

Supplementary Online Content

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eAppendix. Telemedicine Outreach for Posttraumatic Stress in CBOCs

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix

Telemedicine Outreach for Post Traumatic Stress in CBOCs

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Background

Friedman has characterized post traumatic stress disorder (PTSD) as prevalent, persistent, and frequently disabling⁵. The 12 month prevalence of PTSD in the U.S. population is higher than Panic Disorder, Generalized Anxiety Disorder, Bipolar Disorder, or Alcohol Abuse.⁶ PTSD is even more prevalent in the VA healthcare system. Magruder et al. conducted the largest (4 VAMCs, n=746) epidemiological study of PTSD in VA primary clinics and found the prevalence of current PTSD was 11.5% according to the Clinician Administered PTSD Scale (CAPS).⁷ The prevalence of PTSD is nearly twice that of depression³ in VA primary care clinics, and the impact of PTSD on quality of life is significantly greater than the impact of depression.⁸ Yet much of the HSR&D-funded mental health research (including our own) has focused on depression. The recently released, VA commissioned, Institute of Medicine's (IOM) report assessing the evidence on PTSD specifically highlights the lack of "large scale, multi-site initiatives of the type that has been directed towards other psychiatric disorders."⁹

PTSD is also strongly associated with risky behaviors like smoking, illegal drug use, excessive use of alcohol, and suicidal behavior.^{17;19} Perhaps as a result, PTSD is associated with poor physical health,^{20;21} and veterans with PTSD have significantly worse physical health functioning than those without PTSD.^{22;23} Thirty years after military service, the mortality rate for veterans with PTSD is twice that of veterans without PTSD.²⁴ Veterans with PTSD also have significantly worse social and mental health functioning than veterans without PTSD.^{8;13;22;25} PTSD negatively impacts marriages (contributing to physical/psychological partner and child abuse),²⁶ impedes educational attainment,²⁷ and decreases occupational functioning.^{17;22;23;28} Thus, PTSD imposes a substantial burden on military families.

Only 12.8% of individuals with PTSD who seek care for their emotional problems in the general medical setting receive minimally adequate care, highlighting the quality of care problem in primary care settings.³² Detection of PTSD is also a problem in primary care settings. For example, only 46.5% of veterans with CAPS identified PTSD recruited from VA primary care clinics were detected according to medical record review, and only 17.8% of veterans only seen primary care clinics were detected.⁷ Among veterans in specialized PTSD programs, less than half are prescribed an SSRI.³³ Likewise, less than 10% of VA mental health specialists (including PTSD specialists) use manualized psychotherapies for PTSD.³⁴

The Chronic Care model for depression, known as collaborative care,^{38;39} improves depression outcomes in primary care settings in a cost-effective manner.^{40;41} The chronic care model uses patient self-management, delivery system re-design, decision support, and clinical information systems to maximize the effectiveness of interactions between informed activated patients and prepared, proactive care teams.⁴² Based on the chronic care model, disease management programs focus on defined populations of patients with targeted illnesses (e.g., depression) and promote adherence to treatment and self-care strategies.³⁸ Like

depression, the disease management strategies employed in chronic care models are well suited to improving outcomes among patients with PTSD.¹⁹ There have been only two completed randomized trials of collaborative care for psychiatric sequela of trauma, both conducted by Zatzick et. al.^{43;44} Both studies were conducted in civilian populations recruited from large urban level I trauma centers. Although the studies were small (n=34 and n=120), both improved outcomes.^{7;43} Both interventions co-located a PTSD specialist in the medical setting (an approach that is not feasible in small Community Based Outpatient Clinics (CBOCs)). This study will contribute to this growing knowledge base by implementing and evaluating a telemedicine-based PTSD collaborative care model for small and rural CBOCs lacking on-site psychiatrists.

Nearly half (44%) of U.S. Military recruits now come from rural areas and nearly one-third of the soldiers who have died in Iraq are from small towns and communities across the nation.¹ VA faces substantial challenges to providing PTSD care to the growing number of rural veterans. VA operates or contracts nearly 700 CBOCs nationwide, with 253 CBOCs currently providing mental health services via interactive video.² Improving PTSD treatment in CBOCs is an important policy objective due to the limited capacity of VA to deliver specialty PTSD services outside VA Medical Centers. Although psychotherapy and pharmacotherapy treatments for PTSD have been proven to be efficacious in controlled trials, geographic barriers often prevent veterans from accessing these evidence-based treatments. While most parent VAMCs offer specialized PTSD programs, CBOCs often find it unfeasible to hire on-site psychiatrists or other mental health specialists with PTSD expertise. This is especially true of small CBOCs in rural areas where a large proportion of Operation Iraqi Freedom and Operation Enduring Freedom (OEF/OIF) veterans are seeking care. Our group has previously demonstrated that depression outcomes can be improved in CBOCs with telemedicine,^{3;4} and although more clinically challenging, we believe that PTSD outcomes can also be improved.

