HUMAN RESEARCH PROTOCOL APPLICATION

SUBJECT: IRB REVIEW AND APPROVAL

1. The unified/standardized templates to request approval for a clinical investigation study were created, by a task force appointed by the BRAC Integration Research Working Group, for research conducted at the Military Medical Centers (WRAMC, NNMC, and MGMC) and the Uniformed Services University in the National Capital Area. These templates were approved by the respective institutional review boards between February and March 2007.

2. The templates were created under the assumption that the unified research center would be named the Department of Clinical Investigation (DCI) within the new medical center “Walter Reed National Military Medical Center”. The text “DCI” in this template should be replaced with the name of each individual medical center’s own regulatory oversight department until an integrated department is established. Some hyperlinks cited are WRAMC specific.

3. Follow this template and instructions to prepare your protocol. The contents of a protocol should include all the sections in the template. Sections (bolded) are to be retained and completed in the final protocol. Answer NA to any section or subsection that is not applicable. Standardized consent form, HIPAA authorization, and other templates are available in the joint web-site. Submit an electronic copy of your protocol application package to the Point of Contact (POC) below. To facilitate the review by the Institutional Review Board (IRB), a Table of Contents would be helpful, annotating the page number of each section in your protocol.

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MEMORANDUM FOR CHIEF, DEPARTMENT OF CLINICAL INVESTIGATION (DCI), WALTER REED ARMY MEDICAL CENTER (WRAMC), WASHINGTON, DC

SUBJECT: Application and Request for Approval of Clinical Investigation Study Proposal

Check all the sites where subjects will be enrolled: STUDY SITE(s): X WRAMC, ___NNMC, ___MGMC, ___USUHS; Other, please specify: Fort Bliss, Fort Bragg, Fort Stewart, Fort Campbell, Fort Carson, Fort Lewis

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2. ABSTRACT

2.1 Purpose: Despite the significant prevalence of posttraumatic stress disorder (PTSD) among veterans returning from Operations in Iraq and Afghanistan, less than half of service members who are referred for a specialty mental health assessment actually receive specialty mental health treatment. Systematic knowledge regarding access to care and quality of care delivered in civilian, VA, and military facilities for those who encounter barriers or difficulty is scant, and recent policy reviews have strongly questioned availability and quality of care. These problems of access and quality are major, overarching problems in war-related PTSD research. There are scientifically tested strategies from non-military settings and for other mental disorders to improve access to and quality of care; unfortunately, these strategies are unstudied in the military health system and for PTSD. These strategies include care manager coordination (connecting patient, provider, and specialist), collaborative care (negotiated patient-provider problem definition, monitoring of status and treatment response, self-management support, tele-health sustained follow-up), and stepped care (logical, patient-centered and guideline-concordant treatment sequencing). This study aims to fill these gaps and evaluate these systems-level strategies in a military setting for PTSD.

2.2 Research Design/Methodology: We propose a 6-site, two-parallel arm (N = 1,500) randomized controlled effectiveness trial with quarterly follow-up for 12 months. The enhanced care intervention arm is telephone and in-person care management with a stepped and preference-based management package that consists of the following evidence based interventions for PTSD and/or depression: 1) web-based treatment; 2) telephonic cognitive behavioral treatment; 3) pharmacotherapy administered by a primary care provider within a primary care setting and in telephone consultation with a psychiatrist; and 4) specialty mental health referral. This STepped Enhancement of PTSD Services Using Primary Care (STEPS UP) management package will be compared to optimized usual care (OUC), a collaborative care model where psychiatric consultation is readily available within primary care clinics, called RESPECT-mil.

Primary outcomes include symptom-, health related quality of life-, and functioning-based metrics. We will also perform qualitative assessments of perceived intervention acceptability and effectiveness. We will interview patients within both arms of the randomized trial to assess patients’ experience with and perceptions of centralized telephone care management and associated tools, and will also interview providers, the care managers, and
administrators working with the care management capability to gain insights into whether and how the telephone care management may be facilitating their care and management of their patients with war-related PTSD. Lastly, we will assess the incremental cost-effectiveness of STEPS UP over OUC.

3. OBJECTIVES AND SPECIFIC AIMS
The overall objective of this study is to test the effectiveness of a systems-level approach to primary care recognition and management of PTSD and depression in the military health system. More specifically, we will test the effectiveness of a telephone care management with preference-based stepped PTSD care. This experimental enhancement of care is hereafter referred to as “STEPS UP” (STepped Enhancement of PTSD Services Using Primary Care).

Significant Aim 1: To assess whether active duty primary care patients with either PTSD, depression, or both who are randomly assigned to 12 months of the STEPS UP intervention package (centralized telephone care management and preference-based stepped care) will report significantly greater reductions in PTSD and depression symptoms (primary outcomes) compared to those assigned to optimized usual primary care (OUC).

Primary Hypothesis 1. Active duty primary care patients with PTSD, depression or both who are randomly assigned to STEPS UP will report significantly greater reductions in PTSD and depression symptom severity compared to participants assigned to OUC over 12-months of follow-up.

Significant Aim 2: To evaluate whether active duty primary care patients with either PTSD, depression, or both who are randomly assigned to 12-months of STEPS UP will report significantly greater improvements in depression, anxiety, and somatic symptom severity, alcohol use, mental health functioning, and work functioning (secondary outcomes) compared to participants randomly assigned to 12 months of OUC.

Hypothesis 2. Active duty primary care patients with either PTSD, depression, or both who are randomly assigned to STEPS UP will report significantly greater improvements in depression, anxiety, and somatic symptom severity, alcohol use, mental health functioning, and work functioning compared to participants assigned to OUC over 12-months of follow-up.

Significant Aim 3: To examine whether active duty primary care patients with either PTSD, depression, or both who are randomly assigned to 12 months of STEPS UP will have significantly lower direct and indirect costs of care and a more favorable cost-effectiveness ratio (tertiary outcomes) compared to participants assigned to 12 months of OUC.

Hypothesis 3. Active duty primary care patients with either PTSD, depression, or both who are randomly assigned to STEPS UP will have significantly lower direct and indirect costs of care and a more favorable cost-effectiveness ratio compared to participants assigned to OUC over 12-months of follow-up.

Significant Aim 4: To use qualitative methods to examine active duty primary care patient, clinician, care manager, and administrator perceptions of STEPS UP and associated outcomes.

Hypothesis 4. Active duty primary care patients participating in STEPS UP, their clinicians, care managers, and administrators will report that STEPS UP is acceptable, effective, satisfying, and appropriate PTSD and depression care.
4. MEDICAL APPLICATION/MILITARY RELEVANCE
This trial will accelerate fundamental improvements in the care of PTSD and depression for our nation’s service members. Important deliverables will include (1) a web-based cognitive behavioral self-management tool adapted for use with RN nurse assistance; 2) a telephone cognitive-behavioral therapy approach with “how to” guides that will improve delivery of empirically supported treatment elements to service members at remote “hard to access” sites common in military operations; (3) a flexible care management approach that can be delivered centrally with as needed on-site support, which codifies an efficient team medicine approach to maximizing human contact and timely adjustment of treatment; and (4) a computer-automated care management support tool that prevents system errors, facilitates service member tracking, and enhances care management fidelity to the model as well as program and care manager accountability and system benchmarking and reporting. In the event that STEPS UP proves effective, the approach could roll out immediately on a scale commensurate with military health system needs as determined by U.S. military leaders.

5. BACKGROUND AND SIGNIFICANCE
There are major gaps in pathways to PTSD and depression care and recovery. Researchers have reported significant prevalence estimates of PTSD or depression among veterans returning from Operations in Iraq and Afghanistan. Despite estimates that 13%–18% of returning servicemembers have PTSD or depression and 28% have serious symptoms of PTSD, anxiety, or depression, only 10% screen positive for PTSD on screening immediately post-deployment. Of those screening positive, only 22% are referred for a specialty mental health assessment and only half of those referred receive any specialty mental health treatment; the proportion who eventually recover is unknown.

A recent study of Iraq and Afghanistan veterans found that approximately 47% of returnees with PTSD or depression sought care for that problem in the past year. Of those who did seek care from a health provider only about half received minimally adequate care. For military veterans, the path to PTSD and depression care and the subsequent course of that care involves complex transitions across levels, settings, and even sectors of care, and it is unknown for how many service members that treatment offers improvement or eventual recovery. Recent GAO reports, the Department of Defense Mental Health Task Force, and other policy reviews have strongly questioned the availability and quality of PTSD care for our nation’s veterans.

Key systems-level strategies are known to increase continuity of care, concordance of care with existing clinical practice guidelines, and lead to improved outcomes, hence closing key gaps in pathways to adequate care and recovery for depression, panic disorder, and somatic symptoms. These strategies include care manager coordination between patient, provider, and specialist; collaborative care involving self-management support, tele-health follow-up, and monitoring of treatment response with timely treatment adjustment; and stepped care involving efficient patient-centered, guideline concordant treatment sequencing.

There has been a growing chorus of concern over lack of access and poor quality military mental health care. Systems-level approaches to closing gaps in pathways to care and recovery are understudied for PTSD and unstudied in the military health system. The military mental health system provides a safety net for over 9.1 million beneficiaries at an annual cost of $40 billion, yet it lacks a scientifically tested systems-level approach that addresses mental health care quality and outcomes.
The quality of PTSD care is a major problem facing researchers, clinicians, and health policy makers across the U.S. Healthcare system and for DoD in particular. In fact, the problem of access to quality mental health services has been named a DoD Force Health Protection priority. Extant PTSD practice guidelines\(^8\)\(^-\)\(^\text{12}\) suggest that effective clinical interventions are available. Yet availability and utilization of these evidence-based approaches varies widely across the health care system. Furthermore, published trials of systems-level interventions that ease the path to and through high-quality care for depressive disorders, anxiety disorders, somatic symptoms, and other mental health conditions suggest the impact of these interventions is robust may be applicable for improving the quality and outcomes of PTSD care for affected military personnel.\(^13\)-\(^\text{20}\) However, these approaches have not been systematically tested or adopted within the military health system.

