Study Protocol, Including Statistical Analysis Plan

Study Title: The Effect of Reducing Posttraumatic Stress Disorder Symptoms on Cardiovascular Risk

NCT Number: NCT02736929

Document Date: 1/12/2021

Full Protocol: The Effect of Reducing Posttraumatic Stress Disorder Symptoms on Cardiovascular Risk
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A. SIGNIFICANCE AND SPECIFIC AIMS

Coronary heart disease (CHD) remains the leading cause of morbidity and mortality in the U.S., and it is now known that CHD prevalence can be explained by both traditional risk factors and psychosocial risk factors (Lichtman, Bigger, Blumenthal et al., 2008; Wielgosz & Nolan, 2000). An increasing body of evidence suggests that posttraumatic stress disorder (PTSD) may be causally related to accelerated CHD development and may also be a trigger of fatal cardiac events in civilians and in veterans (Boscarino, 2008; Vaccarino et al., 2013). Our understanding of the association between PTSD and CHD risk comes from several recent studies, including several 13-14 year follow-up studies in which PTSD is associated with a 2- to 3-fold increased risk of CHD (Boscarino, 2008; Vaccarino et al., 2013; Kubzanksy, Koenen, Jones, & Eaton, 2009). However, PTSD is also associated with psychiatric comorbidity and with cardiovascular risk behaviors such as smoking, substance abuse, obesity, and poor medical adherence, which may contribute to the observed association between PTSD and CHD risk. Although some studies are thought to indicate the presence of a direct and independent association between PTSD and CHD, they remain confounded by the potential contribution of adverse health behaviors, as well as by the stability of PTSD symptoms during the period over which CHD outcomes were monitored (Boscarino, 2008; Vaccarino et al., 2013). As stated in a recent editorial, an important next step before PTSD can be recognized as an independent CHD risk factor is to address the limitations of our understanding of the mechanisms by which PTSD symptoms convey CHD risk burden, including the need to determine how changes in PTSD symptoms affect CHD risk (Sidney, 2013).

Chronic activation of stress response systems may play a pivotal role in the pathophysiological link between PTSD and accelerated cardiovascular disease (McEwen, 2000; Baker, Nievergelt, & O'Connor, 2012). PTSD is characterized by autonomic nervous system (ANS) dysregulation, with both heightened sympathetic nervous system (SNS) activity (Yehuda, Southwick, Giller, Ma, & Mason, 1992; McFall, Murburg, Ko, & Veith, 1990) and greater parasympathetic nervous system (PNS) withdrawal (Shah et al., 2013). PTSD is also accompanied by chronic systemic inflammation (Vaccarino et al., 2013; Plantinga et al., 2013; Spitzer et al., 2010). The objective of the proposed study is to manipulate PTSD symptoms in order to ascertain whether PTSD symptoms *per se* account for dysregulation of these stress-related biomarkers of CHD risk.

The availability of effective therapeutic approaches to treat PTSD affords the opportunity to address this question. We propose a randomized controlled longitudinal study that will examine the effects of PTSD symptom reduction using a 6-week Cognitive Processing Therapy-Cognitive (CPT-C) intervention (Resick et al., 2008). Our target outcomes are the putative pathways leading to CHD risk, including ANS control measured by heart rate variability (HRV), 24-hour urinary catecholamine excretion, and inflammatory activity estimated by high sensitivity C-reactive protein (hsCRP). In addition, we will assess subclinical atherosclerotic activity indexed by vascular endothelial function measured by brachial artery flow mediated dilation (FMD). Building upon our prior work, the proposed study is designed to achieve the next critical step in advancing our understanding of PTSD by establishing

whether PTSD symptoms convey CHD risk directly and independently of maladaptive health behaviors and psychiatric comorbidity.

A study sample of 120 patients with PTSD will be randomized in a 2:1 ratio to either a 6-week CPT-C intervention, or a 6-week waiting period control (WP-CON) condition, in order to test the general hypothesis that a reduction in PTSD symptoms will result in improved CHD risk biomarkers. In the context of the proposed study design, this objective is rendered in terms of the following specific aims and hypotheses:

AIM 1: To evaluate the efficacy of CPT-C on CHD risk biomarkers among subjects with PTSD.
Hypothesis 1: Compared to WP-CON, the CPT-C intervention will result in improved 24-hour HRV, 24-hour urinary catecholamines, inflammation, and vascular endothelial function.

AIM 2: To examine mechanisms of change in CHD risk biomarker outcomes in a mediation framework.
Hypothesis 2: Improvement in CHD risk biomarkers will be mediated by reductions in PTSD symptom severity.

AIM 3: To explore potential moderators of the effects of PTSD symptom changes on CHD biomarkers.
Hypothesis 3: The association of PTSD symptoms and CHD risk biomarkers will be moderated by individual difference characteristics, including gender and clinical depression.

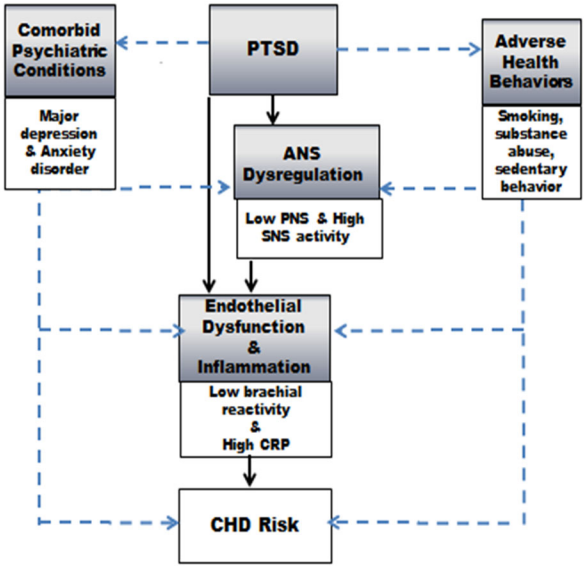
The proposed study will help establish whether there is a direct link between PTSD and CHD risk, as well as ascertain the role of candidate pathophysiological mechanisms. By better defining how PTSD is a risk factor for CHD, as well as identifying the disease pathways involved, the proposed study will help inform strategies for CHD prevention, as well as guide optimal medical management for vulnerable men and women with PTSD, *especially in those who refrain or who are refractory to psychiatric treatment*.

B. RESEARCH STRATEGY: APPROACH

PTSD and CHD Risk. Recent epidemiological prospective studies suggest that a diagnosis of PTSD confers subsequent risk of development of fatal and nonfatal premature CHD. However, trauma exposure is also associated with significant risk of developing other cardiovascular risk behaviors, including other psychiatric disorders (major depressive disorder and clinical anxiety disorders), excessive rates of smoking and substance abuse. Individuals with PTSD are consequently more likely to have comorbid psychiatric disorders and to smoke and do so heavily (Beckham, Roodman et al., 1995; Fu et al., 2007); they are also more likely to abuse alcohol (McFarlane, 1998), and to be obese (Kubzansky, Bordelois et al., 2014). A conceptual model is depicted in Figure 1 showing the hypothesized pathways (solid lines) by which PTSD symptoms directly increase CHD risk and the ways that the comorbid psychiatric conditions and adverse health behaviors increase CHD risk (dotted lines). The proposed study is designed to determine the *independent* effects of PTSD on CHD risk pathways.

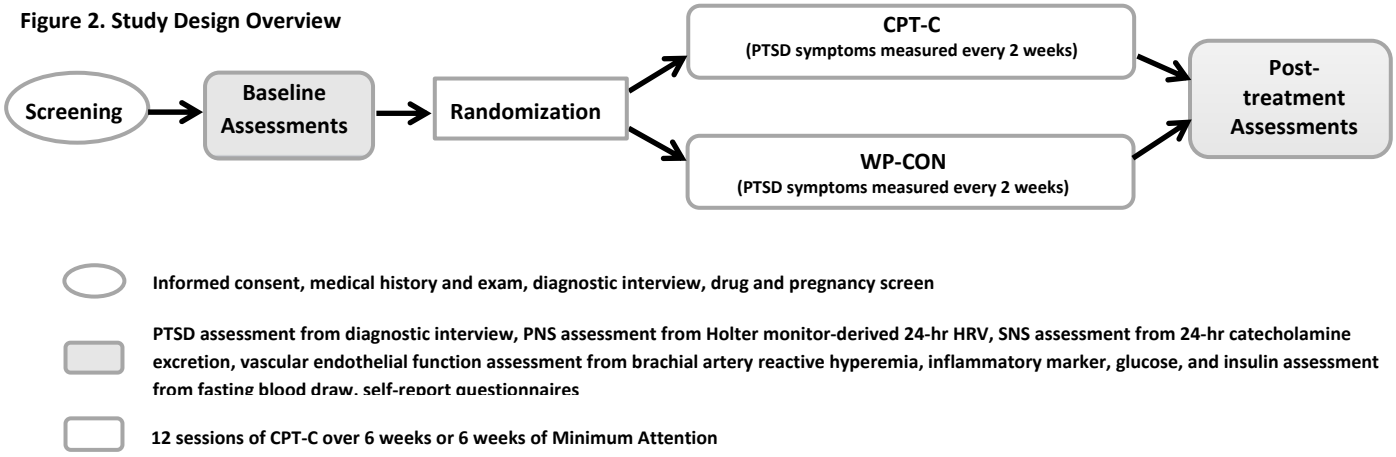
The study will also determine whether successful treatment of PTSD symptoms improves the cardiac biomarkers proposed to underlie the excess CHD risk in PTSD.