Telemedicine technologies include telephones, emails, interactive video, shared electronic medical records, and web-based decision support systems. Telephone care management has been found to significantly improve both depression and alcohol outcomes in a number of studies.^{3;55-59} Patient and provider satisfaction with interactive video encounters with mental health specialists is uniformly high.⁶⁰⁻⁶² Based on a review of the literature, Frueh and colleagues conclude that the reliability of clinical assessments via interactive video is equivalent to assessments conducted face to face.⁶³ One large VA study compared the outcomes of patients with depression who were randomized to either face-to-face or interactive video encounters with a psychiatrist and found no differences in clinical outcomes between the treatment groups.⁶⁴ Research to date also indicates that psychotherapy (including cognitive behavioral therapy) delivered via interactive video appears to be as equally effective as face-to-face psychotherapy.⁶⁵⁻⁷¹ Cognitive Processing Therapy (CPT) lends itself well to telemedicine applications because it is a highly structured therapy and much of the benefit derives from patients completing homework assignments and practicing new skills outside the therapy session. These activities occur between interactive video sessions with the therapist and are not likely to be affected by the mode of delivery. Case reports and pilot studies have demonstrated the safety and acceptability of psychotherapy for PTSD delivered via interactive video.^{72;73} Although safety is a concern with interactive video (as it is more difficult to manage suicidal threats, violence, and other harmful behaviors during an interactive video session), on-site clinicians are able to handle most situations.⁷⁴ One VA randomized controlled trial demonstrated equivalency of psychotherapy for PTSD delivered via interactive video compared to face-to-face.⁷⁵ In summary, the current evidence suggests that core collaborative care components (e.g., care management, psychiatric diagnostic assessment, psychiatric medication management, and psychotherapy) delivered via telemedicine have the potential to be clinically

effective. Collaborative care for depression can be effectively delivered to CBOC patients using telemedicine technologies.³

PTSD accounts for a quarter (25%) of all mental health disorders treated by VA.⁸⁴ Among OEF/OIF veterans, PTSD accounts for half (52%) of mental health disorders treated by VA.¹⁴ The number of veterans receiving VA specialty PTSD services doubled between 1997 and 2005 to approximately 280,000, and this number is expected to increase dramatically in coming years.⁸⁵ Conversely, due to limited capacity, the number of specialty mental health encounters per PTSD patient decreased by 45% between 1997 and 2005.⁸⁵ Likewise, VA officials estimated that follow-up appointments for veterans receiving care for PTSD may be delayed up to 90 days.⁸⁶ Clearly, VA faces major challenges in meeting the growing demand for PTSD services, and the GAO has expressed serious concerns that VA has adequate capacity to address the mental health needs of OEF/OIF veterans.⁸⁶ CBOCs could help address this capacity problem, as they have proven to be an effective way to provide services to rural veterans^{87,88}

The costs associated with PTSD present significant economic burden to society as a whole and to VA in particular. Between 2004 and 2009, VHA spent \$1.4 billion on patients with PTSD. RAND estimates that the average two-year post-deployment cost attributable to PTSD ranges from \$5904 to \$10298. The Congressional Budget Office estimates that the average cost for a patient with PTSD in the first year after diagnosis is \$8300 and approximately half of this total is directly attributable to formal care for PTSD. Veterans of Iraq and Afghanistan with PTSD are more likely to utilize VA services, with two-thirds using VHA at least once within four years after diagnosis. Increased utilization for these Veterans is seen in inpatient days, outpatient visits and prescriptions filled. In patients with depression, comorbid PTSD is associated with higher rates of healthcare utilization especially utilization within the VA. Similarly healthcare costs for patients with PTSD and depression are significantly higher than those without comorbid PTSD; significant elevations are seen in annual outpatient costs (\$4257 vs. \$3173), physical health costs (\$3061 vs. \$2842), mental health costs (\$1196 vs. \$886) and medication costs (\$1482 vs. \$1148).

Research Objectives

The objective of this effectiveness study is to evaluate a telemedicine intervention to improve PTSD outcomes among veterans treated in VA CBOCs lacking on-site psychiatrists. Based on the principles of the Chronic Care Model and Disease Management, the Telemedicine Outreach for PTSD (TOP) intervention is designed to support the delivery of PTSD care in accordance with clinical practice guidelines. An off-site PTSD care team will use telemedicine (e.g., telephone, interactive video, electronically shared medical records and intranet) to enhance the treatment of CBOC patients with newly emerging or chronic PTSD. To maximize versatility, the TOP intervention was designed to support all types of clinicians providing PTSD care to CBOC patients (e.g., on-site primary care providers, on-site psychiatric nurse practitioners, off-site tele-psychiatrists).

