[Protocol Number] Personalizing Cognitive Processing Therapy with a Case Formulation Approach to Intentionally Target Impairment in Psychosocial Functioning Associated with PTSD

Funding Agency: [Office of Research and Development]

Principal Investigator/Study Chair: [Dr. Tara Galovski & Dr. Shannon Kehle-Forbes]

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Abstract

Project Background: Cognitive Processing Therapy (CPT) has been widely disseminated throughout VHA with over 4,000 VHA providers certified to provide CPT through the Mental Health Dissemination Initiative to date. However, as CPT has been implemented, several factors have limited its impact on Veterans' health. Veteran engagement in CPT is suboptimal, outcomes achieved in Veteran populations are more modest than those obtained with civilians, and improvements in functioning and quality of life are more modest than those observed in the core symptoms of PTSD. Strategies for improving patient engagement, enhancing treatment outcomes, and expanding the success of the intervention to functional impairments are needed for Veterans to fully benefit from CPT. Expanding and enhancing the CPT protocol is a promising strategy for achieving these goals. Integrating a case formulation (CF) approach into the existing CPT protocol may enable providers to increase treatment flexibility while maintaining fidelity to effective CPT principles. CF is a collaborative process between providers and patients that enables providers to tailor cognitive-behavioral treatments to specific clients' needs within clear parameters of what justifies deviation from the standard protocol. Early research has demonstrated that CF-integrated CPT (CF-CPT) yields lower levels of dropout and a higher proportion of patients losing their PTSD diagnoses than published accounts of CPT.

Project Objectives: The long-term objective is to build on the success of CPT by directly targeting functional impairments and enhancing patient outcomes. We propose the following aims: 1) Compare the relative effectiveness of CF-CPT to CPT in improving psychosocial functioning quality of life and well-being as well as core PTSD and depression symptoms; 2.) Determine the effectiveness of CF-CPT as compared to CPT in improving treatment engagement; 3.) Evaluate CF- CPT's indirect impact on psychosocial functioning, quality of life, well-being and PTSD/depression as influenced by improvement in the idiosyncratic clinical challenges targeted by the CF.

Project Methods: We are proposing a randomized control trial in which up to 325 , Veterans (up to 15 Veterans per provider) will be administered either CPT of CF-CPT by VA CPT certified or certification eligible providers at up to 10 clinical study sites. Each study provider will deliver either CPT or CF-CPT as assigned to up to 15 Veterans presenting for treatment in clinic. Data sources will include pre- and posttreatment diagnostic interviews, Veteran self-report surveys, administrative data extracted from mental health progress notes, and therapy process data including daily symptom monitoring diaries and therapy materials. Primary outcomes will be standardized measures of functioning, quality of life, and well-being. Secondary outcomes include clinician-assessed PTSD symptomology and comorbid mental health symptoms. Data sources will also include standardized measures of the host of clinical challenges that disrupt therapy and that are specifically targeted by the CF approach as well as novel, idiosyncratic measures (daily diaries, therapy materials) of challenges.

Anticipated Impacts on Veterans Healthcare: Findings have the potential to increase the number of Veterans who benefit from one of the most effective treatments for posttraumatic stress disorder (PTSD), CPT. In addition to reductions in PTSD symptomology, successful completion of CPT results in improvement in functional impairment, decreases in comorbid symptoms, and enhanced quality of life

List of Abbreviations

Abbreviations listed in alphabetical order

- AE = Adverse Event
- ATT = Average Treatment effect on the Treated
- BA = Behavioral Activation
- CAPS-5 = Clinician Administered Posttraumatic Stress Disorder Scale for DSM-5
- CCDOR = Center for Chronic Disease Outcomes Research
- CF = Case Formulation
- CF-CPT = Case Formulation Integrated Cognitive Processing Therapy
- COIN = VA Health Services Research & Development Center of Innovation
- COTO =Challenges to Optimal Therapy Outcomes
- CPCR = Composite Primary COTO Reduction
- CPT = Cognitive Processing Therapy
- CRS = COTO Reduction Score
- CSP = Cooperative Studies Program
- DOD = Department of Defense
- DSMB = Data Safety Monitoring Board
- EBP = Evidence-Based Psychotherapy
- EMA = Ecological Momentary Assessment
- EMR = Electronic Medical Record
- FTP = File transfer protocol
- ICC = Intraclass Correlation Coefficient
- IE = Independent Evaluator
- IPS = Inventory of Psychosocial Functioning
- ITT = Intent To Treat

- JLV = Joint Legacy Viewer
- LAN = Limited Access Network
- LSI = Local Site Investigator
- MCPT = Modified Cognitive Processing Therapy Intervention
- MI = Motivational Interviewing
- NCPTSD = National Center for Posttraumatic Stress Disorder
- NIH = National Institute of Health
- PCL = PTSD Checklist for DSM-5
- PHQ-9 = Patient Health Questionnaire – 9
- PTSD = Posttraumatic Stress Disorder
- RCT = Randomized Controlled Trial
- SAE = Serious Adverse Event
- SD = Standard Deviation
- SMI = Severe Mental Illness
- TAU-CPT = Cognitive Processing Therapy administered as usual
- TBI = Traumatic Brain Injury
- VABHS = Veteran's Affairs Boston Healthcare System
- VHA = Veteran's Health Administration
- VPN = Virtual Private Network
- WBI = Well-Being Inventory
- WHO-DASII = World Health Organization – Disability Assessment Schedule 2.0
- WHOQOL-BREF = World Health Organization – Quality of Life, Brief
- WHSD = Women's Health Sciences Division

Contents

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There are 2 participating coordinating study sites (Boston & Minneapolis) and up to 10 local sites. The lead study sites will both begin start-up at the same time. Providers at each of the study sites will treat participants during the course of the study and therapy materials will be collected at the study site; all other study elements such as veteran recruitment and consent procedures will be conducted by the two coordinating centers and will standardized with no variation by providers or site. Each local site will include a local site investigator (LSI), providers who will function as study staff, and be assisted by a part-time research assistant/project coordinator. The coordinating sites (Minneapolis & Boston) may also serve as clinical sites (e.g., have study therapists and Veteran participants).

Coordinating study sites:

VA Boston Healthcare System
Minneapolis VA Healthcare System

Local clinical sites:

New Orleans VA Medical Center, New Orleans, LA
VA Pacific Islands Health Care System, Honolulu, HI
St Louis VA Medical Center, St Louis, MO
VA Phoenix VA Health Care, Phoenix, AZ
Michael E. DeBakey VA Medical Center, Houston, TX
Salem VA Medical Center, Salem, VA

Six local sites have been identified. All sites have submitted to CIRB and their local regulatory committees for all needed approvals as they are identified and before any activities occur at that site.

Introduction

Rationale for the Proposed Study. Posttraumatic stress disorder (PTSD) is common and complicated. Recent estimates suggest that over 610,000 US Veterans treated by the Veterans Health Administration (VHA) suffer from posttraumatic stress disorder (PTSD), a disorder that can be chronic and debilitating.[1] The heterogeneity of the 20 symptoms of PTSD; comorbidity with disorders such as depression, panic, and substance use; high rates of concurrent and lingering effects of physical injury, and suicidality all contribute to complex clinical presentations[2-5] and can exact a significant toll on functioning, quality of life, and well-being decades after exposure to the trauma.[2] The complex and enduring challenges inherent in PTSD and their effect on patients' functioning pose significant hurdles for patients and clinicians.[4;6-8]

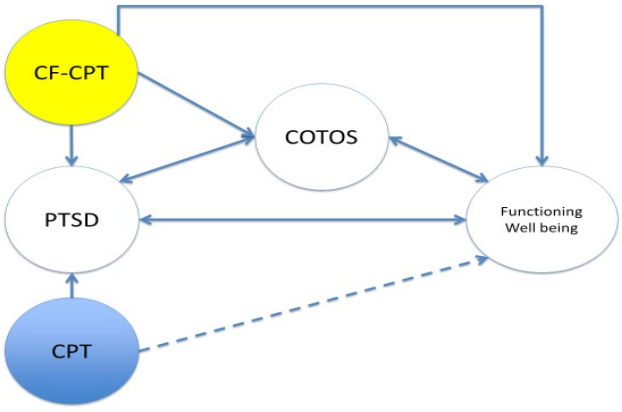
Impairments in psychosocial functioning are an important, but less well-attended, facet of PTSD. While significant impairment in functioning is clearly a requirement for the diagnosis of PTSD as indicated by Criterion G of the diagnostic criteria for PTSD, resolution[6] of functional impairment is not considered to be a *primary* therapeutic target in evidence-based PTSD treatment protocols. Improvements in domains of functioning and, more broadly, quality of life and well-being, are most typically considered secondary outcomes in RCTs, if they are reported at all. This seeming lack of attention to impairments in functioning stands in stark contrast to patients' reports of the meaningfulness of these impairments in their lives. In fact, it is often precisely these types of impairments that drive patients suffering from PTSD to seek treatment, arguably more so than the 20 core symptoms of the disorder.

Researchers and providers alike recognize the importance of well-being and seek to maximize functional recovery. It has theoretically been difficult to directly target impairment in functioning (PTSD Criterion G) in manualized therapies, perhaps because "functional impairment" is quite variable across patients in breadth and scope. Including *explicit* and manualized instruction on "treating functional impairment" is impossible and is likely the reason that no single PTSD psychotherapy exists that is specifically designed to "treat" functional recovery. Trauma-focused EBPs instead are specifically designed to directly target the core symptoms of PTSD. Functional impairment is targeted *indirectly* through relief in the core symptoms. For example, improvement in occupational functioning may be achieved through decreases in avoidance, mood or anger symptoms that might be interfering with job performance. Gains in functioning (e.g., improving marital relations or workplace functioning) and large effects in well-being and quality of life have historically been difficult to operationalize and are often considered more longterm therapeutic goals, perhaps beyond the scope of brief therapies. However, given the importance of functioning to patients with PTSD, intentionally and thoughtfully building on the success of the skills acquired in evidence-based psychotherapies

(EBPs) and expanding those skills to specifically target functional outcomes warrants further exploration.