We believe that systems-level interventions targeting the quality and outcomes of PTSD and depression care are critical to improving the military’s functioning, readiness, and resilience. By creating sustainable, practical solutions that can improve care within the military mental health system, pathways to recovery become reality. To evaluate the effectiveness of such a systems-level solution, we propose to complete a multisite randomized effectiveness trial comparing optimized usual care (OUC) to STEPS UP, an enhanced primary care management package for military personnel with PTSD and depression (see section 6.3.2. for greater detail). STEPS UP uses a coordinated approach to the continuous delivery of evidence-based PTSD and depression treatment elements. These elements rely on empirically validated cognitive-behavioral therapeutic strategies and evidence-based pharmacotherapies. STEPS UP ensures that these strategies are delivered and reinforced in innovative ways that improve the availability, acceptability, and synergy of a feasible continuum of PTSD-related health services. We believe this PTSD management package will improve clinical outcomes of PTSD by improving the continuity of PTSD care and the concordance of PTSD care with evidence-based practice guidelines.

The knowledge gained from this study is crucial for advancing the care process to treat PTSD and depression in our War fighters. PTSD is a common and disabling consequence of OIF/OEF, and previous research suggests that without early intervention PTSD may have significant long-term consequences for many sufferers. An effective stepped system of collaborative care management, utilizing an Internet-based self-management approach and regular telephone support and telephone-based cognitive behavioral therapy (CBT) support that is integrated into VA and DoD primary care may ensure that many military personnel and veterans with war-related PTSD who typically go unrecognized and untreated would receive evidence-based CBT. The study may provide effectiveness data to support the stepped implementation of existing empirically valid interventions in this system of care and delivery. It has the potential to improve outcomes and reduce patient and professional resource demands. It may serve as a model for early intervention for PTSD after disaster, terrorism, and other traumatic events.

6. PLAN

6.1 New Investigational Drugs/ Investigational Devices Exemption Status

No investigational drug or device will be used.

6.2 Selection of Subjects
6.2.1 Type of the Subject Population

a. Participants will be 1500 active duty returnees from OIF/OEF/OND presenting with the diagnosis of PTSD and/or depression in primary care clinics at one of six Army Posts: Forts Bliss, Bragg, Campbell, Stewart, Carson, & Lewis. Participants in the secondary qualitative study will be 15 study participants, 30 healthcare providers (from among those providers treating patients in each arm), and up to 12 study care managers.

b. Not applicable. The proposed research involves no laboratory evaluations or biologic sampling.

6.2.2 Inclusion and Exclusion Criteria

a. Inclusion Criteria
   1. Active duty status at the time of enrollment
   2. Positive PTSD screen (2 or more yes responses on PC-PTSD (reference), per routine primary care screening.
   3. DSM-IV-TR criteria for A) PTSD using the PCL-C (i.e., a “moderate” or greater severity level on 1 re-experiencing, 3 avoidance, and 2 hyperarousal symptoms) and/or B) Depression, using the PHQ-9 (i.e., endorsement of at least 5 of the 9 symptoms experienced “more than half the days” and at least one of those symptoms must include either “little interest or pleasure in doing things” or “feeling down, depressed or hopeless”)
   4. Deployment to Iraq or Afghanistan since 2003
   5. Report of routine computer, internet, and e-mail access
   6. Capacity to consent to participation and provides research informed consent using local IRB-approved form

b. Exclusion Criteria
   1. Treatment refractory PTSD or depression after participation in RESPECT-Mil or specialty mental health treatment.
   2. Acute psychosis, psychotic episode, or psychotic disorder diagnosis by history within the past 2 years.
   3. Bipolar I disorder by history or medical record review within last 2 years.
   4. Active alcohol dependence disorder in the past year by history within the past 12 months.
   5. Active suicidal or homicidal ideation within the past 2 months by history.
   6. Patients on psychoactive medication, unless that medication dosing and administration has been stable and regular for at least 1 month.
   7. Acute or unstable physical illness.
   8. Anticipated deployment, demobilization, or separation during the next six months.

6.2.3 Recruitment

The Initiating PI is the program officer for RESPECT-Mil, a primary care approach to PTSD and depression currently implemented in all clinics involved in the proposed research trial. We are confident recruitment goals will be met based on existing RESPECT-Mil program screening and referral data. There are three to five RESPECT-Mil personnel (nurse care managers, administrative assistants, and physician “champions”) at each of the six proposed study sites. The primary care clinics at each of these sites are already routinely screening and assessing primary care patients for PTSD and depression in a manner consistent with STEPS UP intervention. Moreover, at each of the six study sites, a full-time site research associate will
oversee site specific recruitment and enrollment. Our goal is to enroll 250 participants per quarter for six consecutive quarters (250 x 6 equals 1500), starting in Year 2.

The primary recruitment strategy will be referral from clinician (See Figure 1). Additionally, we plan to use direct-to-patient advertisements to raise study awareness and promote self-referral (See Figure 2).

**Referral from clinician.** Our primary recruitment method will involve integrating STEPS UP into the current primary care screening process already in practice as part of RESPECT-mil. Patients presenting to the clinic receive a MEDCOM774 form, which includes the PC-PTSD and PHQ-2; positive screens then receive the PCL and/or PHQ-9. The patient’s clinician is given the screening responses for review during the visit, at which time the clinician may chose to refer the patient for additional services, including RESPECT-mil or behavioral health. For the STEPS UP trial, we plan to incorporate STEPS UP into the RESPECT-Mil referral process. Clinicians will make a referral to RESPECT-Mil as appropriate via the AHLTA system or a blue referral sheet; these referrals are collected by the RESPECT-Mil administrative assistant assigned to each clinic. The RESPECT-Mil administrative assistant will then contact the patient via telephone and present STEPS UP as a treatment option (see Appendix J). Patients who are not interested in participating in STEPS UP will be enrolled in RESPECT-Mil as usual. Patients who are interested in participating in STEPS UP will have their contact information forwarded to a STEPS UP staff member, and will be contacted within 24 hours to assess eligibility and provide informed consent.

**Direct to Patient Advertisement.** To increase study visibility and recruitment, study pamphlets will be strategically placed throughout the military posts (including the clinics; see Appendix G). Advertisements will briefly introduce the study as well as study risks, benefits, and eligibility requirements. Additionally, the advertisements will provide contact information for both the study PI and site research associate. All advertisements will include a web address to the project’s main website, where potential participants can learn more about the study and complete an eligibility screen. Eligible screens will automatically be forwarded to the site research associate, who will contact the patient to provide more information and answer any questions. Ineligible screens will be provided with a list of additional resources via the website.
Figure 1. Primary Recruitment Method – Referral from Clinician

Primary Care Screening (RESPCT-mil)

- Patient completes PC-PTSD & PHQ-2
  - Negative Screen
  - Positive Screen
    - Patient receives FCL/PHQ-9
      - Patient negative for PTSD and/or depression
        - Patient not referred to R-MIL
      - Patient positive for PTSD and/or depression
        - Patient has visit with Clinician – Clinician reviews screening results, makes referral
          - Patient is referred to R-MIL via AHLTA or blue referral sheet
            - The R-MIL Admin last contacts the patient and presents STEPS UP as an option (in addition to R-MIL)
              - Patient is not interested, goes to R-MIL or other
            - Patient is interested in STEPS UP
              - R-MIL Admin Asst tells patient STEPS UP staff will contact him/her within 24 hours (warm handoff); passes contact info along to STEPS UP
                - STEPS UP staff contacts patient, explains study, administers pre-screen via telephone
                  - Patient not eligible – conduct consent, eligibility assessment, and baseline in Clinic with RA (Randomization to be completed after baseline)
6.2.4 Consent Process

a. Consent will be sought for all patients who wish to participate. The consent process will begin via telephone or in person, with study personnel responding to any questions about the study; explaining the study procedures, and reviewing the risks, benefits, and voluntary nature of the study. Participants will not be financially compensated for taking part in this study; however, they may benefit from the intervention in the form of symptom reduction and/or being able to contribute to the improvement of PTSD and depression treatment for future service members. Patients will be informed that their current treatment and future services and benefits are not contingent on participation in this or any research study. Patients that remain interested in participating will be asked to sign a written consent form. Written consent to participate in the study will be obtained through the following methods for potential volunteers:

- Study personnel will mail a cover letter (see Appendix L), a STEPS UP Project Questions and Answers sheet (see Appendix H), and a hard copy consent form to the potential volunteer, to review and keep for their own personal files. The cover letter will provide contact information for the site’s research associate and will encourage potential participants to call if they have any questions prior to signing the consent form in person.
- The potential volunteer will come in to the responsible local study site research associate’s location to further review and sign the informed consent form, and a copy of the signed consent form will be provided to the potential participant. A hard copy of the consent form must be signed by the participant in person.
Consent storage. Hard copies of consent forms will be stored in a locked cabinet in a locked office of the site principal investigator. At the request of the RTI International and RAND Corporation IRBs, copies of the consent forms may be sent. Consent forms will be stored separately from study data. All consent forms will be kept for six years after the completion of the study, at which time they will be destroyed.