The off-site PTSD care team will include a tele-nurse care manager, tele-pharmacist, tele-psychologist, and tele-psychiatrist. Telephone nurse care managers will educate/activate patients, assess treatment preferences, identify psychiatric comorbidities, address treatment barriers, monitor outcomes (symptoms, side-effects, and adherence), and encourage self-management. Tele-pharmacists will provide medication management to patients by phone. Tele-psychologists will provide Cognitive Processing Therapy (which VA is disseminating

nationally) via interactive video. The team will be supervised by a tele-psychiatrist who will also conduct consultations and provide medication management via interactive video. Because PTSD is highly comorbid with depression and alcohol use disorders, the off-site care team will also follow evidence based protocols to concurrently address these comorbid conditions.

Specific Aim #1: To compare process of care delivered to CBOC patients with PTSD randomized to the TOP intervention group with Treatment As Usual (TAU). Chart review will be used to determine whether patients received an active treatment concordant with VA/DoD Clinical Practice Guidelines for the Management of PTSD. Patient adherence to their chosen treatment plan and satisfaction with care will be measured from self report.

***Hypothesis 1a:** Patients randomized to TOP will have a greater likelihood of receiving a guideline concordant treatment compared to PTSD patients randomized to TAU.*

***Hypothesis 1b:** Patients randomized to TOP will have greater adherence to treatment (pharmacotherapy and/or psychotherapy) compared to patients randomized to TAU.*

***Hypothesis 1c:** Patients randomized to TOP will have greater satisfaction with treatment compared to patients randomized to TAU.*

Specific Aim #2: To compare outcomes of care delivered to CBOC patients with PTSD randomized to the TOP intervention with TAU. PTSD outcomes will be measured from patient self report and will include changes in PTSD severity, depression severity, quantity and frequency of alcohol consumption, mental health functioning, and physical health functioning.

***Hypothesis 2a:** Patients randomized to TOP will experience better outcomes compared to patients randomized to TAU.*

We will also explore whether the effectiveness of the TOP intervention will be more or less effective for OEF/OIF veterans compared to veterans from earlier periods of wartime service..

Specific Aim #3: To collect Quality of Life and Intervention and Self-Reported Cost data to use in future cost-effectiveness analyses.

Specific Aim #4: To collect Administrative Cost data and estimate the incremental cost effectiveness of the TOP intervention relative to usual care.

Hypothesis 4a: The TOP intervention will be cost effective relative to usual care using accepted incremental cost per QALY thresholds for cost effectiveness.

Methods

Recruitment - Patients will be recruited from nine CBOCs associated with three parent VAMCs (Little Rock AR, Shreveport LA, and Loma Linda CA) including seven CBOCs (Searcy, Mena, Mountain Home, Pine Bluff, El Dorado, Conway, and Russelville) associated with the Little Rock VAMC. Three recruitment strategies (referral, screening and opt-out letters) will be used to enroll both recently returning veterans and veterans from previous periods of wartime service. Note that asking patients whether they are willing to be contacted by research personnel does not constitute engagement in research and CBOC providers are not considered research personnel. Having CBOC providers ask patients' willingness to be contacted by researchers was recommended by the VA Office of Research Oversight (See Attachment A). We plan to screen up to 800 subjects at CAVHS (screening includes access to and collection of PHI). We

expect that up to 100 patients at CAVHS will be consented and that up to 50 patients from CAVHS will be eligible and included in the data analysis.

Referral - For patients already engaged in PTSD treatment with a CBOC provider (PCP, psychiatric nurse practitioner, or tele-psychiatrist), the CBOC provider will inform the patient of the study and ask permission for the research team to contact the patient. Patients will be asked by the CBOC provider to sign a form stating that they are willing to be contacted by research personnel and to provide contact information. If the patient agrees, the form will be faxed to research personnel at the Parent VAMC.

Screening - However, because a substantial proportion of CBOC patients with PTSD will not already be engaged in PTSD care, we will also recruit patients screening positive on the 4-item Primary Care PTSD (PC-PTSD) screen. The PC-PTSD was designed for primary care settings, is recommended by the VA/DoD CPG-PTSD,⁴⁶ and is an OQP performance measure for FY08. Annual screening for PTSD is required for the first five years after the date of service separation and every five years after that. Patients screen positive if they endorse 3 or more items. The screen has good sensitivity (78%) and specificity (87%) in VA primary care patients when compared with a diagnosis based on the CAPS.⁸⁹ For patients screening positive for PTSD on the PC-PTSD, a CBOC provider will inform the patient of the study and ask permission for the research team to contact the patient.