Cognitive Processing Therapy (CPT) is effective at reducing PTSD symptoms and is widely used. CPT[9] is one of the therapies with the most accumulated empirical support to date.[10-11] Recent meta-analyses indicate that CPT has the largest effect size of existing evidence-based treatments for PTSD in soldiers and Veterans[12] and across trauma populations (mean ES = 1.69)[27]. The effectiveness of CPT extends across patient populations suffering from a range of comorbid conditions including TBI, chronic child abuse histories, comorbid psychiatric and substance use disorders, and ongoing peritraumatic situations.[14-17] In fact, CPT is arguably our Veterans' best option for attenuation of the 20 core symptoms of PTSD. Given its demonstrated effectiveness, CPT is being widely disseminated through VHA.[18] CPT has been designated a first-line treatment in a number of clinical guidelines, including the VHA / Department of Defense (DoD) PTSD Clinical Practice Guidelines.[19] Since 2007, VHA has dedicated substantial resources and effort to the historic, large-scale dissemination of CPT via the Mental Health Dissemination Initiative.[20;18] To date, over *4,150* VHA providers have been trained in CPT and at least *20,774* Veterans have begun CPT in the last year. Yet the impact of CPT on both PTSD symptoms and psychosocial functioning can be improved. Among randomized clinical trials (RCTs) in active duty and Veteran populations, PTSD symptom effect sizes from pre- to posttreatment range from d = 0.78-1.02, about 35-40% fail to experience clinically-meaningful improvement, and only about one-third of patients no longer meet criteria for PTSD posttreatment.[11] Poor treatment outcomes are in part attributable to Veterans' low rates of treatment engagement. At least 35% of Veterans who initiate a course of CPT in VHA clinics fail to complete therapy, resulting in suboptimal doses of treatment.[21-22] Significant gains in occupational, social, leisure, and sexual functioning, quality of life, and health –related concerns have been realized in CPT clinical trials.[11;22] However, improvement in functioning and quality of life are more modest than those observed in PTSD and depression.[23]

Veterans with PTSD present to treatment with challenges in psychosocial functioning and other clinical complexities; the failure of our manualized treatments for PTSD to provide guidance on how to address these concerns is negatively impacting outcomes. Nearly all (87%) Veterans with PTSD presenting to VHA primary care have at least one comorbid psychiatric condition and, on average, Veterans with PTSD had 2.95 comorbid mental health diagnoses and over 50% reported suicidal ideation.[24] Across trauma populations, PTSD is associated with severe impairments in social and occupational functioning, exerting a more deleterious effect than most mental health diagnoses. Clinical presentations in Veterans suffering from PTSD are further complicated by a host of psychosocial stressors, impairments in major domains of functioning, and comorbid physical conditions. Veterans are more likely to be homeless, be under- or unemployed, and have



poor physical health status as compared to non-Veterans.[25-27] Our prior work suggests that unaddressed difficulties in these domains contributes to suboptimal outcomes and premature dropout from CPT among Veterans. We posit that frontline treatments for PTSD must be expanded to directly and intentionally target functional impairments and improve holistic outcomes.

Case Formulation-Integrated Cognitive Processing Therapy (CF-CPT). The success of CPT in treating the core symptoms of PTSD has been empirically established, but the needle has not moved as far toward recovery in achieving substantial improvement in functioning, quality of life, and well-being. The CF approach alters CPT in two important ways (see Figure 1). Traditional CPT specially targets the core symptoms of PTSD and, indirectly, through improvement in these core symptoms, positively influences functioning, quality of life, and well-being. But effect sizes in these outcomes are more modest than in primary outcomes (PTSD and depression), likely due, in part, to the fact that they are indirectly targeted. The dotted line in Figure 1. represents the scant amount of attention that is paid directly to domains of functioning in traditional CPT. Impairments in functioning are not routinely assessed or incorporated into therapy unless they are trauma-related, and then only at the end of therapy. CF-CPT also targets impairment in functioning indirectly through improvement in core symptoms of CPT (similarly to traditional CPT). Integrating CF into CPT offers the following two *additional* opportunities to intervene in impairment in functioning. First, expanding the protocol to intentionally address impairment in functioning *directly* targets relevant cognitions throughout therapy, increasing the focus on functional outcomes in a primary fashion. Second, enhancing the providers' latitude to explicitly address idiosyncratic challenges to optimal therapy outcomes (COTOS) that threaten patient engagement in and response to PTSD treatment enables more Veterans to realize more holistic outcomes.

While fidelity to the CPT protocol is essential, skillful divergences can be clinically wise. Administering EBPs in a standardized manner is critical to ensuring that patients receive an accurate and adequate dose of the intervention.[28] Yet, as outlined above, strict protocol adherence (e.g., failing to assess and address psychosocial stressors and other clinical complexities) may result in premature abandonment of trauma-focused therapy and/or suboptimal outcomes. Our team has empirically demonstrated that modifications to the CPT protocol can enhance therapy outcomes.[23] The next step in this program of research is to leverage the success of CPT in treating core symptoms of PTSD and expand the protocol to directly target functional outcomes. Thoughtfully and intentionally enhancing the latitude of the CPT protocol to target clinical complexities that pose a risk to holistic outcomes personalizes the delivery of care to best meet the individual patient's needs. Each of our prior trials successfully demonstrated the importance of modifications to CPT[23;29-31], while carefully considering risks inherent in incorporating too much flexibility into the protocol and potentially jeopardizing effectiveness[23;32-34]. We recognize that unstructured, generic counseling approaches for PTSD generally result in inferior outcomes.[35] The advantage of evidence-based protocols is that they provide a structure that

ensures that the clinician's focus remains on the issues that maintain PTSD. Given that avoidance of strong emotions and even therapy itself is common in PTSD sufferers, there is a real risk of clinicians unwittingly colluding with patients' avoidance of PTSD-specific topics, minimizing effective change.[36] Imparting clear parameters around thresholds of "clinical complexities" that warrant divergence from the protocol and principles for protocol-consistent deviations and expansions is necessary in flexing an EBP without compromising its efficacy. Our research also shows that expanding the CPT protocol to personalize the intervention and target the individual patient's concurrent clinical complexities and functional challenges has resulted in better overall response rates,[37] has translated to greater access to care for more patients suffering from complicated clinical presentations,[10] and has ***not*** compromised the efficacy of the traditional CPT protocol.[6]

There is little to no guidance in our trauma-focused therapy protocols to address clinical complexities and modify therapy accordingly. The perception of a forced choice between 1.) adherence to a manualized therapy and 2.) personalizing the protocol to best meet the patient's needs, leads to higher levels of dropout and poorer outcomes. Qualitative data collected by Dr. Kehle-Forbes (co-PI) suggest that overly rigid adherence to the treatment protocol is a common contributor to CPT dropout. Dr. Niles's (co-I) data from one VHA clinic demonstrated that in the face of treatment challenges, one-half of patients received a modified trauma-focused therapy.[39] However, patients who completed modified trauma-focused treatment had significantly worse outcomes than Veterans who completed standard trauma-focused therapy. The rationale for and content of the modifications was unknown. The other half of complex cases were switched to a different type of therapy and PTSD was no longer the target of treatment. Both Drs. Kehle-Forbes and Niles' data suggest that when faced with clinical complexities, there is no guidance for therapists to expand and enhance the protocol to accommodate patient needs, leaving therapists to initiate strategies lacking in evidence (likely resulting in the suboptimal outcomes reported by Dr. Niles) or abandon treating PTSD altogether to target the clinical complexity. Dr. Galovski's consultation experiences with VHA clinicians also suggest that providers struggle to achieve optimal outcomes when presented with the complexity of PTSD.

The unique and deleterious effect of PTSD symptoms on quality of life and psychosocial functioning is well-established within the United States Veteran population.[40] The impact of PTSD on important domains of psychosocial functioning can be chronic and enduring, exacting a significant toll on functioning even decades after exposure to the traumatic event.[41] Recent estimates suggest that over 610,000 US Veterans treated by the Veterans Health Administration (VHA) suffer from PTSD.[1] It is critical that the VHA identify modifiable targets for intervention that are implicated in the significant functional impairment associated with PTSD and, equally critical, to extend and enhance the success of evidence-based practices to address these targets. Controlled clinical trials assessing the efficacy of CPT, the EBP for PTSD most frequently delivered within VHA, have demonstrated large reductions in the primary outcomes of PTSD and depression[9] and have shown corresponding significant gains in occupational, social, leisure,

and sexual functioning, and in health-related concerns, including chronic pain.[42-43] However, improvements in functioning and quality of life are more modest than those observed in PTSD and depression.[44] Our prior work suggests that unaddressed difficulties in impairment in functioning contribute to suboptimal outcomes and premature dropout from EBPs for PTSD among Veterans due, in part, to the perceived lack of flexibility in CPT to attend to the complex and wide-ranging needs of Veterans. Further, the study team's prior research shows that enhancing the CPT protocol to personalize the intervention to target the individual patient's concurrent clinical complexities and challenges has resulted in better overall response rates,[23] has translated to greater engagement in care for a wider variety of patient populations suffering from complicated clinical presentations,[34] and has *not* compromised the efficacy of the traditional CPT protocol.[42] There is a great need to increase flexibility and person-centeredness within the CPT approach. Case formulation is an approach to treatment that is theoretically consistent with CPT and intentionally seeks to increase the Veteran's active involvement and agency in his or her own care.[45] The addition of explicit case formulation to the CPT protocol provides a framework for generalizing the effects of CPT to the significant PTSD-related challenges Veterans face across important domains of functioning. Building on the evidence base of CPT and the investment of the substantial VHA dissemination efforts and resources, we seek to increase the effectiveness of CPT beyond PTSD symptoms to directly address the psychosocial impairments and challenges that accompany this disorder and prevent Veterans from realizing the full benefits of the intervention and engaging fully in society.