Ensuring Informed Consent. Many individuals sign consent forms without thoroughly reading the form or read the form and do not understand what they have read and do not feel comfortable asking questions. In addition to the consent form itself, each person will be given a “frequently asked questions” document that describes the required aspects of informed consent in simple language (Appendix H).

a. Individuals who have indicated at any point that they are not interested in participating in the study, or who do not otherwise consent to participate in the study, will be thanked for their time and referred back to the appropriate medical clinic for further assessment and/or offered other treatment resources as applicable.

b. The consent will be laid out in clear, layperson language, and will explain all risks as well as benefits of the study. Participants will be given ample time to read the consent frequently asked questions document, and will be provided an opportunity to ask questions to study personnel. They will only sign after they give their full informed consent.

6.3 Study Design and Methodology

6.3.1 Study Design

We propose a six-site, two parallel arm (total n=1500) randomized controlled trial with quarterly follow-up for 12 months comparing the following two interventions: a) a flexible telephonic and on-site care management plus stepped PTSD and depression care (STEPS UP) with b) optimized usual care (OUC). Both arms will feature patient decision aids to provide information and guidance tailored to patients’ values on PTSD and depression, and risks and benefits of available treatments and treatment settings.

Systems-level interventions focusing on care management approaches have improved outcomes for several chronic diseases including mental disorders\(^\text{14, 23, 24}\), but these approaches have never been tested in the military health system or for PTSD and depression in a “real-world” multisite design. Consequently, we will test a systems-level intervention that targets service members with positive PTSD and/or depression screening with a history of deployment to Iraq or Afghanistan since 2003 at the 6 Army posts. Each post is a continental U.S. Power Projection Platform. These Power Projection Platforms are the main locations where virtually all troops deploy and return from deployment. The intervention involves several components, each targeting aspects of PTSD and depression. Three components are entirely systems-level approaches (flexible telephone and on-site care management, expert PTSD supervision, and computerized care management tracking). Four components comprise a stepped care approach to patient-level intervention that care managers and their expert mental health supervisor can use to intensify treatment in a logical sequence that is maximally patient centered (Web-enhanced self-management, telephonic CBT, evidence-based pharmacotherapy, local specialty care management).

Our choice of intervention is based on best clinical evidence and targets three major and related problems in the effective delivery of care for PTSD and associated conditions: (1) poor or
stigmatized access to PTSD care; (2) poor continuity of PTSD care, often due to uncoordinated care and complex health care system transitions, and (3) failure to receive patient-centered, clinical practice guideline concordant care (e.g., VHA-DoD Clinical Practice Guideline).

The trial will allow for preliminary analyses of various components (e.g., systems- versus patient-level components, telephonic CBT versus Web-based self-management). It is not intended or designed to assess the efficacy of independent elements. Each component was selected for inclusion in the STEPS UP package on the basis of previously published evidence and its capacity to facilitate implementation of current guideline practices in PTSD care (e.g., CBT, selective serotonin reuptake inhibitor antidepressant medications—SSRIs). That is, no individual component of the STEPS UP package is considered new or experimental. In the event the package proves effective versus optimized usual care, then subsequent research can elucidate independent and synergistic effects of components. This is done much in the way one first studies a new psychotherapy (e.g., CBT) as a package before evaluating its individual components. If the package is ineffective versus usual care, the study of individual components is unnecessary.

We have chosen a randomized (“true experiment”) design because it is the most valid design for making causal inferences regarding the impact of STEPS UP, so we chose the randomized experiment for its strong internal validity. Single-site efficacy trials tend to overestimate the real-world effect of interventions, because single-site trials usually involve experts who are intervention proponents and use narrow inclusion criteria selecting only ideal treatment candidates. In contrast, the multisite approach and the use of relative inclusive eligibility criteria ensure that our estimate of intervention effect approximates the true real-world intervention effect. Hence, we have designed our trial to maximize both the internal validity of causal inference regarding the packaged intervention and the real-world generalizability of observed intervention effect sizes. Randomization of participants will automatically be performed via the RTI web portal upon completion of the eligibility assessments and confirmation of eligibility by the site research associate.

Qualitative data will help us explore the acceptability of the intervention to patients, providers, care managers, and administrative staff. Quality-of-care analyses will allow us to assess the likelihood that observed benefits are the result of improvements in care quality. Finally, cost analyses will estimate the value of observed intervention benefits, providing health policy makers the right information for deciding whether observed intervention benefits justify the added cost to a health system of implementation.

6.3.2 Study Methodology/Procedures

6.3.2.1 Intervention Description/outline:

The STEPS UP package (Figure 3) is systematic approach to offer evidence-based and guideline concordant treatment strategies for PTSD and depression in primary care clinics. The package will provide a critical service for military medicine by implementing a collaborative care model (i.e. the act of doctors engaging patients in making health care related decisions) and facilitating the coordination of patient care to ensure continuity of treatment, to prevent patients from falling through the cracks, and to offer systematic changes in treatment if service members are not improving as expected. The STEPS UP package offers a range of practical, sustainable, and evidence-based treatment options that can improve PTSD and depression care. Examples of treatment options include combined case management, psychotherapy, and pharmacotherapy.
Figure 3. STEPS UP Three Step Intervention Protocol Targeting PTSD and Depression

Conceptual Framework: The STEPS UP package is based on the 3 Component Model\textsuperscript{25} (See Figure 4), a model of collaborative care used in the civilian sector. This model emphasizes the coordination of multifaceted interventions with the aim of integrating effective mental health treatments into general medical care. The model facilitates a patient centered approach by linking the primary care provider, specialty care provider, and patient through a care manager who is responsible for coordinating care. The approach is designed to insure that mental health disorders are recognized early, appropriate evidence-based psychotherapeutic and pharmacologic treatments are prescribed, prescribed treatments are consistent with patient treatment preference, treatment plans are informed through a team process and enhanced specialist input, and consistent follow-up and reassessment occurs. Research has suggested that the 3 CM model is effective in improving primary care outcomes of depression\textsuperscript{26} and is similar to models improving primary care outcomes of common mental disorders.\textsuperscript{14, 22}
The Role of the Care Manager. All participants randomly assigned to the STEPS UP intervention will receive telephone care management. In the STEPS UP approach care managers (CMs) are typically nurses (RN), but rarely social workers (BSW or MSW) or counselors (BA or MA) are used. The flexible STEPS UP care management approach will use a) telephone care management, with CMs being centrally housed in Washington DC and b) on-site CMs, one CM at each study site. All CMs will be extensively trained, and mentored by licensed doctoral level mental health professionals with specific expertise in the treatment of PTSD and depression. CMs will have regular telephonic contact with patients in their caseload (see Figure 5) and facilitate patient care between the patient, primary care and specialty care clinicians during the twelve month intervention period.
CMs and Treatment Engagement: Primary functions of a CM include encouraging patient participation in treatment, maximizing treatment adherence, and helping patients identify their preferred “best next step” for treatment if their current treatment plan (e.g. step) is unsuccessful. To execute these functions CMs will use motivation enhancement strategies to increase the likelihood of treatment engagement and move the patient toward positive therapeutic action.

CMs and the Coordination of Patient Care: CMs will coordinate care by facilitating the flow of key clinical information and recommendations between a centrally located mental health specialist (e.g., psychiatrist, psychologist – note that this specialist is collocated with telephone CMs) with expertise in PTSD and depression management, local clinic-based mental health specialists, the patient’s primary care provider and the patient. CMs will meet weekly with the central call-center located expert specialist who will review the status of patients within each CM caseload once per week (plus intervening contacts as appropriate for urgent or emergent circumstances). CMs will convey specialist advice to patients’ primary care provider (typically completed using the AHLTA telephone consult function for the purpose of documentation and workload capture). Using these methods, CMs insure continuity of care, following patients even if they move to a different location resulting in a change of local clinicians. To accomplish this, CMs will often contact, facilitate referral to, and exchange medical information with a variety of clinicians (e.g., psychiatrists, psychologists, social workers, generalists, other CMs) encountered in the immediate and ongoing care of patients in their caseloads.

CMs and Symptom Monitoring: CMs will regularly monitor changes in PTSD and depression symptom severity using validated clinical measures (PHQ-9 for depression, the PCL for PTSD). They will also screen each patient for alcohol misuse (AUDIT-C) and bipolar disorder. In addition, CM’s will deliver various PTSD and depression care components (described below).

The STEPS UP Package: The STEPS UP package is designed to give a menu of effective treatments and strategies available for patients with different levels of illness severity. Based on the patient’s initial assessment, the health care team in collaboration with the patient will identify the appropriate care step (e.g., STEP-1, STEP-2, STEP-3). If a patient is not improving using their initial step, he/she will be re-assessed and “stepped up” to another treatment STEP. The following sections summarize the STEPS and potential treatment options within each step.

**It should be noted that no experimental treatments will be used in STEPS UP. All STEPS UP treatment components are evidence-based and have demonstrated efficacy in other clinical trials.**

**STEP-1: Patient Engagement, Education, and Preference Development.**

STEP-1 CM activities will be ongoing throughout the 12 month intervention period for all patients in the trial regardless of whether or not the patient is “stepped up” to a higher level of care.

**Engagement.** CMs will employ an “aggressive outreach” approach to engagement.27 That is, CMs will pursue patients to continue follow-up unless patients request to discontinue CM/STEPS UP care. This aggressive outreach strategy will be explained to all potential participants at the time of initial informed consent with intermittent reminders over the course of intervention follow-up for patients that need repeated contacts to keep them engaged.