Opt-Out Letters - We will obtain monthly VISTA queries from a non-researcher in Mental Health Service to identify patients with a diagnosis of or positive screen for PTSD. A research clinician will review the CPRS notes of the potentially eligible patients to identify those who meet exclusion criteria. Potentially eligible patients will receive a recruitment letter from a member of our research team. Enclosed will be a self-addressed stamped envelope and a "do not call" card. The recruitment letters will state that, if we do not receive a phone call or if the postcard is not returned within two weeks from the date of the mailing, a research assistant may call the veteran and explain the study in more detail. At this time, the patient may agree to, or refuse participation without any obligation. This response will be recorded in order to ensure that veterans are called no more than once. In addition, one day prior to a regularly scheduled CBOC appointment, a member of the research team will place a CPRS note in the patient's chart informing the CBOC provider that the patient is potentially eligible for the study. The note will request the CBOC provider to be an additional signer. The CPRS note will encourage the CBOC provider to inform the patient about the study, to offer the patient the study brochure and to encourage them to sign the permission to contact form or call the research personnel directly if they interested. The CPRS note will specifically state that the provider should NOT directly ask the patient whether they want to participate in the study and should NOT directly ask permission for the research team to contact the patient. The reason for this is that we cannot be sure that the provider will record and relay refusals to the research team, and we do not want to attempt to recruit patients who have refused to participate in the study unbeknownst to the research team. The CBOC provider may or may not inform the patient about the study during the appointment, hand the patient a study brochure, or hand the patient a permission to contact form. The opt-out letters will be sent a few weeks before an upcoming CBOC visit and telephone calls to those not opting out will be made after the CBOC visit.

If the patient has time to engage in the informed consent process after their clinical encounter with the CBOC provider, informed consent will be obtained immediately by research personnel. If the patient does not have to time to immediately engage in the informed consent process, research personnel at the Parent VAMC will telephone the patient and set up an appointment to obtain informed consent.

Informed Consent Process - The TOP nurse care manager will be responsible for establishing eligibility and obtaining informed consent via interactive video. The care manager will be located at the VA Medical Center and the patient will be located at the CBOC in the patient exam room that is used to conduct telemedicine encounters with patients. The entire informed consent process will be conducted via interactive video, including assessing whether the veteran understands the purpose, procedures, risks and benefits of the study, and observing that the veteran and witness signed the consent form. Obtaining informed consent via interactive video was specifically recommended for this study by the VA Office of Research Oversight (See Attachment A). Dr. Fortney will personally train the care manager how to conduct the informed consent process. Once the veteran has signed the informed consent document, CBOC staff will: 1) sign as a witness, 2) Xerox a copy of the informed consent document and give it to the study participant, 3) give the study participant four brochures (“Serving Those Who Served”, “Suicide Prevention, Know the Warning Signs of Suicide”, the TOP Study Brochure, “Is the TOP Study for you?”, & “Volunteering In Research”), and 4) FedEx the original signed informed consent document to the Parent VAMC for the care manager (person obtaining informed consent) and the PI to sign. Note that the date of the signature of the person obtaining informed consent will not be the same date as the study participant. Therefore, we will enter a CPRS informed consent process note on the date that informed consent was obtained and this process note will be electronically signed by the person obtaining informed consent. This CPRS note will be electronically signed and dated by the care manager and the date will be the same date as the date the study participant signed the informed consent document. In addition to attaching the scanned informed consent document to this CPRS note, this process note will describe what happened during the informed consent process.

Inclusion Criterion - After consenting the patient, the TOP care manager will administer the Clinical-Administered PTSD Scale (CAPS)¹ via interactive video to determine whether the patient meets diagnostic criteria for PTSD. Patients who do not meet diagnostic criteria will be excluded from the study. All patients who complete informed consent and the CAPS assessment will be compensated \$30 for their time. The CAPS requires 45-60 minutes to administer and is the most comprehensive and validated structured clinical assessment for PTSD. There are nine scoring rules for the CAPS² and we will use the SXCAL rule which has 91% specificity and 84% sensitivity compared to clinical assessment. The SXCAL scoring rule was empirically derived by calibrating each CAPS symptom with the corresponding symptom on the PTSD module of the SCID (used as the gold standard). The SXCAL scoring rule is recommended by the developers to be the optimally efficient rule², as all other scoring schemes have either too low sensitivity (i.e., too many false negatives) or too low specificity (i.e., too many false positives).