Anticipated Impacts on Veterans Healthcare: Findings have the potential to increase the number of Veterans who benefit from one of the most effective treatments for posttraumatic stress disorder (PTSD), Cognitive Processing Therapy (CPT). In addition to reductions in PTSD symptomology, successful completion of CPT results in improvement in functional impairment, decreases in comorbid symptoms, and enhanced quality of life. This project tackles an important question for our colleagues within the Office of Mental Health and Suicide Prevention, who have expressed a need for strategies that enable flexibility while maintaining fidelity to the demonstrably efficacious CPT protocol. This proposal addresses RR&D's priority area of conducting research on cognitive behavioral therapy for Veterans with psychological health conditions.

2.0 Objectives

We hypothesize that integrating a case formulation (CF) approach into the existing CPT protocol will enable providers to simultaneously address Veterans' clinical complexities that interfere with CPT delivery and enhance functional outcomes, while maintaining fidelity to effective CPT principles. CF is a patient-centered, collaborative process between providers and patients.[45-46]CF allows providers to tailor cognitive-behavioral treatments to specific patients' unique clinical complexities within clear parameters of what justifies divergence from the standard protocol.[45-46] While CF is often considered a cornerstone of cognitive-behavioral

therapy, it has been deemphasized as disorder-specific treatments have been manualized for widespread dissemination.[47] A primary benefit of a CF approach is that it provides real-time, global, clinical guidance that enables providers to flexibly navigate the infinite range of clinical complexities and impairments that may present during treatment.[46] EBP treatment manuals and training workshops cannot provide explicit guidance on the universe of individual clinical complexities that may emerge during the course of therapy, nor can case consultation provide clinical guidance during sessions. Thus, guidance in adeptly navigating clinical complexities and associated therapy decision-making processes during therapy is essential.[48] Integrating a case formulation approach into CPT provides therapists with the tools to effectively navigate the fine line between maintaining the trauma-focus necessary to treat PTSD and attending to the clinical complexities and functional impairments that contribute to suboptimal doses of therapy and/or poorer outcomes. In mental health disorders other than PTSD, explicitly integrating a CF approach into EBPs has been associated with the patient becoming more actively involved in his/her own care, greater provider and patient collaboration, and with providers reporting a more robust understanding of their patients' needs.[38-39;49-52] Dr. Nixon's (co-I) open trial[32] and ongoing pilot RCT provides preliminary evidence that integrating a CF approach into CPT yields lower dropout rates and a higher rate of loss of PTSD diagnosis than typically observed in standard CPT. Thus, we seek to improve the clinical effectiveness of CPT by integrating a CF approach that will enable VA providers to directly target impairments in functioning and flexibly address clinical complexities that arise during the delivery of the CPT protocol.

Specific Aims: Recent estimates suggest that over 610,000 US Veterans treated by the Veterans Health Administration (VHA) suffer from PTSD, a disorder that can be chronic and debilitating.[1] The heterogeneity of the 20 symptoms of PTSD; comorbidity with disorders such as depression, panic, and substance use; high rates of concurrent and lingering effects of physical injury (including traumatic brain injury [TBI]); and suicidality all contribute to complex clinical presentations[2-4;5] and can exact a significant toll on functioning, quality of life, and well-being even decades after exposure to the traumatic event.[2]

Cognitive Processing Therapy (CPT), the evidence-based psychotherapy (EBP) for PTSD most frequently delivered within VHA, yields large magnitude reductions in primary PTSD outcomes.[9-10;12] Corresponding gains in occupational, social, leisure, and sexual functioning, and in health-related concerns, including chronic pain have also been demonstrated.[4-5; 40-44;53-54] Despite CPT's effectiveness, there is room for improvement in overall outcomes (about 2/3 retain their PTSD diagnosis) and patient engagement (35-40% drop out prior to treatment completion)[10-12] Further, Improvements in functioning and quality of life are more modest than those observed in PTSD and associated mental health symptoms. Our prior work suggests that unaddressed difficulties in functioning contribute to premature dropout from EBPs for PTSD among Veterans. Directly targeting impairments associated with psychosocial functioning has the potential to substantially increase the scope of recovery beyond the core symptoms of PTSD and facilitate greater patient engagement, resulting in more Veterans benefitting from CPT. Our prior

research shows that modifying the CPT protocol to personalize the intervention for the individual patient has resulted in better overall response rates[23;28;32-34] for a wider variety of patient populations suffering from complicated clinical presentations.[34]

Case formulation (CF) is a well-established approach to cognitive-behavioral treatment that facilitates a collaborative process between providers and patients to guide the tailoring of treatment to meet idiosyncratic patient needs.[38;49-50] Integrating CF strategies into the existing CPT protocol will enable providers to personalize CPT to directly address impairment in functioning as well as provide the latitude to directly intervene with the complex challenges that threaten optimal outcomes within the context of trauma-focused therapy. CF-integrated CPT (CF-CPT) *expands and enhances* the CPT protocol to facilitate a personalized and flexible approach to treating PTSD that prioritizes the administration of the full dose of CPT while expanding the protocol to directly target important domains of functioning and result in more holistic outcomes. Our open trial of CF-CPT has yielded lower levels of dropout and a higher proportion of treatment responders than published accounts of standard CPT.[32]

We are proposing a randomized control trial in which we will randomize a national sample of up to 325 Veterans to receive either CF-CPT or CPT to achieve the following:

Aim 1: Compare the relative **effectiveness of CF-CPT to CPT** in improving primary outcomes:

1. **Veterans' psychosocial functioning** *(*Veterans who receive CF-CPT will demonstrate greater improvements in functioning (and, more broadly, quality of life and well-being) over the course of treatment and 3-month follow-up than Veterans who receive CPT)
2. **Veterans' PTSD and depression symptoms** *(*Veterans who receive CF-CPT will demonstrate greater reductions in PTSD and depression over the course of treatment and 3-month follow-up than those who receive CPT).

Aim 2: Determine the effectiveness of CF-CPT as compared to CPT in improving Veterans' treatment engagement (CF-CPT will demonstrate higher rates of Veteran treatment completion than CPT)

Aim 3: Evaluate CF-CPT's indirect impact on Veterans' psychosocial functioning and PTSD/depression symptomology Change in functioning, quality of life, and well-being & PTSD and depression will be associated with improvement in the idiosyncratic clinical challenges (COTOs) targeted by the CF.

We will also examine between-group differences across secondary outcomes (e.g., anger, anxiety, health concerns, sleep, numbing/reactivity) and describe the frequency and type of the clinical and rehabilitative needs of the Veterans and the type and duration of divergences (e.g. rehabilitative techniques) made by providers. This proposal addresses RR&D's priority area of conducting research on cognitive behavioral therapy for Veterans with psychological health conditions.

3.0 Resources and Personnel

Name	Location	Role	VA Affiliation
Tara Galovski, Ph.D.	VA Boston Healthcare System 150 S. Huntington Ave. Boston, MA 02130	Co-Principal Investigator	Employee
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Barbara Niles, Ph.D.	VA Boston Healthcare System 150 S. Huntington Ave. Boston, MA 02130	Co-Investigator	Employee
Brian Smith, Ph.D.	VA Boston Healthcare System 150 S. Huntington Ave. Boston, MA 02130	Co-Investigator	Employee
Dawne Vogt, Ph.D.	VA Boston Healthcare System 150 S. Huntington Ave. Boston, MA 02130	Co-Investigator	Employee
Jennifer Schuster-Wachen, Ph.D.	VA Boston Healthcare System 150 S. Huntington Ave. Boston, MA 02130	Co-Investigator	Employee
Reg Nixon, Ph.D.	Social Sciences North (SSN341) GPO Box 2100 Adelaide 5001, South Australia	Co-Investigator	None

- **Tara Galovski, Ph.D.** – Co-Principal Investigator, will assume overall responsibility for the management of the proposed project in collaboration with Dr. Kehle-Forbes (PI). Dr. Galovski will have primary responsibility for the recruitment, training, and consultation of study providers. She will also have primary responsibility for coordinating the independent fidelity ratings. Dr. Galovski will oversee the administration of the Clinician-Administered Veteran Assessments. She will take primary responsibility for

initial assessor training and maintaining the reliability of the assessors throughout the study. She will also oversee the tracking and scheduling Veterans for these assessments. Given that consent will often occur immediately prior to the administration of the clinician-administered assessment, Dr. Galovski will also oversee the Veteran consent process. Dr. Galovski will oversee grant administration, co-lead the preparation of manuscripts, co-lead the dissemination of the overall study results, and lead the general project administration team at VA Boston. Dr. Galovski will have access to protected health information, involved in recruiting subjects; obtaining informed consent; administering survey/interview procedures; and performing data analysis.

- **Shannon Kehle-Forbes, Ph.D.** – Co-Principal Investigator, will assume overall responsibility for the management of the proposed project in collaboration with Dr. Galovski (corresponding PI). Dr. Kehle-Forbes will direct the administration and management of self-report measure, data extraction from medical records, prepare manuscripts, co-lead the dissemination of the overall study results, and lead the general project administration team at the Minneapolis VAHCS. Dr. Kehle-Forbes will have access to protected health information, will be involved in recruiting subjects; will participate in obtaining informed consent, administering survey/interview procedures, and performing data analysis.