Figure 1. Pathophysiological Pathway to CHD in PTSD



Overview of the Study Approach. The proposed randomized controlled trial (RCT) uses an evidence-based intervention, CPT-C (Resick & Schnicke, 1992), as a tool to induce greater change in PTSD symptom severity compared to WP-CON. The use of a RCT design strengthens our results by controlling and quantifying variability and reducing potential confounding due to selection bias and will enable us to carry out our main goal which is to examine whether changes in PTSD symptom severity impact changes in CHD risk biomarkers. One hundred and twenty men and women (40-65 years of age) with current PTSD will be randomly assigned in a 2:1 ratio to receive CPT-C or to participate in a waiting period control (WP-CON) condition with minimal attention; CHD biomarkers will be evaluated at baseline and again after completion of CPT-C or after the WP-CON period (see Figure 2). Randomization will be stratified by variables known to be related to both PTSD and to CHD outcomes (gender, age [dichotomization point: 50 years], and comorbid Major Depressive disorder). During the treatment or waitlist phase of the study, PTSD symptoms will be measured every two weeks in each study arm in order to assess changes therein. The WP-CON group will receive minimal attention in the form of weekly telephone calls to assess current emotional state and to provide supportive, nondirective, brief counseling if participants report experiencing a crisis. All pre-randomization baseline and post-intervention assessments of PTSD symptoms, psychosocial measures, health behaviors, and CHD biomarkers will be performed by assessors who are blinded to participants' randomization condition.

Figure 2. Study Design Overview



Determining PTSD symptom trajectory and assessing CHD biomarkers before and after each treatment arm will enable us to test the *objectives* of the current proposed research, which are to determine: (i) the efficacy of CPT-C in improving CHD risk biomarkers in subjects with PTSD (**Aim 1**); (ii) whether changes in PTSD symptom severity act as a mediator of the change in CHD risk biomarkers following CPT-C (**Aim 2**); and (iii) the moderating role of key bio-behavioral variables in the association between PTSD symptom severity changes and CHD biomarkers (**Aim 3**). This innovative approach will allow us to determine whether CHD risk mechanisms are directly related to changes in PTSD symptoms and whether improvement of PTSD symptoms with CPT-C results in improved CHD risk biomarkers.

Strategies to Achieve Specific Aims. Our investigative team has experience and expertise in the evaluation of ANS control estimated from HRV and urinary catecholamine excretion, inflammatory markers, FMD assessment of endothelial function, clinical expertise into the interrelationship between PTSD and psychological and health outcomes, and individuals with expertise in the development and implementation of psychotherapeutic treatments for PTSD.

General Analytic Strategies. We will examine all variables to determine if parametric distributional assumptions are valid (e.g., normality for the continuous variables). Variables not meeting approximate distributional assumptions will either be transformed or modeled using nonparametric methods. In addition, we will explore the variability and correlation structure of the CHD outcome variables and PTSD symptom severity. Evidence of imbalance in baseline demographic (age, gender, veteran/civilian status) or clinical (high blood pressure, diabetes, major depression) characteristics will be noted and discussed as to whether they are clinically significant and we will consider sensitivity analyses including these covariates in models (models described below separately for each aim) , as recommended by the Committee for Proprietary Medicinal Products guidelines (Committee for Proprietary Medicinal Products, 2004). We will also minimize the imbalance on variables known to be related to the predictor and outcome variables by stratifying randomization by gender, age, and major depressive disorder. As the main goal of the aims for this study is to understand how changes in PTSD symptom severity impact changes in CHD markers, we will conduct both an intent-to-treat analysis where participants will be analyzed as part of the group to which they are randomized, regardless of intervention adherence, and a per-protocol or as-treated analysis to strengthen the evidence that the mechanism for the effects of CPT-C vs. control on CHD markers is through PTSD symptom severity changes.

Aim 1: To evaluate the efficacy of CPT-C on CHD risk biomarkers among subjects with PTSD. Although PTSD has been associated with excess risk of CHD, few studies have determined the impact of PTSD treatment on CHD biomarkers. Preliminary findings in small samples (< 10 PTSD cases) suggest that treatment with either fluoxetine or with Cognitive Behavioral Therapy (CBT) results in normalization of HRV (Cohen et al., 2000; Nishith, 2003). Treatment with serotonin reuptake inhibitors was also found to reduce levels of the inflammatory marker, IL-1B, in a sample of 58 men and women with PTSD (Tucker et al., 2004). There is also evidence from randomized controlled trials that CBT reduces SNS-mediated HR responses elicited by exposure to trauma cues (Blanchard et al., 2002; Rabe, Dorfel, Zollner, Maercker, & Karl, 2006). The *objective of this aim* is to examine whether CPT-C results in significant improvements in 24-hour HRV, 24-hour urinary catecholamines, endothelial function, and inflammation. Based on our earlier studies, we anticipate that 50% of participants will show marked

improvement in PTSD symptoms following 6 weeks of biweekly CPT sessions (Monson et al., 2006) and anticipate that these individuals will also show significant improvements in the CHD risk biomarkers. These findings would suggest that PTSD symptoms are directly involved in the association between PTSD and these CHD pathways, and would demonstrate that (i) therapeutic approaches to reducing PTSD symptoms may provide an effective tool for reducing CHD risk in PTSD; (ii) specific CHD risk biomarkers would be useful therapeutic targets in men and women with chronic PTSD.

Approach. We will systematically evaluate four prognostically significant CHD biomarkers that have been implicated in the cardiovascular risk trajectory observed in PTSD. These CHD biomarkers will be assessed before and after either CPT-C or a minimal attention waiting period (WP-CON), and will allow evaluation of whether CPT-C results in greater improvements in the CHD biomarkers than participation in the control arm. Twenty-four hour HRV was selected to provide an index of PNS control because it is a strong independent predictor of incident CHD and cardiac death in both community samples (Dekker, Crow et al., 2000; Rodrigues et al., 2010; Liao et al., 1997; Dekker, Schouten et al., 1997; Tsuji et al., 1996) and in CHD patients (Algra, Tijssen, & Roelandt, 1993; Hikuri et al., 1999) and is significantly reduced in patients with PTSD (Shah et al., 2013; Dennis et al., 2014). Similarly, 24-hour urinary catecholamine excretion has been consistently found to be elevated in PTSD and also is predictive of increased risk of mortality (Reuben, Talvi, Rowe, & Seeman, 2000). It has been established that PTSD is associated with an exaggerated withdrawal of PNS activity and an excessive SNS response to trauma-related cues, and the SNS responses to trauma related cues are significantly reduced following CBT (Norte et al., 2013; Southwick, Morgan, Carneya, & High, 1999). Peripheral inflammation and vascular endothelial dysfunction were selected due to their strong correlation with cardiovascular morbidity and mortality (Wassel, Barrett0Connor, & Laughlin, 2010; Ridker, 2007) and because chronic PTSD has been associated both with substantial elevations in hs-CRP and with endothelial dysfunction (Spitzer et al., 2010; Heath et al., 2013; Gill, Saligan, Lee, Rotolo, & Szanton, 2013).

Expected Results. Because there are limited data and no studies evaluating the short-term effects of CPT-C on CHD biomarkers, HRV was selected as the primary outcome based on our limited pilot data; the other CHD markers will be secondary outcomes. We hypothesize that all CHD biomarkers will show improvement following CPT-C when compared to WP-CON, and the changes will be independent of changes in cardiovascular health risk behaviors, as defined by smoking, alcohol use, and low physical activity measured using the Stanford 7-day physical recall survey (Blair et al., 1985). It is likely that these cardiovascular health behaviors will remain constant or minimally change over the time period of the study.

Analytic strategy. The primary CHD risk biomarker, HRV, and secondary CHD risk biomarkers are continuous measures collected at baseline and 7-weeks (post-treatment) and therefore the same modeling strategy will be used for all CHD biomarker outcomes. To test the primary hypothesis of a CPT-C effect at post-treatment, we will use a general linear model that accounts for the correlation between participants' repeated outcome measurements over time with an unstructured covariance matrix (Verbeke & Molenberghs, 2000; Fitzmaurice, Laird, & Ware, 2004). The general form of the model is $Y_{it} = X_{it}\beta + \varepsilon_{it}$, where Y_{it} is the CHD marker for subject i at time t=0 and 7 weeks. The predictors (X_{it}) in the model will include time and the CPT-C arm by time interaction. We will estimate the model parameters using the SAS procedure MIXED (SAS Version 9, Cary, NC), and contrasts will be written in the context of this model to test the difference of mean change in CHD markers between the two treatment arms at week 7. For improvement in precision, the model will also be adjusted for

stratification variables of gender, age, and comorbid major depressive disorder (Committee for Proprietary Medicinal Products, 2004) and as identified in the detailed description of methodologies and in the general analytic section, sensitivity analysis will also include the potential important covariates of functional comorbidity, smoking status, substance abuse, and habitual physical activity. Our main analysis technique for the primary outcome, general linear models via maximum likelihood estimation, uses all available data on subjects, rather than using only subjects with completely observed information, implicitly accommodating missingess when related to prior outcome, or to other baseline covariates included in the model (defined as missing at random).