Exclusion Criteria - Because the TOP intervention supports a continuum of care from primary care to specialty tele-psychiatric care, exclusion criteria will be kept to an absolute minimum. We will exclude patients with a diagnosis of schizophrenia, bipolar disorder and current substance dependence. CBOC providers at the clinics will be told that these patients are not eligible for the study and to not refer them. In addition, prior to obtaining informed consent, the care manager will review diagnoses in CPRS and exclude those with a diagnosis of schizophrenia, bipolar disorder and current substance dependence (but not abuse). Patients who do not have the capacity to consent or who have a legal guardian will be excluded (as measured by the care manager’s clinical judgment during the informed consent process). Patients with a terminal illness or who do not plan to use the CBOC in the future will be excluded (also determined during the informed consent process). Patients will be excluded if they do not have access to a telephone or have a hearing or speech impediment that would

prevent them from engaging in telephone encounters (as measured by the care manager's clinical judgment during the informed consent process). Importantly, patients who are currently receiving specialty PTSD treatment at the parent VAMC (defined as an encounter in the last six months recorded in CPRS) will be excluded because they are already receiving more intensive treatment than would be provided by the TOP intervention. Patients will not be dropped from the study if they engage in specialty PTSD treatment after enrollment; although per the stepped care protocol they would no longer receive the TOP intervention. Likewise, patients will not be dropped from the study if they are diagnosed with schizophrenia, bipolar disorder and current substance dependence after enrollment; although per the stepped care protocol they would be referred to specialty mental health care. Patients with other mental health disorders such as depression, panic disorder, generalized anxiety disorder, and substance abuse are very common among PTSD patients and will NOT be excluded from the study. Patients who are at high risk for suicide will NOT be excluded; although we will delay recruitment until after the patient's safety has been assured. If we identify a patient who is at high risk for suicide who is not receiving care from the tele-psychiatrist, the care manager will refer them to the tele-psychiatrist. We believe that patients at high risk for suicide will benefit from the TOP intervention, and thus there are ethical reasons to include them in the study.

Stratified Sampling - The Institute of Medicine PTSD report specifically warns that OEF/OIF veterans may be different from veterans from previous service periods and that intervention studies conducted with Vietnam veterans may be minimally informative about treating OEF/OIF veterans.⁹ In order to generate precise estimates of intervention effectiveness among this important, but potentially heterogeneous, sub-group, we will employ a stratified sampling technique to enroll sufficient numbers of veterans in each sub-group. Each sub-strata will be defined by OEF/OIF status. We will enroll veterans into each of these sub-strata until the enrollment target of 200 eligible Veterans has been reached across all study sites. Once the enrollment target has been reached in each sub-strata, we will continue to identify veterans eligible for each sub-strata during the enrollment period in order to calculate sampling weights. The post-stratification sampling weight for veterans in each of the four sub-strata will be calculated by dividing the proportion of veterans in each sub-strata identified during the enrollment period (i.e., all veterans eligible for the study) by the proportion enrolled in the study (50%). These post-stratification sample weights will be used in the statistical analyses.

Randomization - Patients will be the unit of randomization. Computerized randomization will be conducted according to a 2 x 2 latin square design that pairs sequential enrollees from each site and randomizes one to the intervention and one to treatment as usual.

Treatment as Usual (TAU) - TAU will represent the already high standard of care for PTSD at the CBOCs. TAU may include pharmacotherapy from a PCP, psychiatric nurse practitioner, or tele-psychiatrist. TAU may also include counseling/groups from an on-site mid-level mental health specialist. The CBOCs have all implemented depression and alcohol care management programs as a part of the PC-MH Integration initiative. Intervention patients already under the care of a PC-MH care manager when enrolled in the study will be transferred to the TOP care manager. TAU patients will continue to receive care from the PC-MH care managers, who will not manage PTSD. If TAU patients have comorbid depression, the PC-MH care managers will help with antidepressant adherence/side-effects. Likewise, if TAU patients have a comorbid alcohol use disorder, the PC-MH care managers will provide brief counseling.

Telemedicine Outreach for PTSD (TOP) Intervention – see TOP Intervention Protocol

Training/Supervision – During a one hour presentation, Drs. Pyne and Hudson will review the TOP protocol with the tele-psychiatrists and discuss the latest evidence about pharmacotherapy for PTSD. Drs. Pyne, Hudson and Fortney will train the PCMs in their clinical duties and use of the web-based decision support system (NetDSS). The tele-psychiatrists will provide clinical supervision for the PCMs and clinical pharmacists. The tele-psychologists will receive the standard VA training for CPT. VA Central Office has funded Dr. Resick (the developer of CPT) to train and support 600 VA therapists nationally in CPT. Dr. Resick and colleagues have trained qualified trainers to conduct two-day workshops and provide case consultation. Following the standard training, Susie Stephens PhD from the VA National Center for PTSD will provide clinical supervision for the tele-psychologists. The tele-psychologists will be video taped during all CPT sessions and Dr. Stephens will review these with each therapist individually. Dr. Stephens will also lead a monthly conference call with the tele-psychologists.