- **Barbara Niles, Ph.D.** – Co-investigator, will oversee contribution to the development of the provider survey and collection of process data consistent with Aims 2 and 3. With respect to Aim 1, Dr. Niles will assist with continued assessment and refinement of our understanding of challenges and obstacles to implementing evidence-based practices in VA clinics. She will contribute to manuscript and presentation preparation on these outcomes. Dr. Niles will not have access to data.
- **Brian Smith, Ph.D.** – Co-investigator, will be the study team's lead statistician at the Boston site specifically for Aim 1, ensuring that the analyses are conducted appropriately, and he will also collaborate on reports and other research products (presentations and publications) resulting from these data. Dr. Smith will have access to protected health information and perform data analysis.

- **Dawne Vogt, Ph.D.** – Co-investigator, will offer expertise and guidance on the assessment and measurement of our primary outcomes (functioning, quality of life and well-being) and will also collaborate on reports and other research products (presentations and publications) resulting from these data. Dr. Vogt will not have access to the data.
- **Jennifer Schuster-Wachen, Ph.D.** – Co-investigator, will train and supervise the CPT providers in implementing the CF-CPT protocol. She also will organize and supervise performance of CPT session fidelity ratings and share in management of screening evaluations and consensus diagnostic meetings as needed. As a local expert and national trainer in CPT, Dr. Schuster is able to provide the specialized training in this treatment modality (CF-CPT) and supervision in close collaboration with the PI. Dr. Schuster will also participate in manuscript preparation. Dr. Schuster-Wachen will not have access to data.
- **Reg Nixon, Ph.D.** – Co-investigator, will provide ongoing consultation to the study team on the integration of the two therapies. Dr. Nixon will aid the team in maintaining fidelity to the intervention. He will assist in the interpretation of data analyses and manuscript development. No data will be collected or sent to Dr. Nixon.

4.0 Study Procedures

5.1 Study Design

Overview and Rationale for Methods. To accomplish the study aims, we are proposing to randomize up to 325 Veterans at up to 10 VA sites who will be treated by VHA CPT providers. Because the efficacy of CPT is already well-established, we will increase the external validity of the project, by including: (a) broad provider and Veteran inclusion criteria, (b) employing CPT delivered in accordance with VHA's CPT Dissemination Initiative as the comparison condition, and (c) avoiding the use of study-team strategies to improve Veterans' engagement, and utilizing ITT analyses.

In order to achieve study aims, we will randomize up to 325 Veterans at up to 10 VA sites to receive either CPT or CF-CPT. Study providers will deliver the treatment to up to 15 consecutive Veterans who present for CPT treatment in his/her clinic and who consent to study participation.

Our method will include centralized recruitment, enrollment, and data collection. In addition, a local site investigator (LSI) will be at each site (assisted by a part-time research assistant) and providers will function as study staff. Only therapy materials will be collected as data at the clinical sites. This method allows standardization of recruitment and data collection efforts and reduces administrative burden at each study site.

Study Procedures and Data Collection. Participants will be assessed prior to treatment (pretreatment), mid-treatment, two weeks after the conclusion of treatment or fourteen weeks after study initiation for treatment dropouts (posttreatment), and twelve weeks after the posttreatment assessment (follow-up). Over the course of the study, patient data will be collected by a) interviews delivered via phone or VA Video Connect (VVC), b) online survey via Qualtrics or, if preferred by Veteran, via mailed paper and pencil survey, c) retrieval from electronic medical records (EMR) and, d) local site therapy materials collected by clinical site study staff. Veterans will complete the phone interview and survey at each assessment time point (pre, mid, post, and follow-up). Participants will be paid $50 for each completed interview and $25 for each completed packet of questionnaires. Thus, patients can receive up to $75 at each major assessment interval. Participants will not be paid for treatment or completing the therapy materials.

Phone or VA Video Connect (VVC) Interviews. All diagnostic and clinical interviews will be conducted by an independent evaluator (IE), blinded to study condition, by telephone or VA Video Connect (VVC). The use of VA Video Connect (VVC) will decreased barriers for Veterans who do not have access to a cell phone/land line. IEs participate in four stages of training: relevant readings, classroom instruction with an expert in the field, mock interviews with co-workers, and co-rating exercises with previously taped assessments. After the completion of training, all IEs will engage in weekly calibration exercises to ensure that they continue to meet high quality standards and prevent drift in scoring. IEs will collect all data from phone interviews with patients.

Self-report surveys will be used to assess secondary outcomes. Baseline, mid-treatment, posttreatment, and three-month follow-up self-report assessments will be primarily delivered via VA Qualtrics or if preferred by Veteran, paper and pencil survey which can be completed at home or in clinic and returned via mail to the coordinating site via prepaid envelope or given to local clinical site staff who will return it to the coordinating center. VA Qualtrics is an interactive web-based survey program. Participants without access to a device to complete the assessment can opt for paper and pencil surveys completed at home or at their study site. We will track survey response and implement an evidence based multi-modal follow-up protocol, including multiple contacts, reminders, and outreach designed to optimize response rates at each data collection time point. See the Table 1 below for details regarding the electronic survey follow-up protocol. For those participants completing surveys online, participants will receive reminders / notifications via text / email (using all channels previously agreed to by Veteran). Non-respondents will receive up to four reminder emails and/or texts with links to the survey, and we will make up to six outreach calls to confirm email addresses, receipt of survey, encourage completion of follow-up surveys, and answer questions or concerns about the study. Coinciding with the third email reminder, we will implement a sequential mixed mode survey approach, whereby non-responders will be sent a paper and pencil questionnaire and postage paid return

envelope. Mixed-mode data collection procedures such as this can both increase response rates and improve sample composition by reaching non-respondents who have been unable to respond to requests to complete the web-based survey. Additional retention activities (e.g., offering completion of survey while at VA for other medical appointments, completion via phone) will be employed as necessary.

Table 1. Electronic survey delivery protocol.

Time	***Text/Email***	***Phone Call***	***Mailing***
Day prior to scheduled assessment	Alert that survey will arrive next day [mid/post/follow up only]		
Day 0	Confidential link to survey sent		
24 Hours after last survey activity	Reminder to partial survey completers		
Day 3	First reminder with survey link	Begin weekly follow-up outreach calls	
Day 9	Second reminder with survey link	Continue outreach calls	
Day 15	Third reminder with survey link	Continue outreach calls	Hard copy survey with cover letter and postage paid return envelope and therapist prompt
Day 21	Fourth and final reminder with survey link	Continue outreach calls	Hard copy survey with cover letter and postage paid return envelope and therapist prompt
*2 days prior to first therapy appointment [baseline survey only]		Reminder to complete survey	

**If needed*

Paper and Pencil Survey. The choice to complete self-report measures by paper and pencil is available to any patient participant. If the patient prefers this method, the patient can complete measures by paper and pencil and return via mail to the coordinating center. The research team also has extensive experience using mailed surveys to collect reliable and valid information from Veterans with PTSD. We have developed a standardized modification of Dillman's technique.[55] First, an introductory letter is mailed, followed by a cover letter and survey. At one to two-week intervals, non-respondents are mailed a second survey and then a final survey using overnight mailing. Veterans will be instructed to mail the survey back to study staff using a pre-addressed, stamped envelope. If the completed survey is not received within one week of study enrollment, the modified Dillman protocol outlined above will be enacted (e.g., reminder emails and/or texts).

Non responders. Veteran who cannot be reached by the methods described above will be mailed a letter at post and follow-up reminding them it's time to complete their assessment. The letter will provide instructions on how to reach study staff. Veterans may also receive an email/text.

EMR Data Collection. Providers will be instructed to use nationally available CPT progress note templates to document CF-CPT and TAU-CPT delivery (as required by the CPT Dissemination Initiative). During training, providers will be instructed to include two additional items in the templates: 1) CF-specific treatment elements (CF-CPT providers only) and 2) the provider's perception of the Veteran's engagement in the treatment session. A Word document with these elements that can be copied and pasted into the template will be available to providers to facilitate this documentation. To ensure compliance, providers will receive personalized feedback from study staff if they fail to include these elements in their session notes. Two independent study staff members will manually extract data from the progress notes from the national EMR using JLV. Additional information extracted from the national EMR using JLV includes other mental health treatment received during the study period. The national EMR will also be used to determine patients' eligibility.

Therapy Material Data Collection. Data will be collected and managed by the coordinating center sites. Providers will be instructed to collect therapy materials under the oversight of the LSI. Lead study sites will collect the therapy data either through secure electronic VA data transfer or by obtaining hard copies of therapy materials either in person or through the mail.

Treatment Delivery. All treatment will be delivered in individual therapy sessions by rostered or roster eligible CPT providers delivered either in-person or via telehealth using platforms approved for clinical care by VHA. Treatment can be delivered in any type of VA clinic. All therapy sessions will be audio-recorded (recorded directly into the secured study network folder).

Providers. Providers will be VHA clinicians who have been trained in CPT, are listed on the CPT National Provider Roster, or are CPT roster eligible. Clinicians who are currently "in training" to become CPT providers will be excluded from participation. Providers will be assigned to deliver either CPT or CF-CPT. Providers will only deliver one condition to minimize therapist drift and possible contamination effects.

Provider Training. All providers will begin participation in the study with a 3-hour training delivered in an interactive online format (e.g. Lync) in groups of up to 8 providers. This training will differ by condition. CPT providers will receive a 30-minute overview of study-specific procedures (recruitment, tracking, template use) and a generic refresher of CPT currently used by the CPT Dissemination Initiative. The CF-CPT group will receive a similar overview of study procedures and an explicit training of the use of the CF approach. The CF-CPT group will then receive a second 3-hour training delivered one week later and will consist of a series of case examples, role plays, and interactive exercises designed to further instruct the CF-CPT therapists in the administration of case formulation. Both groups will be scheduled for weekly consultation calls for continued guidance in implementing their assigned treatment condition (CF-CPT or CPT in accordance with the CPT Dissemination Initiative).