Aim 2: To examine mechanisms of change in CHD risk biomarker outcomes in a mediation framework. It has been repeatedly demonstrated that individuals suffering from PTSD show excessive SNS, reduced PNS activity, chronic inflammation, and endothelial dysfunction and a number of studies have presented evidence suggestive of the possibility that these CHD markers of risk may be normalized following PTSD treatment (Cohen et al., 2000; Nishith et al., 2003; Blanchard et al.2002; Rabe et al., 2006; Hinton, Hofmann, Pollack, & Otto, 2009). The *objective of this aim* is to examine whether the change in PTSD symptoms explains the change in CHD biomarkers observed following CPT-C. To achieve this objective, we will test the working hypothesis that improvements in CHD risk biomarkers will be mediated by reductions in PTSD symptom severity. These findings will help establish whether PTSD symptoms themselves are determinants of CHD risk, independently of psychiatric comorbidity and health behaviors associated with cardiovascular risk. When the proposed studies for aim #2 have been completed, it is our expectation that the magnitude of the contribution of PTSD symptom load towards each of the evaluated CHD risk biomarkers will be clarified. Such a finding would be of importance, because it would provide support for a direct role of PTSD symptoms in the CHD risk observed in PTSD and would also identify which cardiac biomarker would provide the most utility in screening and CHD risk stratification in order to predict and prevent the onset of CHD.

Approach. This RCT with repeated measurements of PTSD symptoms and CHD markers will provide a mechanism to evaluate the temporal relationship between the change in PTSD symptoms and the changes in ANS control mechanisms, endothelial function and inflammation. Using this temporal relationship, we will examine whether changes in PTSD symptoms mediate the effects of CPT-C on CHD markers.

Expected Results. We anticipate that the change in PTSD symptoms will mediate the relationship between CPT-C and CHD marker change, thereby identifying the role of reduction in PTSD symptoms as a mechanism for the improvement in CHD risk.

Analytic strategy. We propose to conduct mediation analyses using the more commonly known Baron and Kenny approach (Baron & Kenny, 1986) as well as the newer MacArthur approach (Kraemer, Kieser, Essex, & Kupler, 2008). By the MacArthur definition, the potential mediator must be during or post-treatment; therefore, the change in PTSD symptoms severity between week 0 and week 6 will be considered as a potential mediator. The outcome then will be participants' post-treatment change in CHD risk biomarkers, which will be determined at week 7. We will also explore the role of trajectories of change in PTSD symptom severity as a mediator of the post-treatment change in CHD risk biomarkers by deriving an individual-level summary measure of PTSD symptom change using the successive PTSD symptoms assessed at two week intervals. We will first fit a model to examine the relationship between the mediator (C) (i.e., change in PTSD symptoms during treatment) and

treatment group: C = $\gamma_0 + \gamma_1$*treatment. We then fit a model examining the relationship between the mediator and post-treatment change in CHD biomarkers (Y): Y = β_0 + treatment*β_1 + C*β_2. Finally, to show mediation, we will test that the product of γ_1 and β_2 is not equal to 0 using an extension of the Sobel first-order test (Fritz & MacKinnon, 2007); that is, the the effects of CPT-C on CHD risk biomarkers are attributable to its effects on PTSD symptom improvement. To fully understand these relationships, we will also investigate the MacArthur approach, where our second model will be (Y): Y = β_0 + treatment*β_1 + C*β_2 + C* treatment *β_3. Under this approach, improvements in CHD biomarkers are attributable to improvements in PTSD symptoms if there is evidence that γ_1 is not equal to 0, and either β_2 or β_3 are not equal to zero. The model will also be adjusted for stratification variables of gender, age, and major depressive disorder, and as detailed above in the general analytic section in the sensitivity analysis, we will evaluate and include other potentially important covariates, including change in anxiety and depressive symptoms estimated from the changes in HADS anxiety and depression following the intervention. We will also explore an as-treated analysis to maximize the potential mediation effects of PTSD symptom severity changes over time. For these analyses, data will be deemed usable for any individual who drops out of the study after two weeks or more of CPT-C or WP-CON, if PTSD symptom change is available and a repeat CHD biomarker assessment can be performed after the PTSD symptom change is assessed.

Aim 3: To explore potential moderators of the effects of PTSD symptom severity changes on CHD risk biomarkers. Although there is evidence that PTSD increases CHD risk irrespectively of demographics or trauma characteristics, there is some evidence that the causal pathway underlying the CHD risk may differ with gender and with depression. Consequently, improvement in PTSD symptoms may affect CHD risk biomarkers differently in men and women and also in individuals with and without clinical depression. The *objective* of this aim is to explore the role of these individual characteristics in biomarker responsiveness to PTSD symptom changes. To obtain the objective of this aim, we will test the *working hypothesis* that the association between PTSD symptom severity changes and CHD risk biomarkers will be moderated by individual difference characteristics, including gender and current major depressive disorder. This aim is exploratory yet important for understanding whether gender and depression act as moderators of the effects of PTSD symptom changes on CHD biomarkers of risk. The rationale for this aim is that successful completion of the proposed research will inform clinicians which patients are likely to show the most improvement in CHD risk pathways following PTSD treatment.

Approach. A number of individual characteristics may impact the degree of PTSD symptom response to CPT-C and the associated changes in CHD risk biomarkers observed following CPT-C. *Gender* was selected as a moderator of CHD biomarker response to PTSD symptom changes because of gender differences in PTSD chronicity, behavioral coping strategies to trauma, and compliance with treatment. A stronger CPT-C response might also be anticipated in women because they are more likely to use avoidance and disengagement to cope with prior trauma rather than responding with hostility and excessive substance abuse (Kemp, Hovanitz, & Rawlings, 1995). Although PTSD is associated with increased rates of smoking and alcohol consumption in both men and women, there is some evidence that smoking and alcohol consumption explain more of the CHD risk in men than in women with PTSD (Boscarino, 2008; Kubzansky et al., 2009). *Comorbid major depressive disorder* was selected as a moderator because

depression and PTSD have opposing effects on the systems that underlie the dysregulation of the stress response characteristic of PTSD. For example, a vast literature has demonstrated that the activity of the SNS is increased in PTSD (Yehuda et al., 1992; Young & Breslau, 2004; Lemieux & Coe, 1995; Kosten, Mason, Giller, Ostroff, & Harkness, 1987). However, the increase in SNS activity has been shown to be confined to PTSD patients without comorbid depression and depression has been associated with either no change or with a decrease in SNS activity (Young & Breslau, 2004; Yehuda, Siever et al., 1998). Similar findings have been reported with respect to the association between PTSD and inflammation; individuals with clinically significant PTSD showed higher CRP, whereas depression was associated with lower CRP after accounting for PTSD diagnosis (Heath et al., 2013). Opposite effects on glucocorticoid signaling may explain the contrasting impact of depression and PTSD on the autonomic nervous and inflammatory systems. Considerable data supports the hypothesis that reduced circulating cortisol is a core characteristic of PTSD and that this down-regulation of cortisol underlies the loss of homeostatic negative feedback inhibition of the hypothalamic-pituitary-adrenal axis that initiates excessive SNS and inflammatory activity. This view is supported by findings that the degree of PTSD symptom reduction using mindfulness meditation was associated with a significant increase in cortisol, $r=-.75$, $p<.05$, (Kim et al., 2013). In contrast, depression has been associated with opposite effects on cortisol and a more variable pattern of cortisol release (Yehuda, Teicher, Trestman, Levengood, & Siever, 1996).

Expected Results. We anticipate that women will show larger improvements in all the CHD markers of risk when compared with men, and these improvements will be secondary to larger improvements in PTSD symptoms. We anticipate that individuals with comorbid depression and PTSD will show smaller improvements in the CHD risk biomarkers due to both a smaller improvement in PTSD symptoms and also due to a smaller degree of improvement of the CHD risk markers for a given improvement in PTSD secondary to the persistent effects of depression symptoms.

Analytic strategy. We will examine whether the effect of PTSD symptom severity changes on change in CHD risk biomarkers is moderated by patient characteristics of gender and major depressive disorder using the summary measure of PTSD symptom severity change that we defined in AIM 2 and the evaluating the outcome of the participants' post-treatment change in CHD risk biomarkers. We will fit a linear model including the predictors: PTSD symptom severity change, and the PTSD symptom severity change arm by moderator variable interaction (gender of major depressive disorder status) with the addition of covariates for baseline demographic and clinical characteristics. We will estimate 95% confidence intervals from these models for the difference in changes in CHD risk markers for PTSD symptom severity level changes by gender and depression status. As outlined in the section describing more detailed methodologies (C.4), the proposed design will also allow us to explore the role of a number of other patient characteristics as potential moderators of the association between change in PTSD symptom severity and change in CHD risk biomarkers (clinical anxiety disorder, socioeconomic status, and social support).

Potential Difficulties/Alternative Approaches. We anticipate that some participants will drop out of trauma focused therapy (CPT-C). In randomized clinical trials of CPT, drop-out rates have been 20-25% (Resick, Nishith, Weaver, Astin, & Feuer, 2002; Chard, 2005). However, this is not likely to compromise our analytic approach for the following reasons: (i) we have structured our compensation system so that financial compensation is contingent upon completion of the PTSD and CHD biomarker

assessment, and not contingent upon completion of the full CPT-C treatment or control arm, and we will encourage participants who cease therapy to remain in the study to complete follow-up assessments; (ii) our analytic approach incorporates methods that are robust to incomplete data. In our recent study examining cardiovascular health risk biomarkers among younger adults with and without PTSD that included multiple laboratory sessions and measurement of 24-hour HRV our attrition rates were less than 10%.