Evaluation

Intervention Fidelity - Fidelity is the degree to which the TOP intervention is implemented as specified by the TOP protocol. To interpret the estimated effect size of the intervention, it will be necessary to know how closely the protocol was followed by intervention personnel. Following methods adapted from the TEAM study, a trained RA will use care manager progress notes generated by NetDSS to determine whether care manager activities were administered to patients as intended. The following activities will be tracked: 1) whether an initial assessment was conducted (and whether each module was completed); 2) the administration and timeliness of follow-up calls; and 3) whether the intervention was stepped up for patients failing trials. Although we videotaped CPT therapy sessions, IT would not authorize us to install the software needed to view the video files, fidelity to CPT will be measured from chart review.

Chart Review – To measure adherence to the VA/DoD CPG-PTSD, a trained RA will review CPRS progress notes for all intervention and TAU patients during the 12 month treatment period to determine whether the patient was prescribed an adequate dosage of medication for PTSD (as defined by the IPAP medication algorithm) or received at least 8 sessions of exposure based therapy (either face to face or CPT via interactive video).

Patient Interviews – Baseline, six and twelve month follow-up telephone interviews will be conducted by blinded RAs. Due the challenges of contacting veterans by phone at accommodating times, RAs will begin efforts to contact veterans for follow-up interviews six weeks prior to due date through six weeks after due date. Subjects will be compensated \$30 for completing each interview. A Computer Assisted Telephone Interview (CATI) system will be used to automatically score responses in real time and facilitate the navigation of complex skip patterns. The use of the CATI also ensures high data quality by minimizing problems with missing data, out-of-range responses, and incorrect skip patterns. CATI also allows us to systematically check data quality during data collection. This software currently resides on the machine of the Data Manager. The questionnaires are programmed and distributed from that PC. The license provides unlimited "disk field" surveying which means the questionnaire program can be copied to unlimited computers. This study will keep the questionnaire on a VA server behind the firewall. This server is password protected and a back-up is performed nightly. We expect a 90% follow-up rate at 6 months and 85% follow-up rate at 12 months. Missing data due to lost follow-up has been a problem in many PTSD studies,⁹ and we will make every effort to maintain a high follow-up rate without placing undue burden on study participants. Certified letters will be sent to patients lost to follow-up to ensure that they are still living.

Outcomes will be assessed independently of treatment attendance, and thus, outcomes will still be measured for patients dropping out of treatment. In addition, reminder letters about follow-up interviews will be mailed out to patients a month in advance and patients will be called two weeks prior to their scheduled interview to determine whether the interview needs to be rescheduled. At baseline, RAs will collect contact information about friends and relatives, and these individuals will be consulted if the patient cannot be located for follow-up. To minimize any bias associated with loss to follow-up, attrition weights will be calculated using casemix factors collected during the baseline interview. These weights will be calculated using a logistic regression with follow-up completion specified as the dependent variable and baseline characteristics specified as independent variables. Assuming, there are significant predictors, the inverse of the predicted probability of follow-up completion will be defined as the attrition weight. The attrition weight will be multiplied by the sampling weight to generate a composite weight to be used in the analyses.

Process Measures - Satisfaction with care will be assessed using the component of the CHAPS survey (version 2.0) designed for mental health carve-outs. Medication and therapy adherence will be assessed from patient self-report. Prior to administering the follow-up survey, study personnel will use CPRS to determine what medications have been prescribed for PTSD during the previous six months. The three most recently prescribed medications will be entered into CATI prior to the interview and the medication adherence questions will refer to each medication explicitly by name. RAs will first ask if the patient is currently taking the medication, and if not, they will be asked to respond to a pre-specified list of potential reasons why not. If the patient is currently taking the medication, the RA will ask how frequently they take the medication and how much (i.e., dosage) of the medication they take. Those taking less than prescribed will be asked about reasons why they were not taking the medication as prescribed. Those taking their medications as prescribed will be asked to endorse a pre-specified list of reasons why they took their medications. Similarly, study personnel will use CPRS to determine what therapy appointments (either face-to-face or CPT via interactive video) were made during the previous six months and RAs will assess attendance and reasons for attendance/no-shows. Patients will be classified as non-adherent if they report taking their medication <80% of days or attending <75% of therapy appointments.