Delivery of TAU-CPT. Providers delivering TAU-CPT intervention will be asked to continue to deliver the treatment as they have been in regular clinical practice. The only difference will be the additional information requested in the session progress notes. We will describe the study goals - seeking to understand challenges to optimal therapy outcomes during the delivery of CPT and directly target functional concerns of patients. Consultation will ensure that therapists maintain fidelity to the CPT protocol. Variable length CPT is now standard practice and providers conclude treatment as indicated by patient progress. For the purposes of matching the total allowable dose of therapy to the CF-CPT condition, we will stipulate that treatment should not exceed 20 sessions or 26 weeks.

Delivery of CF-CPT. Procedurally, the administration of CF-CPT will map onto that of CPT. Both therapies will be administered on a weekly basis by licensed CPT providers in VHA clinics. The CPT protocols will be modified with the CF-CPT approach in three ways. First CF-CPT will begin with the case formulation assessment. Feedback from the case formulation session will be incorporated into the traditional CPT session 1, allowing time to continue developing the individualized monitoring tool (daily diary). Second, patients in CF-CPT will monitor identified COTOs throughout therapy via the daily diary. Third, patients in CF-CPT will also be instructed to apply CPT specific skills to COTOs and functioning related cognitions during practice assignments, etc. Thus, the assessment, monitoring, and challenging of COTOs in the CF-CPT condition (but not in CPT) will render the two therapy conditions different. In addition to these standardized modifications of CPT with case formulation, for some portion of the CF-CPT group (our ongoing trial suggests approximately 66%), identified COTOs will present increase during the course of CPT. For only those patients for whom it is necessary (as operationalized in the

manual), the content of the therapy may be altered accordingly to personalize the therapy and address the patient's idiosyncratic needs.

Clinical Case Consultation and Fidelity Assessments. To ensure that each condition is delivered in the way in which it was intended, case consultation will be provided to all providers on a weekly basis. Including case consultation in both conditions will also equate the conditions, ensuring that any observed effects are due to intervention differences, not the presence of supervision in one group. The CPT consultation calls will be consistent with those currently conducted in the CPT Dissemination Initiative. Drs. Galovski and Wachen are national trainers and consultants with years of experience in conducting CPT consultation to VHA providers. In addition to weekly consultation to assure ongoing treatment fidelity to each condition, adherence and competence will be determined by independent and expert raters who are not otherwise involved in the project. Consultants will monitor COTOs and divergences (or lack thereof) in each study condition via the fidelity checklist included in the Adherence and Competence Manual. This study will use a hybrid expanded CPT fidelity manual (described in Farmer et al.,[28] which more closely tracks the inclusion of CPT elements as well as proscribed elements) complemented by the CF specific manual developed in the Australian trial and informed by Page et al.[56] The same manual will be used in both conditions so that the presence and/or absence of CF elements in both conditions can be evaluated. All sessions will be recorded for possible selection for fidelity rating. Recordings will be sent via UPS, FedEx, or DHL and tracked for receipt to the raters, will be uploaded to a secure database or will be stored and shared using VA Box. VA Box is a secure, cloud-based, commercial file storage, sharing, and collaboration service. It is a collaboration tool that can be used from any device with the security, scalability and administrative controls that VA requires. The session recording may contain PHI, despite requests do not include sensitive information. Data will be stored, managed, and analyzed in a secure research environment. We will randomly select 15% for rating and determination of inter-rater reliabilities.

Veteran participants will be receiving the same level of care that they normally would have received in a VA clinic for the treatment of PTSD. It is possible that in discussing one's traumatic event and resultant PTSD, the patient can be become distressed. However, the therapy is designed to decrease that distress and so the potential long term benefit greatly outweighs the risk.

Provider Qualitative Interview

VA PATh providers who have delivered CF-CPT or CPT to at least two Veterans enrolled in the PATh are eligible to participate in the qualitative interviews. The rule of two ensures the PATh provider has sufficient experience to provide meaningful insights. Providers will take part in one-on-one qualitative interviews conducted by study staff designed to explore their experiences, challenges, and perspectives related to delivering CF-CPT or CPT to Veterans within the context of the PATh Study.

The interviews will be conducted in person, by phone, or via a secure VA-approved video conferencing platform such as VA Video Connect. Each interview will last approximately 30 to 45 minutes and will focus on open-ended questions to elicit detailed responses about the participants' professional experiences. With participants' consent, all interviews will be audio-recorded to ensure accuracy during transcription and analysis. The recordings will be securely stored on VA-approved, encrypted systems and will be deleted after transcription and analysis are complete.

Recruitment will involve contacting potential providers via email or phone using available PATh Study records. Each individual will receive detailed information about the interview's purpose, procedures, voluntary nature, and confidentiality measures. Participants will not receive financial compensation for their involvement, as their participation is voluntary and based on their professional experience.

Informed consent will be obtained verbally by study staff before the start of the interview. Supervisors or department chiefs will not conduct consenting for qualitative interviews. During this process, participants will be informed about the interview's objectives, procedures, potential risks, benefits, confidentiality measures, right to withdraw at any time without penalty, and that participation will not impact their job, performance evaluations, or employment status in any way, either positively or negatively. All data will be securely stored and accessible only to authorized study team members.

Study population

Up to 400 Veteran participants will be screened and up to 325 Veteran participants will be enrolled.

Our inclusion / exclusion criteria were selected to reflect the population with whom CF-CPT would be used with in routine clinical care. We excluded those without PTSD (as CPT is a PTSD-specific treatment) and also excluded those with other psychiatric conditions that would take clinical precedence or preclude participation (e.g. active mania, active psychosis). We did not exclude any vulnerable populations that would be seeking outpatient mental health care at VA; which means that pregnant women will not be excluded. No specific human subject protections are required for pregnant women; cognitive processing therapy is routinely delivered to pregnant women in clinical care. Untreated PTSD poses a significantly greater risk to pregnant women than participating in evidence-based psychotherapy.

5.2 Recruitment Methods

In order to achieve study aims, we will randomize up to 325 Veterans at up to 10 VA sites to receive either CPT or CF-CPT. We will allow up to 45 study providers across all VA sites. Study providers will deliver the treatment to up to 15 consecutive Veterans presenting for CPT treatment in his/her clinic who consent to study participation. We will identify up to 10 sites with

at least 3 CPT therapists who are each able to treat up to 15 study patients with PTSD over 2.5 years.

Veteran Recruitment. To avoid selection bias in patient population, all consecutive Veterans with whom a study provider is intending to begin a course of individually delivered CPT will be offered study participation until up to 15 Veterans per study therapist are enrolled to reach the total goal of 200 Veterans randomized. Thus, in order to be invited to participate, Veterans will have been identified as PTSD positive per clinic screening processes.

Recruitment materials:

Veterans will be notified of the study by a CPT-TAU or CF-CPT provider at their local clinical site. They will give the Veteran a pamphlet/fact sheet and a brief description of the study and ask the Veteran for consent to be contacted by the study team to learn more. In order to prevent undue influence and coercion of the patient by the study provider, study staff will instruct study providers to assure the veterans that participation is voluntary and that there are no consequences to declining participation in the study (e.g. CPT treatment as usual will be available by the same study provider outside of the study). Further, the potential participant will be made aware of other treatment options including other evidence-based psychotherapy such as Prolonged Exposure, pharmacotherapy, etc.

Subject payments

Veterans can be compensated up to $400 in total. The payments for each activity are as follows; Baseline interview = $50, baseline survey = $25, mid-treatment interview=$50, mid-treatment survey = $25, post-treatment interview = $100, post-treatment survey = $25, 3-month follow-up interview = $100, 3-month follow-up survey = $25.

5.3 Informed Consent Procedure

Once Veterans give consent to be contacted by study staff as described above, they will be mailed an informational handout, a combined informed consent form with HIPAA Authorization, and a stamped addressed envelope to return the documents back to study staff if they choose to use the paper informed consent. Veterans will also receive a phone call from a study staff member by telephone for initial screening and completion of informed consent procedures. During a telephone call, a member of the study staff will complete a phone screen to determine potential eligibility. In addition, the study staff member will walk through the combined informed consent form with HIPAA form; all study procedures (assessment data gathering, intervention, audiotaping) will be fully described to the participant. Participants will be informed of the study design and will receive a full description of the treatment they will

receive before they decide to participate. Staff will solicit and answer all questions, and they will also ask the participants' questions to ensure participant comprehension of the informed consent document including, but not limited to, what their understanding is of the risks and benefits of participation, when assessments will occur and what topics they will cover. After reviewing the study and answering all questions, those who remain interested in participating will sign the informed consent documents. Veterans can sign the paper informed consent and return by mail or Veterans can choose to receive an electronic copy of the informed consent and return electronically as described below. For those who want additional time to consider participation, a follow-up appointment will be scheduled to complete the informed consent process.

Veterans will be provided with a menu of options for providing informed consent remotely including: (1) combined informed consent and HIPAA form mailed to the Veteran and returned by mail to study staff (described above), (2)) combined informed consent and HIPAA form mailed to the veteran are signed, scanned, and returned via MyHealtheVet or encrypted email (Azure RMS), (3) combined informed consent and HIPAA form sent and returned via MyHealtheVet, (4) combined informed consent and HIPAA form sent and returned via encrypted email (Azure RMS), or (5) combined informed consent and HIPAA form sent and signed via DocuSign . Veterans will either receive the document at the time of consent or in advance, depending on the channel used to distribute the informed consent document and patient preference. Specifically, patients who express interest in participating during the initial phone call and eligibility screen and who are able to receive the combined informed consent and HIPAA form document electronically can receive the document and complete the combined informed consent and HIPAA during the phone call immediately. Either during or after the call, they would then sign and return the informed consent document. However, if patients prefer additional time to read the document themselves prior to signing the combined informed consent and HIPAA form, a follow-up call will be scheduled to answer any further questions.