B. METHODS

Participants

A total of 120 male and female adults will be enrolled in the project. We will select for participation 50% men and 50% women and also 50% minorities. Based on our previous study recruitment efforts, we typically recruit at least 40% of the participants who are of minority status so a 50% inclusion rate should be attainable. We estimate that 215 potential participants will be screened, and 120 of these will be qualified to begin study procedures. Inclusion and exclusion criteria are as follows:

Participants must meet **all** inclusion criteria:

- Is between the ages of 40 and 65;
- Has current PTSD lasting at least three months, based on the Clinician Administered PTSD Scale (CAPS), DSM 5 version, with a CAPS total score of 25 or greater; and
- Will have been stable on any current psychiatric medications for four weeks prior to the Time 1 assessment.

Participants who meet **any** one of the exclusion criteria will be excluded:

- Is currently participating in evidence-based trauma focused therapy (e.g., CPT, prolonged exposure) for PTSD (current or past 6 months);
- Has current dementia or other memory loss condition, as indicated by self-report or as indicated by scores less than 20 on the Montreal Cognitive Assessment (MoCA);
- Has current psychotic spectrum disorder or bipolar disorder;
- Has current uncontrolled substance use disorder that would interfere with his/her ability to perform study procedures;
- Has a urine drug screen positive for cocaine and/or methamphetamine and reports regular use of that substance;
- Has severely impaired hearing or speech;
- Is pregnant;
- Has established heart disease, abnormal heart rhythm, cancer, or epilepsy
- Has HIV positive status with unstable disease status and/or unstable medication use;
- Has current exposure to ongoing trauma (e.g., physically abusive relationship);
- Has prominent suicidal or homicidal ideation (as assessed through a clinical interview);
- Has a serious/terminal illness or other health problem that would prohibit participation in the study;

- Has an inflammatory condition such as infection, fever, one-month history of accident or surgery, rheumatoid arthritis, lupus, or inflammatory bowel disease.
- Is unwilling to accept randomization; or
- Cannot agree to attend therapy sessions at least once per week.

Recruitment

Participants will be recruited from the community and from outpatient clinics at Duke University Medical Center (DUMC) and the Durham Veterans Affairs Medical Center (DVAMC). Recruitment at DVAMC will begin only upon Institutional Review Board (IRB) approval from that site. Several methods will be used to recruit potential participants at these sites. The study team members are well connected with clinical resources at DUMC and DVAMC, and initial efforts at recruitment will include consulting with DUMC and DVAMC clinical providers to educate them about study inclusion and exclusion criteria. Additionally, we will educate providers at ancillary VA facilities located in close proximity, such as local Vet Centers and Community-Based Outpatient Clinics. Continued education will be provided to clinical providers across the life of the study in order to encourage referrals.

Recruitment materials such as IRB-approved study flyers and brochures will be placed in mental health clinic areas at DVAMC and DUMC. In addition, study flyers will be placed throughout these medical centers in centrally located posting areas. Study recruitment materials will advertise a research study that includes treatment for persons with PTSD. This recruitment method will be used over the course of the entire recruitment period.

Using standard recruitment procedures at DVAMC, we will identify potentially eligible veteran participants using searches with VAMC's patient databases, which pull diagnosis and contact information directly from DVAMC's computerized patient medical record system. Potentially eligible veterans who are identified via this data pull will be sent a letter asking them to consider participation in the study, and they will be provided contact information for the study coordinator and study PI. This recruitment strategy will be used in years two through four of the study.

We will use a similar procedure to identify potential participants using Duke's Deduce and Maestro Care systems. We will identify potentially eligible participants, using diagnostic and contact information in those systems. Potentially eligible participants will be sent an introductory letter or email asking them to consider participation, and they will be provided contact information for the study coordinator. Potential participants may also be called about a week after they are sent the letter to determine interest. Potential participants will be contacted no more than three times, as indicated by DOCR guidelines. They will also be provided information about how to opt out of additional contact from the study team re: this study.

The study will be registered at clinicaltrials.gov, which will allow for online recruitment during the course of the study. As needed in years one through five, we will advertise the study in local area newspapers, on Duke University's clinical research website, and on online classified advertising websites such as Craigslist.com, DukeList, or JobFinder.com. In addition, we will post study recruitment

materials at local community areas such as laundromats, Bull Connector bus lines, substance use treatment centers, rape crisis centers, battered women shelters/programs, restaurants, and grocery stores.

Our study team will use social media to reach potentially eligible participants. We have developed a Facebook page for posting IRB-approved study flyers and information for this and other studies in the Traumatic Stress and Health Research Laboratory, https://www.facebook.com/Duke-Traumatic-Stress-and-Health-Research-Lab-379366159145563/. We plan to place pictures of our study flyers on the Facebook page, and use Facebook's post boost to draw attention to the post. The post itself will say "Enroll now!" or "Now enrolling!" We will also plan to use Facebook ads to target potential participants within a 50-mile radius of Duke. The proposed Facebook ad photos and text have been uploaded to the recruitment materials section of the eIRB space. If any participant contacts the email associated with the Facebook page (TSHRLab@dm.duke.edu, he/she will be sent an automatic email response. In addition, the Facebook page will contain a link to a RedCap survey that participants may complete if they are interested in talking with the study coordinator about the study. The RedCap survey is here: https://redcap.duke.edu/redcap/surveys/?s=D37TLT94RM. Any participant who completes the survey will be contacted by the study coordinator using the approved telephone script.

We will plan to use a recruitment method referred to as respondent-driven sampling, or "seed recruitment" (Christina Meade, Ph.D., personal communication). Seed recruitment is suitable for sampling "hidden populations" of participants who are best known by their own peers (Heckathorn, 1997). It includes providing incentives to participants for referral of other eligible participants. In our model, each participant, or seed, will receive six coupons to recruit other people in his/her social networks. The recruitment coupons will provide a brief description of the survey and a phone number for contacting the study coordinator. The coupon will be marked with a unique identification number (not the study identification number) so that when the coupons are returned to us, the ID number can be used to provide payment ($20) to the participant who made the referral. The key connecting the participant's study ID number with the seed ID number will be kept in a database separate from other PHI, creating two layers of separation between the seed ID and the already-participating person's identifying information. Any participant who does not wish to recruit in this manner will not be required to do so.

Any participant who contacts by telephone the study coordinator or other study staff regarding the study will be provided more information, and will be interviewed using an IRB-approved telephone screening. If a participant is deemed potentially eligible in the telephone screen, he/she will be scheduled to attend a formal screening visit. We will send, via Duke secured email, appointment reminders to any participant who wants to receive them. Once a participant reports to the laboratory to begin the study, the study staff member obtaining consent will explain the study in detail, provide the participant with an IRB-approved written consent form explaining the procedures and risks, and answer any questions. The initial consent process and documentation takes place in a quiet, private office at Duke University Medical Center, and participants are given the chance to thoroughly read the consent prior to participation. Participants are given a copy of the signed informed consent form, and are given phone numbers to call if they have additional questions about the consent form or the

research, if they have any problems during the study, or if they have questions about participating in research studies in general. With regards to determination of decision making capacity of potential participants, our laboratory has a standard procedure for determining understanding of the study procedures, risks, and benefits. We utilize this procedure if we have any reason to suspect that the participant may have difficulty in the consent process (e.g., traumatic brain injury impacting cognitive function, active psychotic symptoms). In this procedure, the study coordinator providing the informed consent information evaluates understanding of the procedures at several different time points during the process by asking questions like "Do you understand what we're asking you to do?" and "Do you have any questions about the risks of the study? Can you tell me what you understand the risks to be?" Prior to having a participant sign consent, the study coordinator, who has clinical experience in working with persons with psychotic disorders, may ask the potential participant to outline the study procedures, risks, and benefits so that he can make sure that the participant is aware of them. If the participant is unable to summarize these, he/she will not be allowed to sign the informed consent form, and may be referred for other treatment. No study procedures will begin until informed consent has been obtained.

Consent During COVID-19 Pandemic. During the pandemic stay-at-home orders, study consent will occur via e-consent. We will also review with participants a brief consent addendum that describes 1) how some study procedures will be done remotely, 2) the addition of COVID-19 measures, and 3) other small study differences. Verbal consent to these procedures will be documented with a note to file signed by the staff member obtaining consent.

Screening, baseline and post-intervention assessments will require 7 testing days per subject. A typical schedule for the screening, baseline and post-intervention assessments would be as follows:

1. Days 1-3: Medical exam and psychiatric screening, followed by 24-hour urine collectionDay 4: Psychometrics, fasting blood draw, finger and arm blood pressure measurement, baseline FMD assessment, followed by Holter monitoring for one full day and one full night (about 36 hours)
2. Day 5: Post-intervention 24-hour urine collection
3. Day 6: Psychiatric interview, fasting blood draw, finger and arm blood pressure measurement and FMD
4. Day 7: Post-intervention Holter monitoring for one full day and one full night

In addition, each subject will undergo 6 weeks (i.e., 12 sessions) of CPT-C or WP-CON. We recognize that these assessments are time consuming and labor-intensive. However, we have had excellent success in obtaining the cooperation of patients for these kinds of comprehensive assessments in our prior work, and are confident that we will be able to achieve the same degree of success in this proposed study.