Typically patients will have a primary care provider at the time of enrollment in the trial, and for these patients’ CMs will initiate STEP-1 in concert with ongoing primary care treatment.
For patients in transition (e.g., redeployment, change of station), a meeting with a CM prior to engaging their local primary care provider may occur. For these patients, CMs will initiate STEP-1 and facilitate linkage to primary care. If there is no established appointment with a local primary care clinician, then the CM will arrange and confirm primary care clinician follow-up within 3-6 weeks of first CM contact.

**Patient Preference and Education.** Primary care clinicians seldom have the time, motivation, and knowledge to explain the range of PTSD and depression treatment options to patients. CMs will therefore assist the primary care clinician by providing information related to treatment options and selecting the “best step” or the “best next step” (if the current treatment is not working) for a patient’s treatment plan. CMs will provide patient education regarding treatment options and will troubleshoot patient concerns, questions, side-effects, or problems related to specific treatment options. A range of education modalities (e.g., brochures, workbooks, digital media, and videotapes) will be used. Education materials will address post-deployment PTSD and depression, evidence-based treatment options and treatment settings, risks and benefits, importance of treatment adherence, the role of CMs, and features of STEPS UP intervention. Patient education and preference discussions will begin during the first CM contact (occurring less than 1-week after randomization to the STEPS UP study arm) and continue throughout the 12 month period.

**Behavioral Activation (BA).**

Behavioral Activation can be conceptualized as a set of behavioral techniques that constitute structured attempts to engender increases in overt behaviors that are likely to bring a patient with anxious avoidance, or depressive symptoms into contact with reinforcing environmental contingencies and produce corresponding improvements in PTSD and depressive symptoms and overall quality of life. BA is most commonly employed to assist individuals in overcoming avoidance. This technique involves gaining a clear understanding of what the patient is avoiding and developing a series of small steps a patient could take to resume his/her typical or optimal activity level. In the STEPS-UP care management protocol BA may focus most specifically on the scheduling of pleasant activities, prior to formal entry in the DESTRESS cognitive behavioral therapy protocol.

Components of BA will include 1) Assessing the patient’s current level of functioning/activities, pre-trauma level of functioning/activities, and behaviors that may be functioning as avoidance targets, 2) Orientation to Behavioral Activation, 3) Behavioral Activation Intervention: Suggest/discuss specific options for activation:

- To be done collaboratively (e.g., "what do you think would be a realistic first step?"); make suggestions when necessary
- Try to optimize activation without overwhelming patient with too much
- Provide statements that convey hope and encouragement that the follow through on activation plan will move them toward their ultimate goals

CMs will assist patients in setting one or two BA goals relating to specific activities or behaviors (e.g., pleasant physical and social activity, relaxation practice, time with friends/family, small goals, avoiding/minimizing alcohol use, monitoring diet). These active strategies help patients address avoidance behaviors symptomatic of PTSD and depression. CMs will monitor adherence to BA goals with patients at each CM follow-up contact.
Motivational Interviewing (MI). If patients are ambivalent about entering or completing a treatment step, CMs will be trained to employ simple MI techniques which have been found to be effective in helping patients to overcome ambivalence to change and take positive therapeutic action. MI’s approach is in accordance with one of STEPS UP’s goals of promoting patient-centered care. MI emphasizes shared decision making, incorporating patients’ preference when deciding among treatment options, as well as patients’ ability to make choices about whether they are ready to engage in behavior change. Additionally, throughout the process, MI continually aims to improve self-efficacy and increase patients’ confidence in making behavior change.

Within STEPS UP, centralized telephone and in-person care management will be employed to improve the availability, quality, and acceptability of care. To further enhance the function of care management, MI strategies provide care managers tools to help patients make decisions about care and to increase the likelihood of engagement and follow-through. MI can serve different functions each with a particular goal, depending on when it is implemented within the STEPS UP model. The first opportunity to use MI is if patients need help “buying into treatment” (i.e., helping patients decide if they are willing to work on symptoms of PTSD and/or depression). If patients believe that treatment is necessary, MI can help them to identify appropriate targets for treatment (i.e., depression symptoms, PTSD symptoms, or both) as well as what form of treatment may work best (e.g., web-based, phone-based, pharmacotherapy, specialty mental health care). Then, when patients are ready to begin a particular treatment (based on their level of awareness and motivation), MI can be used to maintain adequate engagement (e.g., adhering to treatment sessions, homework completion). MI strategies can be used within each step of STEPS UP care, but they can be especially useful in the initial contacts with patients, when patients are considering treatment and struggling whether to commit to the requirements of various forms of care.

MI does not require specialty mental health experience and MI is not tied to a particular school of psychotherapy or treatment for a particular problem. MI is not a formal psychological intervention. Rather, it is a dialogue used to guide patients in resolving ambivalence about behavior change. MI complements psychological treatments and can be used prior to starting an intervention or initiated in the midst of an intervention, if the patient demonstrates problems with awareness, motivation, or engagement.

Figure 6. STEPS-UP Care Management Integrating Motivational Interviewing
**STEP-2: Enhanced Primary Care Delivery of Evidence-based PTSD and Depression Treatment**

CMs will encourage patients that remain clinically symptomatic after 3 to 6 weeks of STEP-1 care (symptomatic defined as PHQ-9 symptoms consistent with the diagnosis of major depression OR PCL symptoms consistent with a diagnosis of PTSD – see section 6.2.2a, “Inclusion Criteria”) to step up the treatment intensity. Patients in STEP-2 will continue call-center CM contacts and the STEP-1 strategies previously outlined.

STEP-2 will include one or more of the following for PTSD, depression, or both: (a) web-based self-management with CM assist\(^{29,30}\), (b) telephone-based cognitive-behavioral therapy (CBT),\(^{31}\) and (c) evidence-based pharmacotherapy.

**Web-based Care Manager Assisted Self-Management.** DESTRESS-PC\(^{29,30}\) is a six-week Internet-based psychosocial treatment for military and veteran primary care patients meeting diagnostic criteria for PTSD (see Appendix M). Developed and evaluated by Drs. Litz and Engel, this cognitive behavioral intervention was designed to teach various coping strategies that service members can use to manage reactions to situations triggering traumatic recall. Using
DESTRESS, a service member will acquire necessary skills to monitor arousal and negative affect; reduce and manage PTSD symptoms; anticipate and prepare for symptom triggers, and improve work, family, and leisure functions. DESTRESS-PC will be modified to include evidence-based components of depression self-management (e.g., behavioral activation exercises and techniques to address disabling cognitions common in depression). For all patients selecting DESTRESS-PC, the CM will contact them by telephone every two weeks to offer assistance.

An analogous web-based treatment for depression, called Beating the Blues, will also be offered (see Appendix N). Developed by a multi-functional team, the Beating the Blues program uniquely combines multi-media interactive computer technology with empirically-validated CBT techniques and crucial non-specific aspects of therapy. The program is made up of 8 weekly sessions, with each session taking about 50 minutes to complete, and includes homework assignments. For all patients selecting Beating the Blues, the CM will contact them by telephone every two weeks to offer assistance.

Telephone-based Care Manager Delivered CBT. DESTRESS-T is an adaptation of DESTRESS modified for person-to-person telephone administration (see Appendix O). DESTRESS-T is a 6 to 9 week program involving weekly 50 minute person-to-person telephone contacts with an RN nurse (a CM in the STEPS UP approach trained and supervised by a doctoral level mental health practitioner). CMs telephone contacts with patients in DESTRESS-T will focus on web-based exercises and homework used in DESTRESS-PC. DESTRESS-T is a key option in STEP-2 treatment and occupies an essential part of the spectrum of psychosocial strategies available for primary care patients with PTSD or depression. It is appropriate to consider for patients who (1) desire a more interpersonal mode of treatment than DESTRESS-PC; (2) require active CM instruction and involvement to complete the DESTRESS logons and homework; or (3) experienced an incomplete response to the full course of DESTRESS-PC.

Evidence-Based Pharmacotherapy. Expert training in the pharmacologic treatment of depression and PTSD will be provided to primary care clinicians participating in the STEPS UP trial (see Appendix P). Primary care clinicians will also have access to 24/7 consultation with a call center psychiatrist who has expertise in pharmacologic management of depression and PTSD. Only standard pharmacotherapies for PTSD and depression that are safe and effective will be used.

CMs will encourage patients to work with their local primary care providers to complete a trial of evidence-based pharmacotherapy and maintain contact with the treating primary care provider, keeping the PCP informed of symptom progression or side effects related to treatment. We have modeled our medication module in accordance with best practice guidelines. The protocol consists largely of the algorithms for the delivery of FDA-approved SSRIs for PTSD (e.g., sertraline, paroxetine). There is no use of investigative or experimental medications in the STEPS UP program. Pharmacologic alternatives for PTSD or depression with clinical trial evidence of efficacy (e.g., venlafaxine, prazosin) may be used at the discretion of patients and their treating primary care clinician.

CMs will also be available to local clinicians by secure e-mail and telephone to address pharmaco- and psychotherapeutic treatment questions. A 24/7 expert psychiatrist consultation will be available to those local primary care clinicians who complete intensive training in the pharmacologic management of PTSD and depression (See “Risk Management” in Section 6.3.4).
Patients in STEP-3 treatment will continue call-center CM contacts and the STEP-1 strategies previously outlined. Patients with PTSD or depression appropriate for STEP-3 treatment include: (1) patients that request specialty mental health referral; (2) patients the primary care clinician-CM-expert specialist team considers complex enough to warrant specialty mental health referral; (3) patients unresponsive to STEP-1 and STEP-2 primary care treatment (response defined as 50% reduction in PHQ-9/PCL score or loss of current diagnosis); (4) high risk patients (e.g., suicide risk, violence risk); (5) patients with a high degree of illness complexity (e.g., presence of comorbid psychiatric conditions, need for modalities or follow-up unavailable in local primary care); (6) patients the primary care clinician is uncomfortable managing in the primary care setting for any reason.