All study personnel will complete human subjects training prior to consenting patients. All consenting will be done by the Minneapolis & Boston Coordinating center staff. Drs. Kehle-Forbes & Galovski will train study staff at their sites in the elements of informed consent and the procedure for obtaining informed consent; training will include a competence test overseen by the study PIs. The procedures will also be detailed in the study SOP manual.

Informed consent will be obtained before obtaining any baseline self-reports or baseline interviews. The baseline interview is necessary for establishing final eligibility. Veterans will be notified that the baseline procedures are necessary for establishing final eligibility and they may be deemed ineligible for the study after these procedures. Those who meet final inclusion/exclusion criteria and remain interested will begin the treatment to which their provider has been randomized..

The following activities will occur prior to obtaining informed consent:

- Identification & screening of potential participants

5.4 Inclusion/Exclusion Criteria

Once Veterans express interest in participation to the CPT provider and sign the informed consent document, they will complete a diagnostic interview with study staff blinded to condition in order to confirm a full diagnosis of PTSD. Veteran's will receive a confirmation email and/or text message upon scheduling and a curtesy reminder one day prior to the interview to the interview. A full diagnosis of PTSD (per the Clinician Administered PTSD Scale [CAPS-5])[57] is required for inclusion in the study. Study exclusion criteria include active suicidal ideation with intent, homicidality, current mania, illiteracy, psychosis, or serious drug or alcohol abuse that requires immediate medical attention (e.g. inpatient care) as determined by chart review and with follow-up questions and discussions with treating clinician if necessary. Patients should not be participating in another trauma-focused therapy at the time of enrollment but can continue any psychiatric medications (dose must be stable for one month prior to enrollment). Medication changes will not be prohibited for Veterans in either treatment arm following baseline assessment and randomization. In fact, pharmacological additions or modifications may be warranted in response to COTOs in the CF-CPT condition. Changes in psychiatric medications during the study period will be extracted from the electronic medical record (EMR) at study completion.

Study staff will determine final eligibility based upon baseline interview. Study staff will inform the provider and veteran of eligibility status within 7 days of the baseline interview. If eligible, patient begins treatment.

Providers must be existing roster VA Cognitive Processing Therapy providers or CPT roster eligible. They must also receive their supervisors' permission to participate in the study.

5.5 Study Evaluations

Phone or VA Video Connect (VVC) Interviews. All diagnostic and clinical interviews will be conducted by an independent evaluator (IE), blinded to study condition, by telephone or VA Video Connect (VVC). The use of VA Video Connect (VVC) will decreased barriers for Veterans who do not have access to a cell phone/land line. IEs participate in four stages of training: relevant readings, classroom instruction with an expert in the field, mock interviews with co-workers, and co-rating exercises with previously taped assessments. After the completion of training, all IEs will engage in weekly calibration exercises to ensure that they continue to meet high quality standards and prevent drift in scoring. IEs will collect all data from phone interviews with patients.

Online or Paper and Pencil Survey. Baseline, mid-treatment, posttreatment, and three-month follow-up self-report assessments will be collected online via VA Qualtrics or if preferred by Veteran, via mailed paper and pencil survey. VA Qualtrics is an interactive web-based survey program. Participants without access to a device to complete the

assessment can opt for mailed paper and pencil surveys completed at home or at their study site. We will track survey response, and implement an evidence based multi-modal follow-up protocol, including multiple contacts, reminders, and outreach designed to optimize response rates at each data collection time point. Participants will receive reminders / notifications via text / email. Non-respondents will receive up to four reminder emails and/or texts with links to the survey, and we will make up to six outreach calls to confirm email addresses, receipt of survey, encourage completion of follow-up surveys, and answer questions or concerns about the study. Coinciding with the third email reminder, we will implement a sequential mixed mode survey approach, whereby non-responders will be sent a paper and pencil questionnaire and postage paid return envelope. Mixed-mode data collection procedures such as this can both increase response rates and improve sample composition by reaching non-respondents who have been unable to respond to requests to complete the web-based survey. Additional retention activities (e.g., offering completion of survey while at VA for other medical appointments, completion via phone) will be employed as necessary.

If a participant prefers paper and pencil surveys, the patient can complete measures by paper and pencil and mail the survey back to study staff using a pre-addressed, stamped envelope. The research team has extensive experience using mailed surveys to collect reliable and valid information from Veterans with PTSD. We have developed a standardized modification of Dillman's technique.[58] First, an introductory letter is mailed, followed by a cover letter and survey. At one to two-week intervals, non-respondents are mailed a post-card reminder, a second survey, and then a final survey using overnight mailing (UPS).

Measures. See Table 2 for a full list of study assessments. In addition to outcomes specified in the study specific aims, we will measure constructs and conditions associated with each COTO domain. While we are not able to formally assess the universe of possible COTOs for each participant, we selected standardized measures for those that we believe are most likely to arise. For those randomized to CF-CPT, we will also utilize the Daily Monitoring Diary completed throughout the course of treatment as an idiosyncratic measure of all relevant COTOs for the individual patient. These measures will provide an overview of baseline severity in these domains as well as change over the course of the intervention (please note, outcomes that could also be considered COTOs [e.g., depression or functioning] are listed only as Outcomes in Table 1). All interview and survey measures are standardized, well-established, and have excellent psychometric properties. All therapy materials (Daily Monitoring Dairy; weekly PCL and PHQ-9 assessments) will be returned to study staff at treatment completion. Data from the Daily Monitoring Diaries may also be collected by study staff weekly via telephone call prior to treatment sessions. Data collected during these calls will be entered into a locally-stored fillable pdf of the diaries, then stored in secure VA folders as study data. This data will

also be sent to the participant's study provider via encrypted email prior to each weekly session.

Table 1. Assessment Schedule

Construct / Domain of Interest	Measure	Interval Assessed	Source
Aim 1 Outcomes			
PTSD-related psychosocial functioning (primary)	Inventory of Psychosocial Functioning (IPS)[55]	Pre, Mid, Post, FU	Online or Mailed Survey, or telephone
Functioning & disability	World Health Organization – Disability Assessment Schedule 2.0 (WHO-DASII)[59]	Pre, Mid, Post, FU	Online or Mailed Survey
Quality of life	World Health Organization - Quality of Life, Brief (WHOQOL-BREF)[60]	Pre, Mid, Post, FU	Online or Mailed Survey
Well-being	Well-Being Inventory (WBI)[61]	Pre, Mid, Post, FU	Online or Mailed Survey
Clinician-assessed PTSD (primary)	Clinician Administered PTSD Scale-5 (CAPS-5)[57]	Pre, Mid, Post, FU	Telephone or VA Video Connect (VVC)
Self-reported PTSD	PTSD Checklist –DSM-5 (PCL)[62]	Pre, Mid, Post, FU Weekly	Online or Mailed Survey & Therapy Session
Self-reported depression	Patient Health Questionnaire-9 (PHQ-9)[63]	Pre, Mid, Post, FU Weekly	Online or Mailed Survey & Therapy Session
Aim 2 Outcome			
Treatment completion	Final session progress note (indicated by use of final session template or note text)	Post	EMR

Treatment Engagement	Therapist Rating Scale	Weekly	EMR
Potential COTOs / Exploratory Outcomes			
Comorbid mental health conditions	DSM-5 Level 1 Cross-Cutting Symptom Measure [64]	Pre, Mid, Post, FU	Online or Mailed Survey
Minor life events / hassles	Weekly Stress Inventory[65]	Pre, Mid, Post, FU	Online or Mailed Survey
Health concerns, conditions	Veterans Rand Short Form[66]	Pre, Mid, Post, FU	Online or Mailed Survey
Sleep	Pittsburgh Sleep Quality Index (PSQI)[67]	Pre, Mid, Post, FU	Online or Mailed Survey
Chronic pain	PEG Measure[68]	Pre, Mid, Post, FU	Online or Mailed Survey
Anxiety	State-Trait Anxiety Inventory[69]	Pre, Mid, Post, FU	Online or Mailed Survey
Numbing/reactivity	Emotional Reactivity and Numbing Scale[70]	Pre, Mid, Post, FU	Online or Mailed Survey
Anger	Dimensions of Anger Reactions-5[71]	Pre, Mid, Post, FU	Online or Mailed Survey
Suicidal Ideation	Beck Suicidal Ideation Scale[72]	Pre, Mid, Post, FU	Online or Mailed Survey
Alcohol & drug use / Craving	Brief Addiction Monitor (use & craving subscales)[73]	Pre, Mid, Post, FU	Online or Mailed Survey
PTSD-related readiness to change	University of Rhode Island Change Assessment[74]	Pre, Mid, Post, FU	Online or Mailed Survey
Patient use of CPT skills	Skills of Cognitive Processing Therapy Measure – Patient Version	Mid, Post, FU	Online or Mailed Survey
Patient use of CPT skills	Skills of Cognitive Processing	Mid, Post,	Online or

	Therapy Measure – Therapist Version		Mailed Survey
Provider experiences providing CPT	PATh Provider Interview Guide	Post	Telephone or VA Teams
Idiosyncratic COTOs (for use in CF-CPT & Aim 3)			
Idiosyncratic COTOs (CF-CPT only)	Daily Monitoring Diary[77]	Weekly	Therapy Session
Descriptive Measures			
Demographics	PhenX Demographic Questionnaire	Pre	Online or Mailed Survey
Trauma History	Locally constructed trauma interview	Pre, Mid, Post, FU	Interview via telephone or VA Video Connect (VVC)

5.6 Data Analysis

Providers will inform the next up to 15 eligible Veterans who are seeking treatment for PTSD (and willing to learn more) about the study. Study staff will access the national electronic medical record through Joint Legacy Viewer (JLV) in order to confirm no exclusion criteria is present per participants' medical record, to track mental health treatment during the study period, and to collect treatment specific data from progress notes. As this is a multi-site study, access of Veterans' electronic medical records will be needed on a national level using JLV, as well as local CPRS. Because the patients and eligibility criteria will be known to the providers, we anticipate a relatively low screen failure rate. We anticipate that we will screen upwards of 400 patients and enroll up to 325. Based on previous clinical trials, we anticipate that up to approximately 25% will discontinue participation and be lost to follow-up.