Measures

PTSD and Psychiatric Evaluation. In order to determine PTSD diagnosis, the Clinician-Administered PTSD Scale structured interview, monthly version (CAPS) will be utilized (Weathers, Blake et al., 2013). Participants who have PTSD but do not score a CAPS total score of 25 or greater will be excluded from the study. The CAPS will also be re-administered at the post-intervention follow-up visits. The CAPS

administered at follow-up visits will be the weekly version, and participants will also be asked to report frequency of symptoms within the past month in order to establish PTSD caseness. Diagnoses other than PTSD, including major depressive disorder, generalized anxiety disorder, and panic disorder will be assessed using the Structured Clinical Interview (SCID) for DSM-5. Diagnostic raters will be trained using SCID and CAPS standardized training (i.e., manual, videotapes, and co-rating training with a trained rater). Interrater reliability for diagnoses based on videotapes of participant interviews across our previous studies has been high, Fleiss' kappa = .96. PTSD symptom severity will be measured by the PTSD Checklist (PCL5) with criterion A (Weathers, Litz et al., 2013). The PCL will be given at multiple time points (baseline, at each Holter monitoring time point, and at three time points during the treatment/waitlist period). On each of the days that the participant wears a Holter monitor, he/she will complete the PCL 5 and the Positive and Negative Affect Scale (PANAS; Watson, Clark et al., 1988). In addition, trauma history will be evaluated at baseline using the Traumatic Life Events Questionnaire (TLEQ), which collects the occurrence and frequency of each of 22 behaviorally-descriptive potential traumatic events and provides a 23rd open-ended category for "other events" (Kubany et al., 2000). The data provided by the TLEQ will primarily be used to describe the sample, but supplemental analyses will explore the role of trauma exposure chronicity and type as a moderator of the association between CPT-C and the change in CHD risk biomarkers. Participants will also complete the Posttraumatic Safety Behavior Scale (PSBS), which is a brief self-report measure of safety behaviors that persons with PTSD might perform to reduce distress associated with trauma. Psychological resilience will be measured using the Connor Davidson Resilience Scale (CD-RISC; Connor & Davidson, 2003), and interpersonal violence will be assessed using the Conflict Tactics Scale, version 2 (CTS2; Straus, Hamby, Boney-McCoy, & Sugarman, 1996). The presence of sleep problems will be measured using the Pittsburgh Sleep Quality Index with PTSD Addendum (PSQI-A; Buysse, Reynolds, Monk, Berman, & Kupfer, 1989; Germain, Hall, Krakow, Shear, & Buysse, 2005) and the STOP BANG, a measure of obstructive sleep apnea (Chung et al., 2008). The PSQI-A will be given at the Time 2 and Time 3 (if applicable) assessments because it is anticipated that sleep quality could change with treatment of PTSD symptoms. The Everyday Discrimination Scale will measure the perceived frequency of chronic, routine and subtle experiences of unfair treatment that could be one dimension of perceived stress in our sample (Williams, Yu, Jackson, & Anderson, 1997). Shame and guilt related to trauma will be measured by the Shame and Guilt After Trauma Scale (Aakvaag et al., 2016). Hostile interpretation bias will be measured by the Word Sentence Association Paradigm (WSAP; Dillon et al., 2016). At each CPT session, participants will complete the Assimilation Questionnaire, which measures assimilated beliefs and resulting emotions related to the trauma (S. Losavio, personal communication). At the beginning and end of CPT treatment, participants will complete several measures designed to examine cognitions – Cognitive Emotion Regulation Questionnaire, Trauma-Related Guilt inventory, Posttraumatic Cognitions Inventory, and Global Belief in a Just-World Scale.

Medications, Health Risk Behaviors, and Psychosocial Assessments. During the screening period, we will collect demographic, health risk, and other clinical and demographic information, including age, gender, race, weight, height, central adiposity (waist-hip ratio), and current medication use. We will ask participants to describe any counseling treatment for PTSD that they may be receiving. We will also check for the presence of cognitive impairment using the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005). This tool has been used as a short cognitive screening tool for identifying impaired cognitive functioning in the general population; scores range from 0 to 30, and any individual

who scores below 20 will be excluded from participation due to the presence of cognitive impairment (Gallagher et al., 2013). Although the cut score of 26 has good specificity and sensitivity to diagnose mild cognitive impairment (MCI; Hoops et al., 2009), we do not wish to rule out participants with MCI, but rather those with dementia. A cut score of 26 will likely otherwise suitable participants, as CPT has been successfully used in patients with traumatic brain injury (TBI) and MCI. Any participant who is excluded due to low MoCA scores will be informed of the results and encouraged to discuss the findings with their personal physician or care provider for further evaluation and treatment if necessary. In addition, to account for the impact of comorbid somatic disease on the CHD biomarkers, we will measure use a modified version of the Functional Comorbidity Index (Groll, Bombardier, & Wright, 2005), which provides a dimensional score based on the summation of the self-reported diagnoses of arthritis, osteoporosis, asthma, COPD, diabetes, gastrointestinal disease, and degenerative disk disease, which are treated as binary variables. In women, we will also determine menopausal status, and will use the classification system proposed by Tom and colleagues (Tom, Kuh, Guralnik, & Mishra, 2010). Prior to participants wearing the Holter monitor, we will ask them to indicate their smoking and alcohol use on the Coping Behaviors scale, as these factors could affect heart rate variability and catecholamine excretion. Participants will be asked about new onset of infections and exacerbations of any current chronic diseases that might affect inflammation (Medical Disease Change Form).

All participants will complete at baseline and post-treatment 1) the World Health Organization's Disability Assessment Schedule 2.0 (WHODAS 2) as a measure of disability; 2) the Modified Habit Questionnaire (Resnick & Weaver, 1994)); 3) a measure of suicidal behaviors, Suicide Behaviors Questionnaire – Revised (SBQ-R; Osman et al., 2001); and 4) a Daily Hassles measure.

All participants will be asked to provide a urine sample. A urine drug screen will be performed; results will be used to corroborate self-report of illicit substances in the SCID. If any participant has a drug screen that is positive for cocaine or methamphetamine, he she will be asked about current use patterns. Anyone who indicates that he/she regularly uses cocaine or methamphetamine will be ineligible to participate, as both cocaine and methamphetamine have known implications for cardiovascular functioning. Participants will be asked to complete a few questionnaires regarding marijuana use. In addition, for female participants of childbearing potential, we will use the sample to perform a urine pregnancy test. Because pregnancy has effects on the metabolic system that could impact findings, pregnant women will be excluded from participation. Urine samples will be assayed by a trained staff member using a Quidel QuickVue pregnancy test. These pregnancy tests will be completed for women of childbearing potential. We have developed a short interview for female participants; this interview will help us determine which female participants must have a urine pregnancy test, and when the test should be done. Female participants of childbearing potential who are not pregnant must agree to use appropriate contraception during the course of the study, and to notify study staff if they become pregnant during the study.

At the screening visit, we will take participants' temperature in order to determine the presence of any acute infection that would distort CRP values. Any participant who has a temperature that is not within

normal limits will be scheduled for his/her baseline session once his/her temperature has returned to within normal limits.

During both the baseline and the post-intervention assessment period, we will again take participants' temperatures. Any participant who has a temperature that is not within normal limits may be asked to reschedule his/her lab visit once his/her temperature has returned to normal. The following variables will be assessed in our clinical research facility: (i) fasting blood draw (up to 18 mL of blood per draw) to determine lipids, glucose, insulin, and genotype information; (ii) finometer and blood pressure (BP) measurement; (iii) current medications and any change in recent medical history; (iv) smoking status; (v) alcohol use; (vi) sedentary behavior. Blood pressure will be determined according to JNC 7 guidelines (Chobanian et al., 2003). After 5 minutes of quiet rest, four seated BP readings, each 2 minutes apart, will be obtained using a Datascope Accutorr Plus automated BP monitor (Anwar, Tendler, McCabe, & White, 1997). The last three readings will be averaged to define the clinic BP. Before and after CPT-C and the WP-CON, we will also administer questionnaires to determine behavioral and social factors that have been associated with trauma exposure and PTSD. Depressive and anxiety symptoms will be measured using the Hospital Anxiety and Depression Scale (HADS), a commonly used psychiatric self-report questionnaire designed to identify anxiety and depression among populations with high levels of somatic complaints (Zigmond & Snaith, 1983). The HADS has superior psychometrics compared with other instruments commonly used to measure anxiety, has good test-retest reliability ($r>0.8$), and average sensitivities and specificities of 0.8 or higher (Moorey et al., 1991; Lisspers, Nygren, & Soderman, 1997; Bjelland, Dahl., Haug, & Neckelmann, 2002). In order to maximally explore the construct of depression as it relates to PTSD, parallel analyses will be conducted with Beck Depression Inventory-II, a 21-item self-report inventory of depression that has been shown to be predictive of clinical events in CHD patients (Beck, Steer, & Brown, 1996; Frasure-Smith, Lesperance, & Talajic, 1995). At baseline, participants will complete a series of questionnaires designed to examine presence of misophonia (Scott Vrana, personal communication).