CMs will insure successful transition of care to STEP-3 health care providers. Local mental health specialists involved in delivering STEP-3 care may work from the primary care clinic or from the local behavioral health clinic. CMs will continue to follow the patient for continuity even after transition to STEP-3 so that symptoms are actively monitored and that timely changes in the treatment plan are explored in patients whose symptoms are not clinically improved over a 6 to 8 week period since the previous treatment change. Following this transition, the CM will continue to contact the patient at least monthly via phone. Additionally, the CM will communicate with the patient’s primary care provider and STEP-3 care provider in order to monitor the patient’s treatment regimen.

One specialist per participating primary care clinic at each study site will be trained in empirically validated psychotherapies for PTSD and depression. This training will be delivered by members of the STEPS UP investigator team. 24/7 expert psychotherapist consultation will be available to those mental health specialists at each site who complete intensive training in the pharmacologic management of PTSD and depression.

6.3.2.1.2 Cost-Effectiveness
We will assess the cost-effectiveness of STEPS UP relative to optimized usual care using standard methodologies described by Gold and colleagues, Haddix et al., and Hoch and Smith. Data for this analysis will be gathered by a variety of means, include patient self-report of health service use and estimates from existing literature. Information gleaned from conducting the primary effectiveness study and the qualitative study (described elsewhere in this protocol) will inform the specific procedures in the cost-effectiveness study.

6.3.2.1.3 Qualitative Study
We will assess the perceptions of telephone care management and collaborative care among patients and providers. Information gleaned from conducting the primary effectiveness study will inform details of the qualitative study.

6.3.2.2 Risk Management
Overview. The goal of this study is to examine the collaborative stepped care model which utilizes intervention components that have been previously tested and found to be effective for the patient population. Given that each of the intervention components have been tested in other studies and many are frequently used as the standard of care for the patient population in DoD medical facilities, there is no reason to expect that these risks are more than
those anticipated during the course of usual mental health care for PTSD, depression and associated conditions. However, service members involved in treatment for depression and PTSD are at risk for psychiatric instability or situational life crises; protections related to participant safety must be addressed in the research protocol. Thus, the following section describes the steps that the research team will take to manage risk behaviors consistent with psychosocial and psychiatric treatment. The subsequent sections detail procedures that will be initiated in response to behaviors that pose an immediate danger to service members or others, including suicidal or violent behaviors.

Further, roles and responsibilities of research staff members as well as the training these staff members will receive as part of the research program will also be described. Procedures to manage risks relevant to a unique therapy modality/delivery method will be detailed in subsections entitled risk management for each intervention description. Additionally, a plan addressing risks related to data collection is highlighted in “Data Security” under Section 6.3.4. Safety monitoring and the reporting of adverse events (AE) or serious adverse events (SAE) are described in Section 6.5, Reporting Adverse Events.

Psychosocial and Psychiatric Treatment Risks. Service members involved in treatment for depression or PTSD are at risk for psychiatric instability or situational life crises, including evidence of being actively suicidal or any other behavior that poses immediate danger to service member or others. Hence, research team members or providers treating patients may encounter crisis situations throughout the study time period. To minimize this risk, specific procedures with respect to pre-existing medical and psychiatric conditions, screening procedures, risk assessments, and monitoring of adverse events will be applied to protect the safety of service members throughout the course of the study. The following sections describe the procedures that the research team will take to minimize psychosocial and psychiatric treatment risks and protect the welfare of human subjects participating in this trial.

Study Intake Procedures. To facilitate patient safety, all participants will be asked to identify at least one individual that can be contacted in case of an emergency, who will always know how to get in touch with them. Study team members will also identify the clinic where the service member receives primary care services and coordinate with the patient’s primary care provider, if necessary.

Service members will receive a card with the care manager and local emergency contact numbers. The care manager’s primary role is to bridge the gap between all care providers, ensuring both quality and coordination of care.

Pre-existing Medical and Psychiatric Conditions. As stated in the inclusion and exclusion criteria, high risk participants will not be enrolled in the study. Patients excluded for these conditions will provided with a referral commensurate with their level of risk (e.g., patient will be escorted to the emergency room if he/she expresses imminent threat of harm to self). During the study, a participant exhibiting psychiatric instability or other criteria that would deem him/her ineligible for the study will be provided with a referral. If a potential participant is at imminent risk of harm to self or others, a study provider will ensure that the patient is immediately evaluated by clinician in the clinic or the nearest emergency room.
Screening and Psychiatric Symptom Monitoring. Throughout the study, service members will be carefully monitored for signs of clinical deterioration. If a participant endorses an outcome question that indicates a significant risk of self-harm, a trained study staff member will contact the participant and conduct a risk assessment. If this endorsement occurs when a participant is completing questions on the web portal, an automated message will be generated to study staff. Staff will attempt to contact the participant within 24 hours. The STEPS UP web portal will include a separate application designed to review and alert appropriate project staff of concerns about respondents’ mental state. When a research participant endorses suicidality at a clinically significant level while completing the baseline or follow up assessments, the on-call provider will be automatically alerted by the system via an emergency email and text. The aforementioned communication will be de-identified. The on-call provider will then need to log into the system to access the patient's contact information and level of suicidality/homicidality. As detailed elsewhere in the protocol, the provider will immediately attempt to contact the participant to assess further and make appropriate treatment recommendations. Although our response will be urgent, the provider is expected to make contact within 24 hours, a measurable benchmark against which we can hold ourselves accountable. Of note, the system will also have emergency contact information clearly available to the patient, in the event he/she chooses to initiate contact with study staff. Following the risk assessment, a determination will be made about how best to increase the level of care to the participant, which may entail removal from the study.

Participants assigned to the STEPS UP intervention will be regularly screened for suicidal ideation by their care managers via telephone. During these calls, the care manager will assess clinical deterioration and any signs of suicide or other behaviors that pose harm to self or others using the PCL (item #19) and/or PHQ (item #9i). In RESPECT-Mil, (optimized usual care which participants in non STEPS UP arm are offered) the initial survey, symptom monitoring, and coordination of risk assessment care is the responsibility of the nurse manager who is trained in suicide and violent behavior risk assessment (See Risk Assessment Training). These same procedures will be used by study personnel. Any patient who attempts suicide or is believed to be in imminent risk of self harm be treated clinically, reviewed by the data monitoring board, and potentially removed from the treatment protocol. We plan to follow (for intent-to-treat analyses), any patient who withdraws or is withdrawn from the treatment. Randomized patients withdrawing or being withdrawn from the treatment will be asked if they would be willing to continue completing research assessments for the full 12 months. Those who are willing to complete the research assessments will receive e-mail or telephone reminders of upcoming assessment dates for the 3-, 6-, and 12-month follow-up assessments. Participants who decline to complete assessments will no longer be contacted by study personnel. Any clinically relevant information gathered at the time of withdrawal or in these assessments will be relayed back to the PCP for monitoring.

Risk Assessment. If signs or symptoms of significant distress are manifested or reported by a patient at any point in the study (i.e., during the initial face-to-face meeting, phone contacts, or during e-mail contact), the care manager will assess the patient’s level of distress and risk of harm to self or others using a suicide risk assessment survey administered either in person or over the telephone. This suicide risk assessment survey is currently used in all RESPECT-Mil sites to determine risk for suicide (see Appendix B). If the care manager considers the level of risk to be low (i.e. No current thoughts; No major risk factors), follow-up visits and monitoring
by the nurse care manager will occur. If the care manager considers the patient’s level of risk to be intermediate (i.e., current thoughts, but no plans; with or without risk factors), the care manager will contact the patient’s primary care physician or the on-call physician immediately. In addition the care manager will schedule an assessment with a behavioral health specialist that will occur within 48 hours. The care manager will develop a behavioral contract with the patient to encourage him/her to attend this evaluation. A resource list that provides phone numbers for emergency mental health care will also be provided. The care manager will remind the patient to seek the local emergency psychiatric care if his/her homicidal or suicidal thoughts worsen. If the patient does not attend the behavioral health assessment, the care manager will begin contacting the patient once a no-show is documented and re-assess the patient’s symptoms. If the care manager considers the level of risk to be high (i.e. current thoughts with plans), the care manager will remain on the line with the patient or if the patient is at the clinic, remain with the patient, until the primary care physician or the behavioral health specialist joins the call and further assesses the patient’s level of risk to self/others. A STEPS UP psychiatrist (to be named) will be on call for emergency situations (an on-call schedule will be available for all research staff seeing patients), 7 days a week for risk assessments. If the psychiatrist concurs that the level of risk is high, he/she will stay on the line (or in the room) with the patient and contact emergency mental health services on another line to obtain a safe means for transport to the nearest behavioral health clinic or emergency room. If a patient who reported homicidal or suicidal intentions end the call with the care manager/psychiatrist before contact with the local military mental health center can be made, and the address of the patient’s location is known, the psychiatrist will contact police in the patient’s jurisdiction to report the case. Prior to enrolling in the study, participants will be informed that study staff may break confidentiality if the aforementioned emergencies were to occur.

Other care providers. Risk assessment procedures described above will be used by all study staff who have contact with participants. Completed risk assessments will be fed back to the participant’s care manager and behavioral health specialist ASAP and no later than 24 hours of the assessment. Since all control sites are RESPECT-Mil clinics, the procedures listed above will be implemented by these clinics as part of their standard operating procedures (SOPs). Prior to the initiation of the study, the Principal Investigators will review SOPs at each site and revise SOPs when necessary to include staff responsibilities and subsequent actions required to protect participant safety. An example of an existing SOP (Ft Bliss) is found in Appendix I.