With an anticipated sample size of 200 veterans, we should have more than adequate power to detect meaningful differences that may exists between CF-CPT and CPT with respect to improvements in functioning and symptom levels, as well as treatment engagement. To confirm this, we conducted power calculations based on mixed model tests for two means in a two-level

hierarchical design with level-2 randomization to intervention group, as described in Ahn and Zhang (2015)[78] and implemented in PASS 2020. We used data from IIR17-178 to estimate intracluster correlation. Specifically, using administrative data from 2,329 Veterans, we fit a random effects linear model to the change in PTSD Checklist (PCL) scores fitting random effects for therapists. This yielded an ICC estimate of .075. Based on a standard deviation (SD) of 17.01 for the total IPF score (Bovin et al., 2018),[55] with at least 80% power we are able to detect a difference of 8.49 change in mean psychosocial functioning score due to the intervention for alpha= 0.05 and a 1:1 sample size allocation with 8 patients per provider and 12 provider per arm. With respect to examining symptom improvement, estimating SD=14.5 and the same design and alpha functions for the analyses listed above, we will have 80% power to detect a minimum of 7.24 point difference between the group means on the CAPS-5. It is clear that smaller standard deviations and/or intra-correlation coefficients, either the power would be more than 80% or smaller differences can be detected with this power.

The data analysis will be conducted primarily by Dr. Brian Smith (VA Boston). Dr. Smith will be assisted by study staff including project coordinators, research technicians, and clinical assessors. Oversight of data analysis will be conducted by PI Galovski and Co-PI Kehle-Forbes.

Analyses will follow ITT methodology. We will first examine the distribution of all study variables (data verification). We will then evaluate bivariate associations between condition and study outcomes and covariates to determine unadjusted measures of treatment effect and identify imbalance in baseline covariates. Due to randomization, we do not anticipate between-group imbalances, but we will adjust for any differences by including these variables as covariates. We will then examine the impact of missing items and adjust for their influence. After testing and identifying the mechanism underlying any missingness (missing at random, non-ignorable), we will use the implied specific imputation methods to impute missing covariates and factors and generate five imputed data sets. Final analyses will include complete case analysis and an aggregated analysis based on the multiply imputed data.

We will test **Aim 1** hypotheses using generalized linear mixed models. Continuous patient Aim 1A & 1B outcome measures (all but treatment completion), within the assumed and appropriate fitted distributions, will be modeled with treatment and training wave as fixed effects and a random provider effect (clustering by provider). The time (pretreatment, mid-treatment posttreatment, three-month follow-up) by treatment interaction term will provide the test of our primary hypothesis that CF-CPT will be superior as compared to CPT.

For the dichotomous measure of treatment completion (**Aim 2**), logistic mixed models with a random provider effect will be used. Given that the amount of divergence from the CPT protocol will vary across patients, we will augment our primary analysis with secondary analyses comparing subsamples of the CF-CPT group (e.g., those with and without divergences) to the CPT group. This secondary analysis will require adjustments for possible covariate imbalance, as

we will lose the balance induced by randomization. We will use propensity analysis and will estimate average treatment effect on the treated (ATT) and the corresponding sensitivity analysis to gain more insight on the magnitude of the effect. Post hoc power will also be calculated to assess the generalizability of these estimates.

Finally, we will examine the COTO reduction score as a predictor of improvements in functioning and symptoms – i.e., testing whether more improvement in COTO scores is associated with greater improvement in study outcomes (**Aim 3**). We propose adapting an idiosyncratic method of assessment via locally constructed diaries used in previous studies to track PTSD symptoms to monitor idiosyncratic COTOs and provide data to evaluate the effectiveness of the CF intervention on the individual challenges in patients' lives.[81-82] [Previous research has shown this method of assessment to have good sensitivity to treatment effects. Using these daily diaries, we will calculate a single index, called a Composite Primary COTO Reduction (CPCR) score, following the method of Blanchard & Schwarz (1988). This score is an index of overall change in COTO level and serves the function of reducing potential Type I error from analyzing multiple COTOs singly (allowing patients and providers to track as many COTOs as necessary). It can be conceptualized as a percentage of improvement. The CPCR score also provides a means for describing clinically significant improvement in symptomatology, functioning, etc. This score can easily be calculated at by the therapist for the individual participant and inform treatment decisions. The following formula is used to calculate the CPCR score. The symptoms used in the calculations are example only.

COTO Reduction Score (CRS):

$$\frac{\text{Average pretreatment anger outbursts ratings - average anger outbursts ratings}}{\text{Average pretreatment anger outbursts ratings}}$$

A CRS is calculated for each COTO endorsed. CRS scores are then used to calculate overall CPCR scores:

$$\text{CPCR score} = \frac{\text{Anger reduction score + urge to fight reduction score + etc.}}{\text{6 (or 7 or 8, etc.) (depending on number of COTOs present}}$$

These CPCR scores can be calculated on the entire diary or any subsection. For instance, a CPCR score could be calculated for overall improvement, or on improvement on subdomains of psychosocial functioning. We will include CPCR (as a measure of improvement in COTOs) as well as scores on relevant standardized assessments and an interaction between these scores and time in the multi-level model we propose.

5.7 Withdrawal of Subjects

In the event of any clinical or psychiatric emergency that would take precedence over routine clinical care, the participant will be withdrawn from the study. If such an emergency is reported by a participant in the context of the study, the PI, co-PI, or project manager (a clinical psychologist) will contact the disclosing participant by phone, assess for risk and safety, and provide the participant with appropriate referrals. In the case of a psychiatric emergency, we will access local (treating clinician) and national mental health resources available through the VA, including the suicide prevention hotline, risk assessments through Mental Health during regular business hours (Psychiatry Urgent Care), or the facility's Emergency Room during off hours. All potential collaborators and providers on these research activities will have completed comprehensive training in the areas of research ethics, protection of human subjects, and suicide prevention. They will also have completed all VA required trainings pertinent to cyber security, VHA privacy policy (HIPAA), research data security and privacy, ethical principles of human subjects' protection, good clinical practice, and suicide prevention.

Suicide risk will be assessed throughout the study in a number of ways, including through the course of clinical care in each treatment condition by the study clinician, by patient report during the phone assessments with trained study staff, and by patient self-report on standardized measures (specifically the BSSI and the PHQ-9) at each assessment interval.

If a study clinician determines there is suicide risk based on clinical judgement, the responding clinician will implement all that apply:

1. Provide the participant with the VA National Suicide Prevention Hotline number (1-800-273-TALK).
2. If talking by phone, offer to transfer the participant to the VA National Suicide Prevention Hotline (585-393-7938) in accordance with the VA Warm Transfer Protocol.
3. Offer to provide the participant with information on VA facilities and/or contact the participant's treating clinician, within 24 hours. If the participant identifies barriers to using VA facilities, the participant will be provided with local/regional resources, including treatment referrals.
4. Take steps to reduce participant risk, including asking the participant to remove weapons/medications from his/her access.
5. Help the participant identify important protective factors such as religious beliefs, dependent children, belief in treatment, future oriented goals, and leveraging social supports.

Elevated suicide risk may also be detected by study staff during clinical interviews. All five steps noted above will be taken by study staff. In the event of imminent risk, study staff who are under the direct supervision of the PIs will immediately call the local first responders and report the emergency and request a wellness check. Study staff will inform PIs Dr. Galovski and Kehle-Forbes immediately and will inform the treating clinician of the participant's reported distress.

With respect to self-report questionnaires, all surveys (mail and online) will include information on how to seek immediate assistance in the case of distress including the Veteran Crisis Line phone number and instructions. Questionnaires completed by the study participant at each interval will be routinely checked with specific attention paid to item number 9 on the PHQ-9. If a participant reports a score of 1 or greater on this item, study staff will follow up with the treating clinician and proceed with suicide risk mitigation measures as described above. If the participant is no longer engaged in clinical care with the provider, trained study staff will contact the participant and follow VA clinical guidelines to assess risk.

During consent and if the participant expresses ambivalence about continuing in the study, participants will be reminded that their participation is voluntary and they may withdraw at any time. VA patients will be informed that their care at the VA will not be affected by their decision to participate or not to participate in the study. All VA Medical Centers are mandated to provide cognitive processing therapy (the treatment provided in this research study) for patients; in the case that a patient withdraws from the study, CPT will remain accessible through regular clinical processes. There are no experimental procedures involved in this study.

If a subject withdraws from the intervention portion of the study, the participant will be invited to return and complete the posttreatment and follow-up assessments in the same time frame in which treatment would have occurred had they continued in the intervention (e.g. for posttreatment assessments, scheduling approximately fourteen weeks after the intended treatment start date followed by a follow-up assessment scheduled approximately three months after the posttreatment assessment date.)

5.0 Reporting

We follow CIRB and VA guidelines (VHA Handbook 1058.01, Research Compliance Reporting Requirements, and the VA Central IRB Table of Reporting Requirements) for reporting Unanticipated Problems Involving Risks to Subjects or Others, Serious Adverse Events, Protocol Deviations, Apparent Serious Noncompliance, and Information Security Incidents including prompt reporting of any deaths or serious AEs, defined as AE that results in death, a life-threatening experience, inpatient hospitalization, prolongation of hospitalization, persistent or significant disability or incapacity, congenital anomaly, or birth defect. An AE is also considered serious when medical, surgical, behavioral, social, or other intervention is needed to prevent such an outcome. Any event that does not fall under prompt reporting requirements will be reported at the time of DSMB meetings and CIRB continuing reviews. Study providers will be instructed to report these events to the PIs or study coordinators. The PIs will be notified by the study coordinators immediately of any serious adverse events occurring in conjunction with this study. We will also query, track and report all these events during weekly consultation with study providers.

