDS score >= 28), as patients with elevated scores are at increased risk for PTSD. Scores will be automatically calculated through the Filemaker database. If eligible based on this score, then a research coordinator will approach the patient about participating.

Enrollment and Consent. Potentially eligible participants will have the study explained to them while still hospitalized; patients who are discharged prior to being approached in the hospital will receive a phone call inviting to come for an in-person at which they can provide written informed consent for the trial. Patients can also be approached at clinic visits in the medical center that occur within 1 week of discharge. Written informed consent will be obtained prior to collecting any data.

Randomization. Randomization will take place only after it is confirmed that participants meet all eligibility criteria for participation and after written informed consent has been obtained (See Table 3 below). Randomization will occur in a 1:1 ratio and will be stratified according to whether the participant was admitted with ACS, stroke/TIA, or cardiac arrest, based on a computer random number generated code. The sequence will be unknown to RAs enrolling participants. The RA will notify the data management team once they enroll a new participant by logging on to a secure website; a member of the data management team will then assign the new participant to the intervention or control group according to the randomization list.

Intervention. Participants in the written exposure therapy intervention group will be scheduled for 5 therapy sessions. Sessions will be scheduled such that they occur 2-3 times per week for a total of 5 sessions over 3 weeks. The sessions can occur while the patient is still hospitalized or can occur after discharge. All study therapists conducting the written exposure therapy sessions are trained providers with a Master's or PhD in clinical psychology or social work, and they completed training in the written exposure therapy protocol with the creators at the National Center for PTSD in Boston. The study therapist will first provide psychoeducation regarding PTSD symptoms that can ensue after medical trauma and then introduce the rationale for the writing exercise. Participants will then be left alone to write for 30 minutes about the emotional experience of their recent trauma. Participants will be instructed to write about the event from a distance, including details about their thoughts and feelings. The study therapist will briefly check in with the participant at the end of the writing session to see how it went (<10 minutes), and he/she will review the writing sample before the next session. At the subsequent 4 sessions, each 40 minutes duration, the study therapist will first provide some brief feedback on the previous session's writing sample and offer advice on how to more closely follow the recommended writing exercise as needed. The guided writing exercise will then be repeated with participants asked to write about the same traumatic medical event.

Usual Care. Participants assigned to usual care will receive care that is typical for those administered to ACS, stroke or TIA, and cardiac arrest patients.

1-Month Phone Call. At 1 month, participants in both groups will be contacted by a member of the study team to assess their CVD-event induced PTSD symptoms, depressive symptoms, QOL, and their satisfaction with the treatment. Participants will also be queried about whether they had any acute care visits (ER visits, hospitalizations) since their baseline hospitalization.

6-Month Phone Call. At 6 months, participants in both groups will be contacted by a member of the study team to assess their quality of life. Participants will also be queried about whether they had any acute care visits (ER visits, hospitalizations) since their baseline hospitalization.

4. Study Devices

None.

5. Study Instruments

Data will be collected from 1) patient questionnaires; 2) medical records from NYP or outside hospitals if participants reported an admission there within the 1-month follow-up period; and 3) the written trauma narratives done by patients in the written exposure therapy intervention, provided that patients do not ask to keep them private. Patient interviews will be conducted in the respondents' primary language (English). Outcome assessments will be performed by RAs who are blinded to group assignment. The following measures will be collected in person during hospitalization and/or by telephone at 1-month later.

Outcome Measures will be assessed by telephone interview 1 month after hospital discharge.

PTSD symptoms: PTSD Checklist-Civilian (PCL-5) for PTSD due to the cardiovascular event. The PCL-5 is a 20-item PTSD screening instrument developed by the National Center for PTSD. Participants rate the extent to which they have experienced each of the 20 diagnostic criteria for PTSD described by *DSM*-5. Participants respond with reference to PTSD symptoms due to the index ACS, stroke, TIA, or cardiac arrest event that led to their hospitalization. The PCL-5 has excellent psychometric properties and excellent sensitivity and specificity for PTSD clinical diagnosis prediction and has been used in numerous patient populations. It yields a continuous PTSD symptom severity score (with a cutoff for "probable PTSD").

Adherence to cardiovascular medications: This is measured by the scoring from the DOSE-Nonadherence questionnaire (3-items) that can be used to dichotomize patients as adherent or nonadherent.