The Fagerström Test of Nicotine Dependence (Heatherton, Kozlowski, Frecker, & Fagerström, 1991) and a smoking history questionnaire (e.g., number of cigarettes smoked/day, age of first smoking, number of previous quit attempts) will be used to measure smoking behaviors. Self-reported alcohol use will be assessed with the three-item Alcohol Use Disorder Identification Test (AUDIT-C; Bush, Kivlahan, McDonnel, Fihn, & Bradley, 1998). We will measure habitual physical activity using the Stanford 7-day physical activity recall interview (Blair et al., 1985). We will measure hostility using a short 27-item form of the Cook-Medley Hostility Scale (CM; Cook & Medley, 1954). The CM has shown high test-test reliability and a number of studies have supported its construct validity as a measure of hostility (Barefoot & Lipkus, 1993). We will measure social support using the Perceived Social Support Scale (PSSS), a 12-item self-report scale that assesses perceived availability and level of satisfaction with support. Socioeconomic status (SES) will be estimated by combining total years of education with income to derive a global socioeconomic status measure (Nam & Powers, 1987). Exploratory analyses will consider the possibility of a moderating role for smoking, alcohol abuse, habitual sedentary behavior, social support, and SES in the association between PTSD symptom change and change in biomarkers of CHD risk. We will also evaluate whether the change in anxiety or depressive symptoms

estimated using the HADS scores act to mediate the association between CPT-C and the proposed improvement in CHD risk biomarkers.

During the screening session, some measures will be completed in the office. Participants will be given the option to complete all measures in the office, or if they prefer, they can take a subset of questionnaires with them to complete at home at their convenience. Any questionnaires that leave the Duke premises will be deidentified. Participants who choose to take questionnaires home will be asked to return them to the study coordinator at their baseline assessment.

Temporary Measures During COVID-19 Pandemic. Given that exposure to COVID-19 stressors and potential trauma may occur during the pandemic, we would like to ask participants to complete measures related to stress, trauma, and coping strategies. Participants will be informed about these new study procedures verbally, and the study team member who informs them will provide a note-to-fil indicating so. Participants can refuse to complete these measures. We will ask ongoing participants to complete these measures at their next study visit or follow-up session. When study enrollment begins again, participants will complete these measures at the screening session. We are adding the CAIR Pandemic Impact Questionnaire (Lang, 2020; https://www.nlm.nih.gov/dr2/CAIR-PIQ_scoring.pdf), and another measure, COVID Core Questions, with variables of interest. If a participant endorses any item marked with an asterisk on the COVID Core Questions measure, we will ask them to complete a PTSD Checklist 5 related to that specific event. Finally, we have added a measure designed to evaluate participants' satisfaction with remote study procedures.

CHD Risk Biomarkers : Parasympathetic Cardiac Control (PNS). Continuous ECG data will be recorded for one full day and one full night using a DigiTrak XT Holter recorder (Philips Healthcare, Andover, MA, USA). A checklist used to ensure that the skin is prepared properly and the electrodes and leads are intact, and the signal quality will also be confirmed by visual inspection of each of the three ECG channels. The recorder will be placed in a carrying pouch which fits onto a shoulder strap and belt apparatus. Following instrumentation, patients will be reminded to engage in their normal pattern of activity and will be instructed to remove the Holter device and electrodes at the specified time on the day following instrumentation. FedEx will be used to pick up monitors from participants' homes following the screening and last assessment so they can be returned to our research facility at DUMC South. FedEx will be provided the name and address of the participant, but no health information will be included. The Holter recording will be prepared for HRV analysis; the ECG recording will be downloaded, scanned and edited using Philips Holter 2010 Plus software (Philips Heathcare,Andover, MA, USA), with verification of labeled beats performed by an experienced ECG researcher. The labeled beat-to-beat file will then be processed using customized HRV analysis software.

Participants will be queried regarding variables that may affect HRV including caffeine, alcohol, and cigarette consumption. The primary outcome variable to estimate PNS control will be HRV estimated from the standard deviation of all normal R-R intervals over 24-hours (SDNN). SDNN has been widely demonstrated to provide a robust, independent predictor of increased risk of mortality (Dekker, Crow et al., 2000; Rodrigues et al., 2010; Liao et al., 1997; Dekker, Schouten et al., 1997; Tsuji et al., 1996; Algra, Tijssen, & Roelandt, 1993; Hikuri et al., 1999).

CHD Risk Biomarkers: HRV, Blood Pressure Variability and Baroreflex: Fifteen minutes of beat-by-beat HR and BP using a noninvasive BP measurement device, the Finapres. This blood pressure measurement will be performed during following the FMD assessment in order to minimize time demands on the patient. The Finometer device, which is a small finger blood pressure cuff, will be placed on the middle finger of one hand. During the first minute of the recording, the participant will be asked to take 6 deep breaths, with each respiratory cycle lasting for 10 seconds. This will be followed by 10 minutes of quiet rest during which participants will be asked to rest quietly. Following this rest period, participants will be asked to stand for 5 minutes in order to examine the effects of postural challenge on sympathetic control of blood pressure and heart rate. Data will be saved for later derivation of blood pressure variability, heart rate variability, and baroreflex sensitivity. Specifically, baroreflex control of HR will be estimated from the degree of HR variation associated with the spontaneous BP variations during rest and during standing.

CHD Risk Biomarkers: Sympathetic Nervous System (SNS) Activity. Participants will be asked to collect urine into sterilized plastic bottles (containing a small amount of preservative) over a 24-hour period and to store the bottles in a small portable cooler that will be provided. Samples will be assayed for norepinephrine, epinephrine, and creatinine. In order to normalize the catecholamine values for body size and urine volume, catecholamine excretion will be provided in units of µg of catecholamine (i.e., norepinephrine or epinephrine) per mg creatinine for each sample (White, Brunner, & Barron, 1995). In prior studies, urinary catecholamine data have proven informative, with low subject burden and excellent compliance (Sherwood, Steffen, Blumenthal, Kuhn, & Hinderliter, 2002). In the proposed study, 24-hour urinary catecholamines will be measured to estimate SNS activity before and after the CPT-C and WP-CON intervention arms. Coded urine samples will be sent to Lab Corporation of America for liquid chromatography/tandem mass spectrometry.

CHD Risk Biomarkers: Vascular Endothelial Function assessed by Flow-Mediated Dilation (FMD). Our technique for assessing FMD follows procedures first described by Celermajer and colleagues (1992) and conforms to current consensus guidelines (Thijssen, Black et al., 2011). FMD of the brachial artery will be assessed following overnight fasting. Longitudinal B-mode ultrasound images of the brachial artery, 4-6 cm proximal to the antecubital crease, will be obtained at end-diastole. Peak hyperemic flow and shear stress will be derived by standard formulae based upon Doppler velocity measurements during the first 10 seconds following deflation of the occlusion cuff (Pyke, Hartnett, & Tschakovsky, 2008; Mitchell et al., 2004). Peak FMD response will be assessed from 10-120 seconds post-deflation of the cuff, with peak arterial diameter quantified using polynomial curve fitting, and FMD defined as the maximum percent change in arterial diameter relative to pre-inflation baseline. These assessments will be performed at baseline and post-intervention.

CHD Risk Biomarkers: Inflammatory Marker Assessment. Blood samples (18 mL) will be collected after an overnight fast for the determination of high-sensitivity C-reactive peptide (hs-CRP) at both baseline and post-intervention. Blood will be drawn by a trained phlebotomist on the study team at Duke. Participants will be asked to refrain from taking anti-inflammatory medications such as aspirin or ibuprofen, antihistamines, or antibiotics for a minimum of two weeks and compliance will be checked

the day of assessment. In the case of acute infections/fever, assessment will be delayed until the condition resolves. All participants will be screened for current medical conditions and medications the day of the assessment. A blood sample will also be collected at this time to determine fasting glucose and insulin in order to provide an estimate of glycemic control and insulin resistance, respectively. For assessment of CRP, glucose, and insulin, 10 cc of blood will be taken from a peripheral vein and collected into a single purple-top tube containing ethylenediaminetetraacetic acid and immediately cold centrifuged at 3000 g for 10 minutes. Plasma will then be extracted and stored at -80^{o}C until analysis. Analysis of coded blood samples will be performed by Lab Corporation of America. Genetic analysis of coded blood samples will be performed at Biomarkers Shared Resource, Duke Molecular Physiology Institute.

There is evidence that glucocorticoid-related genes may be subject to environmental regulation, that psychotherapy may be a form of such regulation, and that certain genes may be associated with treatment prognosis (Yehuda et al., 2013). Collection of DNA and RNA will allow for evaluation of these phenomena. At each blood draw in screening and posttreatment (or wait period if assigned to control), we will ask participants to participate in an optional additional blood draw in order to collect RNA and DNA. If participants choose to participate, the phlebotomist will draw an additional 16.5 mL of blood (approximately 1 tablespoon). The blood draw will be completed at assessments two and three. Although we are enrolling healthy participants, in order to reduce risk associated with blood draws, we will ensure that each blood draw will occur at least eight weeks after the previous blood draw so that the maximum amount of blood drawn during any eight week period will be 35 mL (18 for CHD biomarkers; 16.5 for DNA/RNA). Participants will be asked to allow banking and future use of genetics specimens and other phenotypic data (e.g., PTSD diagnosis status, demographic information) collected at both time points. Subjects will also be asked permission to combine their study information with similar data from other genetic studies. The purpose of combining the data from other studies is to increase the power analysis numbers required to perform complex genetic analyses, especially genome wide association study (GWAS). Complete confidentiality of all subject protected health information will be accomplished in a three-step process. First, information from this study will be completely de-identified. Second, information from other similar genetic studies will be completely de-identified. Lastly, this information will be merged into one database. The purpose of this combined database is to acquire the power of analysis needed in order to study the possible genetic risk factors that may be related to psychiatric illness. The blood samples will be stored in tubes that are labeled using a bar-code system and will not be labeled with any identifying information. All blood specimens will be banked at the Durham VA Medical Center (DVAMC) as part of Dr. Beckham's "Management of Two Databases in the Nicotine Lab," Duke IRB PRO0002947 (and VA IRB #1080). Blood samples are stored in a -80 degree freezer in a locked building at DVAMC. Genetic analyses will be performed by the Genetic and Epigenetics team at Duke's Molecular Physiology Institute (DMPI). Results from any and all analysis of blood samples will not be shared with the family, employers or physicians of subjects. The laboratory is not CLIA approved; in fact, most genetics research done at Duke is not performed by CLIA approved laboratories. In addition, the research focus of the proposed GWAS is PTSD and related psychiatric disorders, not on other conditions and their genetic predispositions. Per a geneticist at DMPI, the likelihood of incidental findings in other areas that might pose an immediate threat to study participants is extremely low (Michael Hauser, personal communication). For these reasons, we do not

plan to share any incidental findings with participants. Please note that these procedures are optional to participants. Any participant can refuse to participate in genetic testing and still be allowed to participate in the other portions of the study. There are no limitations on the participants' rights to withdraw from the research, withdraw data, or withdraw genetic material. All participants will be provided with an address to which they should send any requests for withdrawal of data or genetic material.