Risk Assessment Documentation. Documentation of all risk assessments, outcome, and plan will be required for patients in either the STEPS UP treatment arm or in RESPECT-Mil (as part of optimized usual care), this documentation will take place in the patient’s medical record and FIRST STEPS (“Fast Informatics Risk & Safety Tracker and Stepped Treatment Entry & Planning System”), DoD-approved software designed to manage symptoms, treatment response, and risk. A note will be placed in the regular medical record to ensure the patient’s treating provider is aware of high-risk patients. This will ensure that patient’s do not ‘slip through the cracks,’ where a clinical provider would be thinking that a study provider was managing the patient, and vice versa.

The FIRST STEPS tool is located on a secure system which uses technology similar to that used to protect credit card information in e-commerce applications. The server is two –way encrypted for the purpose of preventing tampering or data forgery. Password protection further
safeguards use allowing only approved clinicians to view and edit data for their specific patients. This tool is currently used in RESPECT-Mil sites and facilitates the monitoring of patient symptoms and supervision sessions. The tool provides clinicians with the ability to document and monitor suicide risk, providing a set of standardized questions. For participants randomized to optimized usual care who decline participation in REPECT-Mil, study staff will coordinate continued risk assessment and necessary follow-up care with the patient’s primary care provider.

**Risk Assessment Training.** All study personnel who have direct contact with study patients (i.e. care managers, behavioral health specialists, research associates, assessment technicians) will be trained by a licensed psychiatrist/psychologist in conducting suicide and homicide risk assessments. Training will be delivered as a workshop. A refresher risk assessment course will be offered every six months and will be required by all study personnel.

**Supervision.** Supervision for care managers and phone therapists will occur weekly. Nurses will be responsible to present all cases that are low, intermediate, or high risk during these meetings.

**Enhancing the Feasibility of Intervention**

During the development of the intervention, we will gather feedback from health care providers, care managers, and administrators to inform design and improve the feasibility of the centralized telephone care management capability. This information will enable us to understand and address practice-level or provider-level barriers to implementation. As relevant and appropriate, we may ask health care providers and care managers to participate in a working meeting to talk about overcoming system level barriers to collaborative care models.

**Patient adherence. Website.** We will take steps to increase the likelihood that patients can access the intervention easily and learn and practice its techniques. Patients will receive a primer on PTSD and depression, available treatment options, and clear instructions about how to access any web-based material. Throughout the intervention, the care managers will initiate regular phone contact with patients and provide support, instruction, and corrective feedback regarding application of the intervention techniques via telephone or e-mail. Patients are asked to log into the website 3 times a week, ideally every other day.

**Initial face-to-face session.** Before each patient begins the intervention, the assigned care manager will meet with him/her for a single 30-60 minute session. All initial sessions will follow a standard agenda: highlighting key points from the introductory materials, applying motivational interviewing techniques (e.g., coming up with pros and cons of complying and not complying with the intervention, problem solving for barriers to accessing or applying the intervention), and providing assistance on the use of the website intervention.

**Regular phone and electronic support.** Care managers will be accessible to patients via telephone and electronic messaging throughout the course of the intervention. Throughout the intervention period, care managers will periodically call patients. At a minimum, CMs will contact patients monthly to monitor symptoms and facilitate treatment. CMs may also contact patients more frequently depending on current treatment utilization (for example, at least weekly and bi-weekly contact for telephone-based and web-based therapies, respectively), response to treatment, and
patient preference (see Figure 6). In an effort to establish rapport, the CM will refer to the patient by his/her name during phone contacts; however, data records produced by these contacts will identify the patient by study identification number only. These phone calls will focus on praising patients’ efforts to learn and apply the intervention’s techniques, problem-solving barriers to accessing or applying the intervention, and making themselves available to answer questions and concerns. Patients will also be encouraged to call or send electronic messages to their respective care manager if they have questions or experience difficulties accessing, learning, or applying the intervention techniques. A care manager will reply to participants’ messages within a 24-hour period. Additionally, automated email alerts will be sent to the care manager when the patient has not logged on to the DESTRESS website for four days.

Provider fidelity. We will take steps to increase the likelihood that providers will receive adequate training in the treatment approach as well as sustain fidelity to the treatment approach.

Training: Care managers will receive several days full days of training plus ongoing clinical and administrative supervision by the study staff. For example, care managers will receive 15 hours of training in the web-based intervention, which will include the goals of the intervention, ways to enhance motivation (i.e., motivational interviewing), assessing suicide risk, and responding to crisis situations. Dr. Brett Litz and a postdoctoral fellow will provide training. Care managers will receive routine supervision by a postdoctoral fellow working under the supervision of Dr. Litz. Both scheduled and unscheduled supervision will be provided as needed to review and discuss remarkable sessions.

Adherence: For each care manager, a percentage of the sessions will be audio-recorded and reviewed to ensure sustained fidelity to the treatment approach and that all of the required content is being covered sufficiently. Participants will be informed of audio-recording during the consent process, and CMs will also provide consent to participate in this procedure (see Appendix V). We will make every effort to protect the confidentiality of the audio recordings. To this end, CMs will refer to patients only by first name or a nickname and patients will be asked not to disclose any PHI during recorded sessions. Recordings will then be reviewed by the CM and the site research associate, and any PHI accidentally recorded will be erased. Audio recordings will be labeled only with patients’ study ID numbers. The research associate will be responsible for maintaining a log of who performed the final PHI check for each recording prior to release.

Audio recordings will be shipped to the University of Washington (for care management supervision) and to BVARI (for supervision of DESTRESS-PC and DESTRESS-T procedures). They will be stored in a locked cabinet in a locked office at the University of Washington and BVARI, and will be destroyed upon the completion of the study. Dr. Unützer, Dr. Katon, and Dr. Zatzick and a postdoctoral fellow working under the supervision of Dr. Litz will review audio recordings, and care managers will be provided with prompt feedback about their performance.

The Control Intervention—Optimized Usual PTSD and Depression Management

Service members randomized to the control condition will get usual treatment at the site. Usual care is optimized by feeding back the results of eligibility, baseline, and follow-up
assessments to the local provider of the patient’s choice. Optimized usual care at each site is RESPECT-Mil, a collaborative care model which differs from the STEPS UP intervention in several ways. First, the care manager is attached to the primary care clinic and has a physical office in the clinic. Second, there are no specific psychosocial interventions delivered by the care managers, although the care managers in RESPECT-Mil do help the patient with goal setting and minor problem solving. And third, participation in RESPECT-Mil ends if a patient’s care is transferred to another physician outside of the primary care setting. Like STEPS UP, RESPECT-Mil is voluntary and patients in the optimized usual care arm are free to be enrolled in the study while refusing RESPECT-Mil.

6.3.3 Collection of the Human Biological Specimens
Not applicable. The proposed research involves no laboratory evaluations or biologic sampling.

6.3.4 Data Collection
Overview. We will develop and maintain a Web-based portal that will be used to collect baseline and 3-month, 6-month, and 12-month follow-up data from study participants. Each study participant will create a user name and password that will allow him or her to log in and complete the scheduled assessment during each data collection period. Furthermore, each respondent will be assigned an ID that will allow the data collection staff to track each respondent throughout data collection.

We will structure data collection procedures to maximize response and data quality. Several procedures will be used that have proven effective in other Web surveys, including sending electronic message follow-up invitations with hyperlink and conducting reminder telephone calls to nonresponders. The following steps outline the protocol we will follow in administering the assessments.

As service members screen in from primary care, they will be recruited into the study via the recruitment mechanisms discussed in Section 6.2.3.

Eligible sample members will be asked to complete a 60-minute baseline assessment. Upon completion of the baseline assessment, respondents will be randomly assigned to either STEPS UP or OUC.

At each follow-up interval, we will send an electronic message to each respondent inviting him or her to complete the scheduled assessment. A hyperlink to the website will be included in the electronic message.

One week following the initial electronic message invitation, an electronic reminder message will be sent to those who have not responded to the assessment. A hyperlink will be included in each reminder electronic message.

One week following the fourth electronic message invitation, we will make telephone calls to all non-responding study participants to encourage participation. This will promote the timely completion of the instrument and provide support in the event of technical problems. Up to ten reminder calls, will be made to those who do not respond to the scheduled assessment. Reminder calls will direct patients to the study Web site where they can complete the scheduled
assessment; provide participants with the option of providing data via a phone interview, or provide participants with the option of mailing data to the study team. If a participant states that he or she no longer wishes to participate in the study, emails and telephone calls will cease. We will develop and maintain a control system for monitoring data collection. Tracking respondents’ data and updating contact information and other important information will allow the data collection team to track production and ensure the timely completion of all scheduled assessments. All data gathered via the assessments will be housed on a secure server located at RTI (Building 8) in North Carolina, and will be maintained as confidential. In all reports, any assessment data presented will be discussed in aggregate.

Data security.
As the STEPS UP coordinating center, Partnering PI Dr. Robert Bray and his team at RTI will have responsibility to ensure information obtained during the project is kept secure. RTI has implemented an information security program based on the Defense in Depth concept. This strategy combines the capabilities of people, operations, and technology.