Depression symptoms: These will be assessed using the 8-item Patient Health Questionnaire (PHQ-8). The eight-item Patient Health Questionnaire depression scale (PHQ-8) is established as a valid diagnostic and severity measure for depressive disorders in large clinical studies. Scores range from 0 - 24 and a score of 10 or greater is consistent with at least moderate depressive symptoms.

Quality of Life: This will be assessed using the Short Form health survey Version 2.0 (SF-12v2) score. This is to measure quality of life. A health survey that uses 12 questions to measure functional health and well-being from the patient's point of view.

Patient Characteristics

Data pertaining to medical characteristics will be obtained during baseline visits of the REACH cohort studies, and not part of this study. Key characteristics are described below.

Sociodemographic characteristics that describe the study population will be assessed by surveying participants upon enrollment. These include age, gender, race, ethnicity, household income, marital status, educational attainment, health insurance, and work history.

Intervention Delivery

Attendance at written exposure therapy sessions

Treatment fidelity: Written exposure therapy sessions will be audiotaped, and reviewed by the experts at the National Center for PTSD in Boston who developed the intervention to determine adherence to the intervention protocol.

6. Study Participants

To be eligible, participants need to be enrolled in the REACH-ACS, REACH-Stroke, or REACH-Arrest study. Key inclusion/exclusion criteria are summarized below.

Inclusion:

- Hospitalized with acute stroke, TIA, ACS, or cardiac arrest
- Enrolled in REACH-stroke, PHS, or REACH-cardiac arrest observational cohort studies

- Elevated ASD symptoms (ASD score >=28) and/or elevated threat perceptions during index hospitalization (ED threat score >=12)

Exclusion:

- Unavailable for follow-up for written exposure therapy sessions
- Unable to read and write in English

7. Recruitment

Once the study is approved, we will recruit a convenience sample of 20 patients who present to NYPH with a primary diagnosis of ACS, stroke, TIA, or cardiac arrest and who have elevated symptoms of distress that put them at higher risk of subsequent PTSD related to the current cardiovascular event. We will recruit patients for this substudy from among patients previously enrolled in the REACH-ACS, REACH-Stroke, and REACH-Arrest studies. After patients complete the baseline questionnaires, which include measures of ED threat perceptions and ASD symptoms, the data tracking system will automatically identify patients who are potentially eligible for this pilot RCT (i.e., elevated threat perceptions and/or ASD symptoms, English speaking, consented to hearing about other related research studies). Such patients will be approached by a research coordinator to be informed about this pilot randomized trial. Those patients who remain eligible and are interested in participating, will sign written informed consent.

8. Informed Consent Process

The protocol and informed consent will be approved by the Institutional Review Board at Columbia University. Consent forms will be worded in language that a person with an 8th grade education can understand. At the time of enrollment, the staff member will give a complete description of the study to the participant in clear, easy-to-understand language. After reading and understanding the consent and the procedures, those who choose to participate will sign and date the consent in the presence of a staff member who will then countersign and date the form. All staff involved in this study will have completed and passed GCP and HIPAA training, and will have been provided with materials and instruction in the proper and ethical manner in which consent should be obtained.

Consent will be obtained before any research procedures are performed. Consent will be obtained wherever the patient is located on an inpatient hospital unit at New York-Presbyterian Hospital. Each patient will have an opportunity to ask questions and will be encouraged to discuss participation with friends and family members if he or she desires. If the patient has any reservations, he or she will be encouraged to think about enrolling and sign the consent form only if and when he or she feels comfortable. Patients will be assured that their medical treatment will be neither helped nor hindered by participation in the study, and that they can decide at any point to discontinue participation with absolutely no consequences for their care.

A member of the research team will explain the procedures involved in this study and review the IRB approved consent form with the patient in detail. To ensure that participants understand what their participation will entail, they will be asked to reiterate in their own words the purpose of the research, what they will need to do as participants in the study, and what the potential risks, potential benefits, and alternatives are. Once the participant agrees to participate, he or she will sign and date the consent document. The member of the research staff obtaining consent will also sign and date the consent form. One copy of the consent form will be given to the participant, one copy will be placed in the patient's medical record and the original will be placed in the participant's research record.

Vulnerable participants will not be preferentially enrolled in the study. Socially and economically disadvantaged persons are not discriminated against entering the study. All potential participants will be treated equally. There will be no covert or overt coercion to participate.