Primary Outcome Measure - The primary outcome measure will be PTSD severity as measured by the Posttraumatic Diagnostic Scale (PDS).¹¹¹ It is necessary to use a scale that is different from the one used by the PCMs. The interviewer administered version of the PDS has 49 items and four sections. The PDS yields a total severity score (ranging from 0 to 51) that primarily reflects the frequency of the 17 symptoms. At follow-up, only symptom and functioning questions will be re-administered, using baseline responses about traumatic events to formulate the questions. To facilitate comparison with recently published PTSD RCTs, the primary outcome will be specified as the change in symptom severity as measured by the PDS. The PDS has been shown to have excellent validity including excellent internal consistency overall ($\alpha=0.92$) and very good internal consistency for symptom subscales (α s ranging from 0.78 to 0.84).¹¹² Reliability is excellent with 87% agreement ($\kappa=0.74$) with clinical diagnosis and adequate temporal stability with respect to symptom severity (correlations across subscales range from 0.77 to 0.85).¹¹²

Secondary Outcome Measures - Depression will be measured using the SCL-20 which is a commonly used measure in depression trials. Alcohol use will be measured by the quantity times frequency of alcohol consumption and frequency of binge drinking. Improvement in general health status will be measured by the change in the Mental Component Summary

(MCS) and Physical Component Summary (PCS) scores of the SF12V.¹¹³

Casemix factors - Case-mix adjusters include seven demographic variables (age, gender, race, ethnicity, education, income, and marital status), Social support will be measured using the Medical Outcomes Study (MOS) social support instrument. OEF/OIF status (determined by asking participants when they were deployed (as well as how often and for how long). Six prognostic indicators (baseline PTSD severity, PTSD treatment history, combat exposure, presence of specific psychiatric comorbidities, number of co-occurring physical health problems, and status of disability claim for PTSD). Disability claim status will be categorized as: not applied, applied and pending, or applied and denied.⁷⁶ In addition treatment preference will be measured by adapting an instrument originally designed for depression for PTSD. The Quality Improvement for Depression treatment preference instrument ask about the acceptability of four treatment options: 1) medications, 2) one on one counseling, 3) group counseling and 4) wait and get over it naturally. The MINI¹¹⁴ will be used to measure comorbid depression, panic disorder, generalized anxiety disorder, and alcohol use. The CIDI will be used to measure drug use. The CAPS (used to determine eligibility) will be used to measure PTSD symptom severity.

Measurement of QALYs - The Quality of Well-Being scale (QWB-SA) will be used to measure health-related quality of life. The QWB was specifically designed to calculate Quality Adjusted Life Years (QALYs) for cost-effectiveness analyses.¹¹⁵ QALYs will be derived from the SF-12V standard gamble to QALY conversion formula and the QWB.

Measurement of Costs – Costs will include both intervention costs, self-reported costs and costs from administrative data.

Intervention Costs: Direct fixed and variable intervention costs will be collected in real time using the “accountant perspective”.¹¹⁸ Fixed costs represent the expenditures on training intervention personnel (including CBOC providers) and will be estimated from the duration of the trainings and salaries of trainers and trainees. Variable intervention costs will be measured by training intervention personnel to use log books to record the time they spend on specific clinical activities. PCMs will record the time they spend on the following activities: attempted patient contacts, initial assessments, follow-up calls, progress note writing, and communication with providers. Tele-pharmacists will record the amount of time spent conducting medication histories and medication management. Tele-psychologist and tele-psychiatrist will record the amount of time they spend providing psychotherapy and pharmacotherapy respectively. Standard salaries (based on step and grade) will be used to convert time to costs.

Self-Reported Costs: Self-reported non-VA service utilization will be calculated during 6 and 12 month follow-up surveys. Self reported non-VA outpatient encounters will be converted into costs using Medicare reimbursements. Self-reported emergency department use will be converted into costs using estimates from the literature. Self-reported non-VA psychotropic medication use will be converted into costs using wholesale process listed in the Red Book of Prescription Drugs. Self-reported patient costs will be calculated from the survey responses. The survey asked about co-payments, travel costs, travel time, and clinic wait time.

Costs from Administrative Data: VA Health care expenditures will be collected to assess the cost effectiveness of the intervention from the payer's perspective (Veterans Health Administration). The VA expenditures will be assessed using VA Decision Support System (DSS) National Data Extracts, which are based on an activity-based costing allocation method and include fixed direct, variable direct, and fixed indirect costs. Inpatient and Outpatient VA

medication expenditures will also be assessed using VA Decision Support System data. The cost of each prescription will be determined based on the drug product costs and the supplies needed to dispense the prescription based on the dispensing location (centralized mail order pharmacy vs. pharmacy window) To extract data from DSS, a SAS file with study participants' social security numbers and study enrollment and discharge dates will be uploaded to the Austin Automation Center and converted to scrambled SSN (SCRSSN) using the cross-walk file. DSS cost data will then be extracted by merging the SCRSSN file with the DSS files. The resulting files will then be appended into one file and the enrollment/discharge dates for each subject will be used to generate total cost for the 12 months after enrollment (to be included in the calculation of the dependent variable) and the 12 months before enrollment (to be used as a casemix adjustor). These files will then be downloaded to the HSR&D server at Central Arkansas Healthcare System for analysis.