Interventions

Waiting Period Control (WP-CON). The WP-CON group will receive minimal attention in the form of weekly telephone calls to assess current emotional state and to provide supportive, nondirective, brief counseling if participants report experiencing a crisis. Any participant assigned to the WP-CON group will be given the opportunity to receive CPT-C after the post-waiting period assessment. Clients who call in distress during the 6 week control period will be offered the same supportive counseling, and if desired, they will be offered immediate therapy and be referred by Dr. Beckham and will no longer be included in the study.

Cognitive Processing Therapy-Cognitive (CPT-C). CPT-C is a brief cognitive behavioral treatment for PTSD that has been found to produce a more rapid clinical improvement and lower dropout than the standard CPT (Resick, Galovski et al., 2008). CPT-C is equally effective as the full version of CPT. Similar to the standard CPT, CPT-C consists of 2 hours of therapy each week for 6 weeks (i.e., two sessions). Any participant who cannot attend two sessions weekly will be allowed to participate in once session per week for a 12-week period. Study therapists will include two designated mental health providers trained in person by Dr. Resick. Initial didactic training (covering session by session procedures and core components of CPT-C) will last three days and be followed by training cases. Therapists will not be allowed to provide the intervention to research participants until they have demonstrated 100% competence and adherence with the required elements of all treatment sessions. Drs. Resick and Dedert will provide biweekly supervision throughout the duration of the trial, conduct spot checks of videotaped sessions, and will provide as-needed individual consultation and an in-person refresher didactic training halfway through the trial. All therapy sessions will be recorded, and a random selection of 20% will be rated for fidelity checks during the study. In order to protect against drift, the frequency of fidelity checks will occur equally across the beginning, middle, and end of the intervention period. Two independent raters, Drs. Carolina Clancy and Sara Tiegreen, will code therapist treatment fidelity/adherence using the Cognitive Processing Therapy: Therapist Adherence and Competence Protocol Individual Version-Revised (Macdonald, Wiltsey-Stirman, Wachen, & Resick, unpublished). Videos will be rated on the presence/absence of CPT-C elements, competence on these elements as well as proscribed elements.

Study therapy sessions will occur at DUMC South Clinics Building or at Traumatic Stress and Health Research Laboratory space at Hock Plaza. So that participants can park easily at Hock, we'd like to provide participants with parking passes in advance of their appointments. Because notification of randomization for therapy vs. waitlist control occurs by telephone, whenever possible, we will email (via Duke secured email) parking passes and directions to Hock to participants.

The standard of practice for psychologists providing Cognitive Processing Therapy is to encourage participant who has an existing mental health care provider that he/she is participating in the therapy. Often providers have questions about the therapy that cannot easily be answered by the participant, especially regarding the nature of the therapy. If this situation arises, a study therapist may ask the study participant for permission to contact his/her mental health care provider. We will plan to use the Duke Health Enterprise Authorization for Release of Protected Health Information to document this permission.

Risks, Benefits, and Protections From Risk

Study Risks. There are no known psychological hazards or risks associated with completing questionnaires. Both the clinical interviews to establish diagnosis and participation in CPT-C can cause some psychological distress in the form of a temporary increase in anxiety or PTSD symptoms, but any ensuing distress is usually well tolerated. The blood draws may cause pain, bruising, and rarely, fainting or infection. During the FMD procedure there may be some arm pain. If any participant has his/her chest shaved, there is a risk of minor cuts. Removing the electrodes (small discs) may sting slightly, similar to removing a Band-Aid. Participants may experience skin irritation at the sites where electrodes are placed.

The optional genetics components of this study confer additional medical, psychosocial and economic risks. These risks may include, but are not limited to, loss of insurability, employability, confidentiality, and social stigmas. Participants will be informed that their genetic information is used for research purposes only, and are given a choice regarding receipt of any information related to incidental findings (see informed consent form).

Risks of participation, including interviews, are described in the consent form. Potential risks will be minimized by carefully screening participants according to the inclusion/exclusion criteria, closely monitoring symptom levels, and following established laboratory procedures. The Holter tapes will be read by automated software that generates summary reports identifying the occurrence of clinically serious arrhythmias (i.e., ventricular tachycardia). In these cases, the reports will be sent to the study cardiologist (see “Data Safety and Monitoring Board” below) who will provide feedback to the study team. The study team may inform the patient's primary care physician, when appropriate. If a participant with abnormal findings does not have a physician, we may share the results directly with the participant. There is a risk of loss of confidentiality. Serious adverse events will be promptly reported to the IRB as required. All project staff will complete educational units required by the Duke University Institutional Review Board and the DVAMC Human Subjects Committee.

Participants will be informed that if they are Duke patients, Dr. Watkins and/or members of her study team may review medical records in Maestro Care to become informed of any conditions that may impact participation or referral to a physician.

Table 1. Possible Payments for Participants

TASK	AMOUNT PAID	Which arm?
Screen	85	Both
T1 baseline assessment	100	both
T1 urine/Holter monitoring	100	both
Control arm phone measures or CPT measures	45	both
T2 baseline assessment	130	both
T2 urine/Holter monitoring	200	both
CPT measures for control arm	45	Control only
T3 baseline assessment	130	Control only
T3 urine/Holter monitoring	200	Control only
Seed recruitment	120	Both
TOTAL for Control arm	1155	
TOTAL for Active arm	780	

The study is completely voluntary and participants are informed that they are free to refuse to answer any items on the questionnaires or questions from the interview that they do not wish to answer. They are also informed that they are free to decline participation in any procedure and can withdraw from the study at any time.

Subject Reimbursement. Table 1 summarizes participant payments for each phase of the study. Reimbursement to participants will offset the costs in time, effort, and possible lost wages associated with commitment to the study. Participants will be paid up to $1155 for completion of all aspects of the study. In order to encourage study retention, a staggered reimbursement schedule will be used. Participants will therefore receive $85 for completing the screening session and $100 for completion of the baseline assessment, $100 for completing the in-home urine collection and Holter monitoring,), $130 for completion of the second session, , and an additional $200 for completion of the second urine collection and Holter monitoring. Participants in the CPT condition are paid a total of $45 for completing symptom measures at the therapy sessions, and participants in the waitlist control condition are paid $45 for completing six telephone calls to assess PTSD symptoms during the waitlist period. Any participant who was assigned to the waitlist group will be offered participation in 12 sessions of CPT and additional monitoring, and therefore may make an additional $375 [$130 for office assessment, $200 for urine collection and Holter monitoring, and $45 for completion of questionnaires at each CPT session]. Participants can also earn up to $120 for referring other participants to the study. Participants will be provided parking passes and/or bus passes to encourage attendance at all sessions.

Data Storage and Security. Two key personnel members outside Duke will have access to specific study data. Dr. Hinderliter, a member of the Data Safety and Monitoring Board, will have access to coded data, as he provides review of potentially problematic Holter monitor readings. He will not have access to PHI. Dr. Hinderliter will review a pdf file of readings in one of two ways: 1) he will review in person during his visits to DUMC South, or 2) he will be provided a copy using Box@Duke. Dr. Sara Tiegreen is a Duke-paid consultant who will provide expert fidelity reviews of the CPT-C therapy sessions. Dr. Tiegreen will access therapy videos, which contain PHI, via Box@Duke. Dr. Tiegreen has completed CITI good clinical practices modules as a VA Medical Center affiliate, as she is a clinician and research at the Durham VA Health Care System. After video recordings are reviewed for fidelity, they will be deleted from Box@Duke. If a participant chooses to participate in the optional video recording of his/her screening interviews, those video recordings will be shared with Vickie Carpenter, MS, LPCS or Jill Triana, MS, LPCS via Box@Duke. After video recordings are reviewed, they are deleted from Box@Duke and no copies will be retained.

Data that links participants to information collected in the course of a given study will be kept separately from identifying information in an electronic, password-protected MS Access database stored at duhsnas-pri\dusom_psych\private\irb\watkins\accept; the key connecting identifying information and data will be stored here as well. Hard copy paper records will be stored in a locked filing cabinet in the study coordinator's locked office, within Dr. Watkins' laboratory space at Duke University Medical Center South. Information from the interview and/or questionnaires may be entered into a computerized database that will be stored on the DUMC server at duhsnas-pri\dusom_psych\private\irb\watkins\accept in a password-protected database. This database is accessible only by Dr. Watkins and study staff. Any staff members who leave the study for any reason will have access to study resources, including data, removed immediately.