Regardless of severity, these events will be recorded in the study application AE tracking system by study coordinators.

With respect to gathering information, we (the PI's, Project Managers, and Providers) will log all phone calls received from any participants and carefully evaluate any concerns raised about the protocol or impact of the study. Reporting will cover: 1) safety of study participants (e.g., unanticipated serious adverse events), 2) study enrollment relative to expectations, 3) data analytic plan, 3) characteristics of study participants, 4) retention of study participants at the posttreatment and 1-month follow-up assessments.

The DSMB will have access to treatment condition assignment of the participants. The study personnel will follow additional steps and recommendations from the DSMB. Any SAE, whether or not related to study intervention, will be reported immediately to both the IRB and the DSMB. All AEs and SAEs will be analyzed by the DSMB and their analysis will be used by the PI to determine course of action. The DSMB will evaluate all AEs and SAEs in order to determine whether study protocol modifications are required to protect patient safety.

6.0 Data Safety Monitoring Board (DSMB)

PIs Galovski and Kehle-Forbes will work to develop a Data Safety Monitoring Board (DSMB) and standard operating procedures (SOP) of the DSMB. We will first identify three to four potential DSMB members. When identified, we will notify the IRB. DSMB members may require access to PHI in performing duties outlined below. We will follow VA procedures for PHI protection. We will include individuals who are independent of our study with expertise in the patient population and disorders being studied in this trial (e.g., Veterans, PTSD, comorbid conditions), the conduct and methodology of clinical trials, and biostatistics/epidemiology. DSMB members may be from the VA Boston Healthcare System and/or from agencies outside the VA, as long as there are no conflicts of interest present between our study and the DSMB members. Details and procedures related to ensuring and documenting any conflict of interest will be provided in the DSMB SOP.

Items to be reviewed by the DSMB include the following:

- Adverse events (AE) and unanticipated problems (UP)
- Data quality and completeness
- Annual performance of individual centers/sites (Boston and Minneapolis)
- Compliance with recruitment and retention goals
- Protocol adherence

- External factors that may influence study ethics or patient safety

After the initiation of the study, the DSMB will hold its first meeting within the first 6 months of the study, after which it will be at the discretion of the DSMB as to how often it chooses to meet, holding a minimum of one meeting per year. Meeting agenda will include ongoing monitoring of the progress of the study and the safety of participants performed by the PIs, Project Managers, and providers. We will log all phone calls received from any participants and carefully evaluate any concerns raised about the protocol or impact of the study. Reporting will cover: 1) safety of study participants (e.g., unanticipated serious adverse events), 2) study enrollment relative to expectations, 3) data analytic plan, 3) characteristics of study participants, 4) retention of study participants at the posttreatment and 1-month follow-up assessments. The DSMB will have access to treatment condition assignment of the participants. In the proposed study we will use the FDA definition of adverse events (AE) and serious adverse events (SAE). Any SAE, whether or not related to study intervention, will be reported immediately to both the IRB and the HSR&D DSMB. All AEs and SAEs will be analyzed by the HSR&D DSMB and their analysis will be used by the PI to determine course of action. The DSMB will evaluate all AEs and SAEs in order to determine whether study protocol modifications are required to protect patient safety. When the annual IRB continuing review is due, the PI will include the most recent DSMB report(s) from the past year for the IRB to review. DSMB will also review all AE's and UP's within 5 working days from learning of the event/problem. Below please find a schematic that illustrates AE reporting procedures.

7.0 Privacy and Confidentiality

- The study will use PHI gathered from interviews, self-report and medical records.
- All research data will be maintained for six years following the end of all research related activities (e.g., publishing of manuscripts) in accordance with the VA Research Records Control Schedule. All data (raw, interim and final) will be destroyed in accordance with VA policy and with oversight from the Principal Investigator and the Information Security Officer (ISO) at VA Boston and the Minneapolis VAHCS. Any confidential research data or records in paper format will be cross-shredded. Any confidential research data and records in electronic format (including recruitment information, study databases, etc) will be destroyed by reformatting and over-writing data files.

- **VA Boston**

1. All forms with participant information will be marked with a code number and not with the participants' name.
2. The PI will keep the link between the participant code number and name in a password protected file in a secure drive behind the VA firewall.
3. Any information about a participant will never be released to outsiders without their explicit consent, except in the event of abuse of children/elderly/handicapped or a

medical emergency, when pertinent medical information will be given to the medical personnel caring for the individual.

4. Data will be stored on the servers of the National Center for PTSD (NCPTSD) at the VA Boston Healthcare System. NCPTSD has well-established procedures to protect the privacy of research participants. Names and contact information will not appear on any study materials. Instead, only unique study identification numbers randomly assigned to each unique record will be used. Other individuals referred to by participants during the interviews (e.g. other providers) will not be referenced by name in the study materials but only by salient but non-identifiable characteristics.
5. All electronic recordings and analytic notes will be stored in VA servers.
6. Handwritten notes will be stored in a locked cabinet in Dr. Galovski's VA office.
7. At the conclusion of the study, data will be destroyed in accordance with VA policy. De-identified data will be maintained in a larger data repository entitled Cognitive Processing Therapy: Treatment Outcome Research and maintained with VA Boston Healthcare System IRB oversight (IRB #3055).
8. Site lead investigators (Galovski and Kehle-Forbes), project coordinators, clinical assessors, and research assistants will have access to an encrypted crosswalk table linking study identification numbers to identifying information. In addition, study staff will be able to access the encrypted crosswalk table linking study identification numbers to identifying information at their site only. The PIs, project coordinators, and clinical assessors will need to be able to access the participants' contact information in the event of a clinical emergency. The research assistant will have access to the participant's contact information for the purposes of sending subject payment and study materials. The NCPTSD, in partnership with IRM staff, maintain several secure servers, access to which is granted only to project personnel who are authorized by the study investigator and approved by the IRB. Identifiers will be destroyed as quickly as possible. Audio recordings (i.e., clinical interviews and *intervention* sessions) will be stored digitally on NCPTSD servers and only accessible to the principal investigators and project coordinator. Recordings without identifying information (e.g., without PHI) will be available to conduct independent fidelity ratings. Participants will be asked not to use last names or provide identifying information during recorded interviews or intervention sessions. The possibility of incidental disclosure of a name or other identifying information on audiotapes cannot be ruled out despite these precautions. However, independent therapy evaluators are licensed clinical psychologists and national experts in the study therapy, CPT. As such, they are bound by confidentiality in accordance with their professional code of ethics.

- **CCDOR**

1. All forms with participant information will be marked with a code number and not with the participants' name.

2. The only copy of the key linking actual names to code numbers will be kept in a password protected file, stored on a secure server.
3. Other individuals referred to by participants during the interviews (e.g. other providers) will not be referenced by name in the study materials but only by salient but non-identifiable characteristics.
4. All electronic recordings and analytic notes will be stored in VA servers.
5. Handwritten notes will be stored in a locked cabinet in Dr. Kehle-Forbes's VA office.
6. At the conclusion of the study, data will be destroyed in accordance with VA policy.
7. The CCDOR Statistical and Data Management (SDM) team maintain several secure servers accessible only SDM team members who have been screened and obtained proper security clearance. One common-access server contains individual project data. Access to that data is granted only through authorization by the principal investigator. Other VA investigators have used these procedures in previous studies and they have proved both feasible to execute and acceptable to multiple IRBs.

- All collaborators will have completed appropriate human subjects trainings in the areas of research ethics and protection of human subjects.

- There will be no collection of biological specimens.

8.0 Communication Plan

- Dr. Galovski and Dr. Kehle-Forbes will provide oversight of the entire project and development and implementation of all standardized policies, procedures and processes. In these roles, Drs. Galovski and Kehle-Forbes will be responsible for the implementation of the scientific agenda, the specific aims and ensure that the proposed research is in compliance with US laws, VHA regulations and policies including human research, protection of human subjects, data and facilities. Drs. Galovski & Kehle-Forbes will each be responsible for supervising study staff at their site and informing staff of any changes in study procedures.

- We follow CIRB and VA guidelines (VHA Handbook 1058.01, Research Compliance Reporting Requirements, and the VA Central IRB Table of Reporting Requirements) for reporting Unanticipated Problems Involving Risks to Subjects or Others, Serious Adverse Events, Protocol Deviations, Apparent Serious Noncompliance, and Information Security Incidents including prompt reporting of any deaths or serious AEs, defined as AE that results in death, a life-threatening experience, inpatient hospitalization, prolongation of hospitalization, persistent or significant disability or incapacity, congenital anomaly, or birth defect. An AE is also considered serious when medical, surgical, behavioral, social, or other intervention is needed to prevent such an outcome. Any SAE, whether or not related to study intervention, will be reported immediately to both the IRB and the

DSMB. All AEs and SAEs will be analyzed by the DSMB and their analysis will be used by the PI to determine course of action. The DSMB will evaluate all AEs and SAEs in order to determine whether study protocol modifications are required to protect patient safety. If there is an AE or SAE that could potentially affect course of treatment, then we will notify their provider or mental health treatment coordinator of this event.

The PIs and study staff at the coordinating sites will meet at least monthly as a full team. At these meetings, Drs. Galovski & Kehle-Forbes will discuss any changes to the study protocol and review any protocol deviations that occurred since the last meeting. The project manager will also have weekly meetings with all study staff, during which s/he will review all aspects of the protocol to ensure ongoing compliance. The project manager will track participant study participation, including participants' withdrawal from or completion of participation. Local site investigators will meet with the lead site project coordinator biweekly for the first six months and then on a monthly basis for the remainder for the project and by request as needed.

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