Data Analysis

Hypothesis Testing (Specific Aims #1 and #2)- Patients will be the unit of the intent-to-treat analysis. A dummy variable representing treatment group assignment will be specified as the explanatory variable of interest. An alpha significance level of 0.05 will be used to reject/accept the null hypothesis. Separate regression analyses will be conducted for six and twelve month outcomes. Those patient case mix factors found to be significant ($p < 0.2$) in bivariate analyses will be included as independent variables. Mixed-models (logistic models for dichotomous dependent variables and linear models for change scores) will be used.^{120;121} The mixed-models will include a random effect for the intercept and fixed effects for the patient-level variables (including treatment group assignment). The variance-covariance matrix will be specified to be unstructured. If necessary, the mixed-models will be specified to account for nesting at the VAMC level. The potential problem of missing data will be addressed using multiple imputation methods described by Rubin^{122;123} as implemented in SAS (MI and MIANALYZE). For the exploratory analyses associated with Specific Aim #2, we will add interaction terms (intervention status times OEF/OIF status) to the regression models while controlling for main effects. These regression analyses will test whether the TOP intervention is significantly more or less effective for OEF/OIF veterans compared to veterans with previous periods of wartime service.

Cost Effectiveness Analysis (Specific Aim #4) - Incremental costs and QALYs will be calculated using intent to treat analysis. Because total costs are likely to be non-normally distributed, we will use generalized linear models (GLMs) to estimate the effect of the intervention on total costs. We will also use GLMs to estimate the effect of the intervention on QALYs. To calculate the incremental treatment effect on costs, we will compute two predicted expenditures for each participant based on the coefficients from the GLM regressions and the covariate values for each participant. The first expenditure prediction will be for expenditures as if the participant had been randomized to the TOP intervention, and the second expenditure prediction will be for expenditures as if the participant had been randomized to usual care. The difference between these two expenditure predictions represents the incremental effect of the intervention on expenditures for a particular participant because all covariate effects will be identical for the two estimates in a given patient. Increment treatment effect on QALYs will be calculated in the same manner. The numerator of the Cost Effectiveness Ratio will be the incremental difference in total costs between the intervention and usual care. The denominator will be the incremental difference in QALYs between the intervention and usual care. We will use a nonparametric bootstrap with replacement method and 1000 replications to generate an empirical joint distribution of incremental expenditures and QALYs and acceptability curves representing the probability of falling below CER thresholds ranging from \$0 to \$150 000 per

QALY.

Power Analysis - Power analyses are presented for the primary outcome measure (treatment response). The power analysis is based on an alpha significance level of 0.05 and a sample size of 265 subjects from all study sites with complete data at the twelve month follow-up (112 in each arm). Assuming zero intra-class correlation, there will be 96% power to detect a group difference of 4 points (s.d.=8.0) assuming zero intra-class correlation. The higher the intra-class correlation, the lower the statistical power.¹²⁴ If the intra-class correlation at the VAMC level is 0.01, statistical power drops to 81%. There are no power calculations for the cost-effectiveness analysis.

Data Security

Electronic data (containing personal, confidential information on human research subjects) will be stored at server vhalithsr.v16.med.va.gov (S:\TOP). This location is on a VA server at CAVHS. Access will be restricted to study personnel approved by the CAVHS IRB. Study personnel who do not maintain CAVHS IRB approval requirements will lose access to this data. Hard copies of data (e.g., consent forms and enrollment logs) will be stored in a locked file cabinet or drawer, in a locked room of Building 58 of the North Little Rock VAMC campus. All data (hardcopy and electronic) with personal identifiers (e.g., name, SSN, telephone number, address, etc.) will be kept physically separate from the research data (e.g., symptom severity). All data will be maintained indefinitely, and no data will be removed from the CAVHS facility servers. The only exception will be that a SAS file with study participants' SSN and study enrollment and discharge dates will be uploaded to the VA Austin Automation Center and converted to scrambled SSNs (SCRSSN) using a SSN-SCRSSN cross-walk file. DSS cost data will then be extracted by merging the SCRSSN file with the DSS files. The cost data will then be downloaded to the CAVHS HSR&D server for analysis. When data are uploaded and downloaded from the Austin Automation Center, we will use SFTPs (Secure File Transfer Protocols). The VA Austin Automation Center offers its customers "Total Information Assurance." All data and applications are stored on secure servers in a secure environment using the market's number one intrusion-detection software. Certified security staff run the operations and security is regularly reviewed by a variety of recognized commercial and Federal information security specialists. A Data Use Agreement per se is not required to transfer data to and from the Austin Automation Center. Programmers must complete a Access Form 9957 and a VA Privacy statement.

In the event of theft, loss of data/storage media, or non-compliance with security controls, we will adhere to VHA regulation by reporting each incident immediately to the CAVHS Information Security Officer, Privacy Officer, ACOS/Research and to the IRB.

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