The consent process will be handled carefully and documented appropriately. Study personnel obtaining consent will explain in detail the research protocol using a language that the patients can understand. The consent document is written in the language (English or Spanish) that potential participants can understand. Extra care will be taken to ensure that all patients comprehend that their ability to receive medical care, or the quality of care they receive, at Columbia University Medical Center is not affected if they decide not to participate in the study and that participation in the study is voluntary with the option of terminating participation at any time after enrolling in this study.

9. Confidentiality of Study Data

The information obtained during this research (Research Record) will be kept confidential to the extent permitted by law. All documents containing personal identifiers will be kept in a locked cabinet. Only those researchers and physicians involved in the medical care of the participants will have access to these files. To minimize the risk to confidentiality, subject information will be assigned a numerical code, and will be stored in a locked cabinet or secured computer database in the Center for Behavioral Cardiovascular Health on PH 9. Although every reasonable effort will be made to protect the confidentiality of records, such protection cannot be guaranteed. By law, representatives of the sponsoring organization, Columbia University's Institutional Review Board (IRB), and other regulatory authorities may inspect these records. All personal information made available for inspection will be handled in strictest confidence and in accordance with data protection laws.

All PHI and PII captured for this study will be kept on a CUMC IT Security certified system. Our research center stores nearly all of its electronic information on a CUMC IT-managed O- and P-drives (system ID no. 34). Since this is a multi-user system, which does contain PHI and PII, it is encrypted and access to it is well documented and controlled. Most end point devices (e.g., CUMC IT managed desktops) in our research center do not allow data to be saved on the hard drive (locally); even so, all storage devices and hard drives on all end point devices are encrypted. To further ensure confidentiality, files saved on our O- or P-drives containing PHI or PII are password-protected.

10. Privacy Protections

To ensure confidentiality, data will be associated with an individual participant only by an assigned identification number, the code for which will be kept in a single electronic file. This electronic file will be stored on a secure server and be password-protected. Study staff are assigned a user ID and password to assess the server. Only the PI and study personnel listed on this protocol will have access to the file password. All hardcopy data will be stored in a separate locked, secure facility. Names will not be stored with data. The Principal Investigator will be responsible for ensuring that the confidentiality of the data is maintained at all times. These data will be obtained specifically for research purposes.

Note: All data will be used specifically for research purposes. Only authorized personnel, those who have official status as part of the authorized research team, will have access to any records containing identifiable participant data.

11. Potential Risks

Participation in the study posted minimal risk of psychological, social, and economic harm. The questionnaires pose minimal risk of psychological discomfort, and some participants may wish to complete the questionnaires by hand rather than by interview so as not to be overheard. Participants will be made aware of these risks, and will be assured they can terminate their participation in the study at any time without penalty. Similarly, individuals assigned to the written exposure therapy may find that writing about their traumatic experience is stressful and brings up negative emotions. All study therapists conducting the written exposure therapy sessions are trained providers with a Master's or PhD in clinical psychology or social work, and they completed training in the written exposure therapy protocol with the creators at the National Center for PTSD in Boston. Further, if psychological issues arise and a participant needs further attention, he/she will be escorted to the CUMC emergency room for further evaluation.

A potential risk from this study is the possible violation of the participant's privacy, since patient medical information will be used as a source of data.

There is the possibility that we will discover during screening that participants have cognitive or alcohol/drug impairments that disqualify them from participating in the study. We may also discover during screening or during assessment that a participant has depression that warrants immediate treatment. We will immediately notify the participant's treating providers if this should occur.

12. Data and Safety Monitoring

Although no adverse events are expected, the co-investigators and research assistants will meet weekly to discuss any problems with the study, in particular, whether there were any

unexpected complaints about the study procedures or questionnaires, or whether there were any breaches in data confidentiality. The co-investigators will be responsible for reporting any breaches in data security to the IRB. If unexpected complaints about the procedures or questionnaires are generated, then the study may be stopped or altered prior to recruiting the full sample. Finally, we will convene a data safety and monitoring board, comprised of 3 individuals, to review all safety and privacy issues that may arise during the conduct of the pilot study.

13. Potential Benefits

Participants randomized to the intervention may benefit from receiving increased oversight by a member of the study team in cases that they are nonadherent. Participants will be informed that their decision whether or not to participate in this study will have no effect on the medical care they receive at this hospital or participating clinic. While participants in this study may not directly benefit from their participation, we anticipate results from this study to benefit future research that seeks to help reduce preventable readmissions among heart failure patients which is also expected to improve heart failure-specific quality of life.

14. Alternatives

The alternative is not to participate in this research study.

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