Video recordings of therapy sessions will be made using a Duke-owned iPhone or iPad that is encrypted at levels compliant with FIPS 140-2 standards. The device to be used will be hardened such that only the video recording capability will remain. Video recordings will be moved from the device to the Duke shared server (file path above) as soon as possible after the recordings have been made, and will then be deleted from the mobile device. Any device that is not in use will be stored in a locked filing cabinet in Dr. Watkins' office. Video recordings will remain on the Duke shared drive until the fidelity raters are ready to evaluate them. Copies will then be moved to Box@Duke, where they can be viewed and evaluated by the raters. The recordings will be copied to an encrypted hard drive for permanent storage, and the copies on the Duke shared drive will be deleted. The encrypted hard drive will be stored in a locked file cabinet in Dr. Watkins' or Dr. Beckham's lab space at Duke South. Only the key personnel listed on the staff listing will have access to the encryption password and/or the hard drive.

Participants enrolled during the COVID-19 pandemic may be sent study equipment or study documents via FedEx. If that occurs, FedEx will be provided the name and address of the delivery recipient. No other information (including health information) will be included with the name and address.

Suicidal and/or Homicidal Ideation. The Traumatic Stress and Health Research Laboratory (TSHRL) has established standards of practice for the evaluation of risk of suicide and homicide. The policy includes a thorough risk assessment including evaluation of risk factors and protective factors associated with both suicide and homicide. Also included in the policy are differential recommendations for action based on determinations of low, moderate, or high risk. Any staff member conducting an interview in which moderate or high risk is determined will contact a senior staff person with clinical expertise in risk assessment [including the PI, co-investigator(s), and/or DUMC's Emergency Room]. Although we are not selecting PTSD patients based upon their level of depressive symptoms, our assessments may determine the presence of severe depression. If patients are acutely suicidal, they will be evaluated and appropriate referral or admission procedures will be initiated, and they will be dropped from further study. At several time points throughout the study, participants are reminded that they are asked to inform the study therapist, study coordinator, or study PI if they experience a psychiatric emergency such as homicidal or suicidal ideation. In addition, participants are provided the telephone

number of study staff who they can call in the case of psychiatric emergencies, including an after-hours contact number.

Post-Study Referrals for Participants. It is not unexpected that participants may complete the study with residual PTSD and/or major depressive disorder symptoms. Because participants complete the PTSD Checklist (PCL5) and the Beck Depression Inventory -II (BDI-II) at multiple time points, we will refer to these scores at the end of the study as a gauge of residual symptoms. We will provide referrals for continued treatment to anyone with a score of 38 or higher on the PCL5 and/or a BDI-II score of 20 or higher (i.e., moderate to severe depression range). Additionally, referrals will be provided to participants who self-report distress at symptoms of PTSD or depression (regardless of measure scores) and wish to continue with another form of treatment.

The TSHRL has developed patient educational materials regarding available resources, including portable resource cards for both veteran and civilian participants. Civilian resources may include local community mental health centers, local private mental health providers, Duke Adult Psychiatry Clinic, Duke's Psychology Clinic, and other resources such as emergency clinics and substance abuse treatment centers. Veteran resources include peer support (www.vtvettovet.org), local Vet Centers, and information about treatments available at various clinics at the DVAMC and local VA community-based outpatient clinics, including the PTSD Clinic, Mental Health Clinic, Mental Health Access Clinic, Psychiatric Emergency Clinic, and Women's Health Clinic. Where applicable and convenient to the participant, direct referral will be made in addition to providing resource cards.

Data Safety and Monitoring Plan. The individuals responsible for data safety and monitoring will be the PI, the co-Investigators, the study coordinator, and a Data Safety and Monitoring Board (DSMB). Mechanisms for monitoring and reporting of data safety and adverse events (AEs) will include ongoing participant contact via study personnel, to include check-ins about any adverse events, and weekly meetings between the PIs and study personnel.

Study staff members and the co-PI (Beckham) will monitor ongoing clinical status throughout the project via direct interaction with the participants or through review of laboratory notes that will be completed at each visit by clinical and research staff. The PI will meet at least weekly with study personnel to discuss participants' reactions to the intervention, proper delivery of the intervention, and any adverse events or unanticipated problems. Regular meetings between investigators and the project manager will allow for ongoing progress reports, including the number of participants currently involved in the study groups, attrition rates, and scheduled data collection from participants, as well as notification and review of any AEs. Safety monitoring for AEs will be conducted in real time by the PI and/or project manager. The following information about adverse events will be collected: 1) the onset and resolution of the AE, 2) an assessment of the severity or intensity (use existing grading scales whenever possible), 3) an assessment of the relationship of the event to the study (definitely, probably, possibly or not related), and 4) action taken (e.g., none, referral to physician, start or increase concomitant medication). The PI will determine the severity of the event, will assign attribution to the event, and will monitor the event until its resolution. Any adverse events will be reported to the IRB in accordance with local guidelines. All research projects conducted at DUMC are

required to have yearly IRB review, including a safety review. Additionally, any changes to the project between review periods must be approved by the IRB prior to fielding.

Data Safety and Monitoring Board. This study will also utilize a Data Safety and Monitoring Board (DSMB) to enhance participant protection. Three consultants will serve as members of the Data and Safety Monitoring Board (DSMB) created for this project: 1) Dr. Alan Hinderliter, University of North Carolina at Chapel Hill, will provide expertise in cardiology; 2) Dr. Eileen Burker, University of North Carolina at Chapel Hill, will provide expertise in mental health; and 3) Dr. James O'Malley, Dartmouth Institute for Health Policy and Clinical Practice, will provide expertise in biostatistics. The Data and Safety Monitoring Board (DSMB) will review adverse events and monitor the safety of participants and the quality and completeness of the accrued study data during regularly scheduled meetings. The DSMB will convene every year, but is consulted at any time in the event of study-related, unanticipated and/or serious adverse events. The DSMB performs the critical function of monitoring all studies for adverse events and determining whether a favorable risk-benefit ratio justifies continuation of a given study. The DSMB plays a complementary role to the Duke University IRB, which focuses mainly on the prospective review of study protocols (although the IRB may also be involved in halting a study in the face of serious, reportable adverse events). Decisions of the DSMB are made by majority vote, with the results of each vote and relevant discussion recorded in the meeting minutes (which, after circulation and emendation, are approved by each member).

Additional Information Regarding Data Analyses

Power Analysis. The sample size estimate of n=120 subjects (80 in the CPT-C arm and 40 in the control arm) is based on a 2:1 randomization and the AIM 1 comparison of HRV improvement between CPT-C and control arms at 6 weeks. For sample size calculations we used methods appropriate for ANCOVA type analyses (Borm, Fransen, & Lemmens, 2007), which are equivalent in terms of efficiency to our linear model for randomized trials (Fitzmaurice, Laird, & Ware, 2004). Quantities needed for this sample size calculation include the baseline standard deviation and the correlation between baseline and follow-up. As we have limited pilot data, we assumed a range of correlations between 0.3 and 0.6 and standard deviations (SD) of 40 and 50. **Table 2** presents effect size differences with 120 subjects. Using the most conservative assumptions, with 80% power, alpha=0.05, SD=50, rho=0.3, and 20% attrition rate by 7-weeks we can detect an effect size difference of 0.60 (Cohen, 1988), corresponding to a difference of 30 units in mean HRV levels at 7-weeks between CPT-C and control. For the AIM 2 mediation analysis, we will test that the effect of CPT-

Table 2. Effects size and mean differences of HRV detectable with 80% power in 120 randomized subjects.

Correlation (rho)	Standard Deviation	Effect Size Difference	Mean HRV difference
0.30	40	0.60	24.0
0.30	50	0.60	30.0
0.40	40	0.55	22.0
0.40	50	0.55	27.5
0.50	40	0.55	22.0
0.50	50	0.55	27.5
0.60	40	0.50	20.0
0.60	50	0.50	25.0

C on CHD biomarkers is attributable to changes in PTSD severity. We determined detectable effect sizes for mediation based on empirical power estimates for the product-of-coefficient test (i.e., the product of γ_1 and β_2) given by Fritz and MacKinnon (2007). With 120 subjects and a type-I error of 0.05, we will have 80% power to detect medium to large effect size differences for each of the parameters individually (e.g, γ_1 and β_2) that are part of the product test.

Missing Data. Our plans for preventing and dealing with missing data follow the guidelines set forth by the National Research Council's Panel on Handling Missing Data in Clinical Trials. First, , we have numerous strategies in place to prevent attrition; based on prior experience with a similar design and population, we anticipate that we will have less than 20% attrition. Second, as recommended by the panel, we will conduct two general types of sensitivity analyses for our primary analysis. If the missing values are related to measured factors, such as treatment group or baseline comorbidities, then multiple imputation will be used to incorporate information for these auxiliary variables while still preserving a parsimonious main treatment effect model (Collins, Schafer, & Kam, 2001). As a first sensitivity analysis, we will construct a general, multivariate imputation model using all observed CHD markers, treatment group, and any covariates predictive of missingness (Olsen, Stechuchak, Edinger, Ulmer, & Woolson, 2012). The primary analysis models will then be fit to the multiply imputed data and the estimates and standard errors will be combined using appropriate combining rules. We acknowledge the possibility that data may be missing not at random and propose as a second sensitivity analysis to explore pattern-mixture models and the toolkit of methods recently advocated by O'Kelly and Ratitch (2014).

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