Since some of the information contained will be sensitive in nature, security will play an important role. The Web portal is a secure gateway to the underlying data collection, where access is restricted and only authorized users are allowed entry into specific areas and are granted certain functional privileges. Access is controlled via security roles, which will be administered by project staff. Only members of certain security roles have viewing and/or editing permissions within the Web portal. All portal access will begin with the general information page, which contains the portal login. Anonymous access to the portal will not be allowed.

As an additional level of security, the data will reside in RTI’s Enhanced Security Network (ESN). The ESN is RTI’s implementation of the network security controls required to comply with Federal Information Processing Standard (FIPS) 199 Moderate requirements and the National Institute of Standards and Technology (NIST) standard for federal information systems. The Certification and Accreditation of RTI’s ESN was performed in accordance with NIST SP 800-37 guidelines. Data transmission through Web applications will be done over Secure Sockets Layer (SSL) to ensure data encryption during internet transmission. As needed, applications will require authentication with a strong username/password combination. Collectively, these two tiers—coupled with a strong, NIST compliant IT infrastructure—will secure data both at rest and during transmission.

Several initiatives will be taken to ensure confidentiality is maintained and web-stored data are secure. The STEPS UP website is designed in a manner that permits only subjects with a personal password to log onto the web-page that contains the personal data. All communications via the web will be conducted in terms of an identification number that will be provided to the subject. Subjects will be instructed to keep their passwords private. Additionally, all subjects will be encouraged to access the website only in a private setting and a single keystroke will close the application should a subject be unexpectedly interrupted during their sessions. Only authorized study personnel will be allowed to access web-based data. All data transmitted between subjects and researchers will be protected by state-of-the-art encryption technology at both ends of the exchange, thus reducing the already-remote risk of unauthorized data interception. All transactions will occur in a secure-server environment. Researcher access to
subject data will also be password-protected; thus, only authorized personnel will have access to actual data.

We will use Extensible Markup Language (XML) and Portal software that allows connectivity between the Internet and a defined database program. XML is a programming language that spans web platforms and document formats allowing for translation of data from web input to databases. A web portal is a doorway to a server that has security features ensuring that only subjects can access the intervention and assessment areas, and are allowed access only their own materials. Data will be aggregated in a SQL Server 2005 database that is compliant with Clinical Data Interchange Standards Consortium (CDISC) standards. This setup has built in HIPAA and 21 CFR 11 technical compliance required by the FDA for electronic management of subject data, will allow for real time monitoring of subject progress by therapists, and integration with statistical software. Information will be encrypted and protected with the best encryption software in the industry - SSL (Secure Sockets Layer). An SSL-enhanced browser uses encryption to scramble the data the subject sends to a web-site into an unintelligible string of seemingly random characters. The data is then unscrambled on the server and processed by the appropriate script. Access to the servers for the portal and the stored data will be secured behind alarmed and locked doors, and the data will be secured in password protected systems.

Personally identifiable information will be stored on a separate server accessible only to research team members. Only team members who need the information to perform a specific job (for example, a project manager or database administrator) will be granted access to personally identifiable information by the PI. Finally, the servers that store personally identifiable information will be kept in a secure, locked environment in a separate location from the portal and website servers.

For the qualitative study, RTI will select a random sample of participants to be invited to participate in interviews, on a rolling basis, and will transfer their names and contact information to the PI at RAND via an encrypted, password protected datafile sent via mail. Once at RAND, the information will be stored on secure, password protected computer by the PI and interview staff. Each participant will be assigned a new ID for this portion of the study, and notes and digital audiotapes from the qualitative interviews will be marked with identification numbers only and stored in password protected files. Audiotapes of interviews will be destroyed as soon as they are transcribed.

**Systems Security Overview**

The STEPS UP collection will adhere to the IT security guidelines and principles published by the National Institute of Standards and Technology (NIST). Using the formulas provided by NIST, the STEPS UP team will determine which level of security is required and implement either RTI's Standard Security Infrastructure (for data defined by Federal Information Processing Standards FIPS 199 as low potential impact) or RTI's Enhanced Security Infrastructure (for data defined by FIPS 199 as moderate potential impact).

The STEPS UP collection will utilize RTI's a self-contained Enhanced Security Network (ESN), which is Certified and Accredited at the FIPS 199 moderate level for both Confidentiality and Integrity. The ESN forms a dedicated network segment within the confines of the RTI corporate
network and employs a highly restrictive set of IT security controls, allowing it to compliantly host project systems requiring protection at the NIST moderate level.

Both RTI's corporate and Internet Accessible Standard Security Infrastructures have been Certified and Accredited and received an Authority to Operate in accordance with NIST special publication 800-37 (Guide for Applying the Risk Management Framework to Federal Information Systems: A Security Life Cycle Approach). Finally, data availability is ensured through the maintenance of two separate data centers on RTI's main campus and the use of an off-site storage facility for all network backups.

**STEPS UP Data Structure**
The STEPS UP data collection protocol will utilize both the FIPS-LOW and FIPS MODERATE Networks located at RTI International's data center. A portion of the STEPS UP application will reside in the FIPS LOW environment and will collect so very basic personally identifying information (PII) limited to contact information like name, address, phone number, and email address. The PII data (contact information) will be stored in the FIPS LOW environment so the call center, care managers, and others project staff can follow-up with the respondents. This will be simply contact information and not include any survey response data or PHI.

All Protected Health Information (PHI) including linking information to the PII will be stored in our FIPS -Moderate Environment. To access any of the PHI or links to the PII, a user must be authenticated into RTI's Enhanced Security Network via 2 factor authentication (includes a random digit generated token) and have expressed privileges to access the data. Inside the ESN, most approved project staff will only have access to de-identified PHI data so they can run analysis or monitor response rate status. A very limited number of project staff (including but are not limited to the study PI, project director, project coordinator, high-level RTI IT specialists, and study on-call providers will have access to the table that links the PHI with the PII. Linking PII and PHI will only occur when the risk management plan is executed or as required by applicable law or military policy. Securing the link between the PII and PHI is a priority.

**Alerts Based on Patient Response**
The STEPS UP instrument will include a separate application designed to review and alert appropriate project staff of concerns about the respondent’s mental state. When a research participant endorses suicidality or homicidality at a clinically significant level while completing the baseline or follow up assessments, the on-call provider will be automatically alerted by the system. The on-call provider will receive an emergency email and a page/text. The aforementioned communication will be de-identified. The on-call provider will then need to log into the system or call a specific number set up to access the patient's contact information and level of suicidality/homicidality. The provider will immediately attempt to contact the participant to assess further and make appropriate treatment recommendations. The provider will make contact within 24 hours. Of note, the system will also have emergency contact information clearly available to the patient, in the event he/she initiates contact.

As stated elsewhere in the protocol, PII will be stored separately from PHI. PII will be linked with PHI in the event of an emergency situation so that a risk assessment can be conducted. In particular, PII and PHI will be linked if a participant endorses clinically significant suicidality or
homicidality as part of the research assessments (i.e., those assessments that take place at baseline, 3-months, 6-months, and 12-months). As described below, linkage between a participant’s study ID and their secure data will only be accessible to those who may need that information in an emergency scenario, plus 2 to 3 other high-level study leaders.

If a participant indicates a significant risk of suicide or homicide during a research assessment, the computer system will generate a generic "emergency alert" email and text message to a study on-call clinician who will be responsible for contacting the participant as quickly as possible, and within 24 hours. The email and text message will indicate that an urgent message is awaiting the clinician in the STEPS UP computer system. The clinician will log into the secure STEPS UP system and will retrieve a message that provides the random participant ID number and along with an alert for suicide or homicide risk.

The clinician will then access a secure table within the STEPS-UP system, which will be only accessible by a minimal number of pre-identified clinical staff and 2 to 3 study high-level administrators, which contains the individual participant’s ID number and contact information. (Note: the table accessed by clinicians will only contain the contact information for the individual that needs to be contacted- no information about other participants will appear in the table.) Finally, the clinician will be able to access a separate secure table within the STEPS-UP system, again only accessible by the same pre-identified clinical staff and administrators as those with access to the ID number/contact information table, which will show the participant’s responses to the suicide and homicide items.

**Risk Management**
When symptoms are learned, the on-call mental health specialist will be asked to contact the patient, assess, and make the disposition. Web-based instruments will be programmed to alert study personnel of potential signs of suicide or other behaviors that pose harm to self or others. For example, instruments, such as the PCL (item #19) and/or PHQ (item #9i) with items specific to signs of suicide or harm behaviors will automatically send an alert to the on-call behavioral specialist’s pager when an item is endorsed. As stated previously an on-call behavioral specialist (e.g., licensed psychiatrist or psychologist) will be available 24/7 to manage patient emergencies. The on-call behavioral health specialist will be able to access the data and link the data to identifying information. The on-call behavioral specialist will then contact the participant for the purpose of conducting a risk assessment (see Section 6.3.3.2 for risk assessment procedures). If data is collected via telephone, the study staff member will page the on call behavioral health specialist immediately when a suicide symptom or harm item is endorsed. Study staff members will encourage participants to stay on the line until the behavioral health specialist is able to speak with the patient directly to assess risk. For all data collected via mail, study staff personnel responsible for data collection and entry will immediately open the assessment package upon receipt and review suicide or harm behaviour items. If any of these items are endorsed, the study staff member will contact the on-call behavioral health specialist who will be responsible for immediately contacting the participant to conduct a telephone risk assessment. For more detail, please see section the full Risk Management plan in Section 6.3.2.2.

**Assessments.**
Eligibility Assessment (30 minutes)
The eligibility assessment will be conducted by a trained interviewer, either in person or over the telephone. Site-based research associates will be carefully trained in the study protocol and facilitate recruitment at site-specific primary care. Research associates will consent referred participants, ascertain deployment history, check for computer/Internet access, and collect basic demographic information. Demographic information gathered at the eligibility assessment will include date of eligibility assessment, date of birth, ethnicity, education, branch of military service, and dates of last Iraq/Afghanistan deployment.

The purpose of the eligibility assessment is to identify an eligible sample for study intervention based on inclusion/exclusion criteria and who expressed interest in participating. We have planned the study with relatively broad eligibility to enhance the external validity of study findings. Those eligible for randomization after the eligibility assessment will immediately undergo baseline assessments, randomization, and introduction to assigned intervention (centralized telephonic stepped care management or optimized usual care). All eligibility criteria will be assessed prior to random assignment. Respondents who do not meet eligibility criteria will be offered a resource list, referred for treatment (e.g., primary care), and/or assessed for suicidality as appropriate. For respondents whose symptoms of PTSD and/or depression are not severe enough to meet eligibility for this study, we will relay any clinically relevant information from this assessment back to the PCP for monitoring. After informed consent is obtained and eligibility assessment completed, contact information, including e-mail addresses, will be exchanged with the potential study participant, including contact information for a friend or family member who would know the participant’s whereabouts should study staff have difficulty making contact.

After informed consent is obtained and eligibility assessment completed, contact information, including e-mail addresses, will be exchanged with the potential study participant, including contact information for a friend or family member who would know the participant’s whereabouts should study staff have difficulty making contact. See also Section 6.2.3 for recruitment details and estimates of the feasibility of recruitment goals.

Baseline and Follow-Up Outcome Assessments (60 minutes)
Baseline and follow-up outcome assessments will occur online as soon as is feasible and agreed upon by the participant. All baseline and follow-up outcome assessments will be initiated and performed centrally at the STEPS UP website. This will ensure uniform baseline and follow-up assessments and maximize research quality control. If the baseline assessment occurs more than 2 weeks after the eligibility assessment, the PCL-C will be readministered to ensure all participants meet study criteria for current PTSD at the time of randomization. Information collected at the baseline outcome assessment will serve as a baseline from which to evaluate changes in outcomes that occur with time across the two study intervention groups. Effectiveness of the study intervention will examine differences in symptom change across the two groups with regard to the PTSD symptom severity (the primary outcome) and secondary outcomes to include depression, generalized anxiety, and somatic symptom severity; severity of alcohol misuse; and mental health, physical health, and occupational functioning. Information about concurrent treatment that may moderate or mediate intervention effectiveness (“cotherapies”) will be gathered at the baseline assessment (e.g., mental health specialty visits, PTSD-related pharmacotherapy use, vet-center care, and chaplain or similar community support resources) and throughout the course of the 12-month active intervention period. Follow-up outcome measures
are administered at baseline, 3-month, 6-month, and 12-month follow-up (for details see Section 6.3.5).

Other completed assessments will involve qualitative interviews of patients, providers, care managers, and administrative staff; cost data from patient surveys, provider interviews, and information from sites; and quality-of-care data involving patient outcomes, provider assessments of structure of care, and medical record reviews (paper and electronic) to capture the process of care.

Descriptions of Outcome Assessments, Questionnaires, and Measures

Eligibility Pre-screen. Patients who express interest in participating in the trial will be administered the 3-question pre-screen, which will determine eligibility based on active duty status, plans to stay at installation for at least 6 months, and regular access to internet and e-mail.

Eligibility Determination

In order to assess participant eligibility for the trial, we will conduct additional assessments following screening for the study. Except where noted, these questionnaires are for research purposes only.

Primary Care PTSD Screen (PC-PTSD). The PC-PTSD is a 4-item brief screen for PTSD. Results show good internal reliability (.79) and good test-retest reliability (.84). Criterion validity has been established with the Clinician-Administered PTSD Scale (CAPS). This questionnaire is part of the standard of care.

PTSD Checklist-Civilian Version (PCL-C). Determination of current PTSD for the purpose of study eligibility will be based on the PTSD Checklist-Civilian Version PCL-C. The PCL-C is a self-report measure developed for measuring PTSD symptom severity and has often been used for estimating PTSD caseness and severity when administration of a structured clinical interview is not feasible. Respondents rate PCL-C items on a 5-point scale (“not at all” through “extremely”) to indicate the degree to which they have been bothered by each of 17 PTSD symptoms during the past month. Possible PCL-C scores range from 17 to 85, and the most accurate cut-point for PTSD caseness has been the subject of debate, with investigators advocating cut-points from 30-43 based on data from studies comparing PCL scores to structured clinical interviews. We operationalize PTSD caseness according to the PCL-C as a “moderate” or greater severity level on 1 re-experiencing, 3 avoidance, and 2 hyperarousal symptoms, which is consistent with the DSM-IV-TR criteria. This questionnaire is part of the standard of care.

Patient Health Questionnaire-9 (PHQ-9). The PHQ-9 is the nine-item depression scale of the Patient Health Questionnaire. The PHQ-9 is has been used by primary clinicians to diagnosis depression as well as monitoring response to treatment. The PHQ-9 is based on the DSM-IV diagnostic criteria for major depressive disorder. We operationalize depression caseness as the following: endorsement of at least 5 of the 9 symptoms experienced “more than half the days” and at least one of those symptoms must include either “little interest or pleasure in doing things” or “feeling down, depressed or hopeless. This questionnaire is part of the standard of care.

Mini International Neuropsychiatric Interview (MINI)-Plus – Suicidality Module (C1-C6). The MINI-Plus is an extensive structured interview that encompasses 23 psychiatric disorders. We will be using the 6-item suicidality module of the MINI-Plus as a secondary screen to assess suicidal ideation. Patients will be administered these questions ONLY if they respond “Several
days or more” on item 9 of the PHQ-9. Any patient scoring greater than 9 on this scale will be excluded from the study. STEPS UP personnel will follow site-specific SOPs in the event that a patient indicates SI.

We will also assess homicidal ideation using a scale adapted from the MINI-Plus suicidality module. For these four items, it will be explicitly stated that the participant is not to consider enemy combatants. Following completion of the baseline instrument and submission of the data to the web-based system, a STEPS UP staff person will be alerted if the participant indicates homicidal ideation. The staff person will immediately administer a standard assessment to determine the degree of risk the participant represents, and will respond accordingly. If a patient indicated in the four screening items that they have ever tried to harm/kill someone and that they have thought about doing so in the past two months, the participant will be excluded from the study. In these instances, the STEPS UP staff administering the baseline will be instructed to get immediate medical assistance. If the participant indicates that they have wished they could physically harm/kill someone during the past two months, and that they have actively planned to do so during the past two months, the STEPS UP staff person will be directed to seek immediate medical assistance. If the participant indicated that they tried to harm/kill someone in the past 2 months, the staff person will be instructed to seek emergency medical assistance. Finally, if a participant indicates that they have ever tried to physically harm or kill someone, they will only be allowed to participate in the study if they respond negatively to the other three homicidal ideation items.

*Alcohol Use Disorders Identification Test – Alcohol Consumption Questions (AUDIT-C)*. The AUDIT-C is a brief screen for heavy drinking and/or active alcohol abuse or dependence consisting of the three alcohol consumption questions from the AUDIT. The AUDIT-C has been shown to perform comparably to the AUDIT for detecting heavy drinking and/or active alcohol abuse or dependence (area under the curve 0.880 vs 0.881), although the AUDIT performed better for detecting active alcohol use or dependence (area under the curve 0.811 vs. 0.786). The AUDIT-C will be used as a primary screen for exclusionary alcohol use. Patients who screen positive on the AUDIT-C (a score of ≥4 for females and ≥5 for males) will be administered the full AUDIT to determine eligibility based on this criterion.

*Alcohol Use Disorders Identification Test (AUDIT)*. The AUDIT will be used as a secondary screen during the eligibility assessment to assess alcohol use, alcohol dependence symptoms, and alcohol-related problems, focused on the recent past. This 10-item scale is widely used and has been shown to be consistent with ICD-10 definitions for alcohol dependence and harmful alcohol use. A score of ≥15 on the AUDIT will be result in disqualification from the study.

*History of Bipolar I or Psychotic Disorder*. We will exclude patients with acute or history of (within the past 2 years) bipolar I disorder/psychotic disorder. A “yes” response to any of these four questions will result in disqualification from the study.

*Medical Board/Medical Retirement*. We will exclude patients who anticipate separation from the military within the next six months. A “yes” response to this question will result in disqualification from the study.

*Physical Health Status*. We will exclude patients with unstable or severe acute physical illness from the study because participation may interfere with their medical care. A “yes” response to either of these two questions will result in disqualification from the study.
Descriptive Baseline Characteristics and Comparability of Groups

**Demographics and Military History.** We plan to assess demographic variables, military and deployment history, and beneficiary status at baseline for descriptive purposes, using survey items from prior studies.

**DRRI Combat Experiences Scales (CES).** Studies have repeatedly found associations between the risk of developing PTSD among military veterans and the degree and nature of exposure to combat and other war zone stressors. In order to minimize respondent burden, we do not plan to assess combat exposure in the screening or eligibility assessments for the current study; however, measures of exposure to combat and other high-intensity deployment-related stressors will be included in the baseline assessment. Because prior studies have found associations between mental health outcomes and lower magnitude stressors experienced during deployments such as long duty hours and difficult living conditions, the baseline assessment also will include a measure of low-intensity deployment-related stressors. High- and low-intensity deployment-related stressors will be assessed using items from the Unit Support and Post-deployment Life Events scales from the Deployment Risk and Resilience Inventory (DRRI), an instrument developed at the National Center for PTSD for studying deployment-related experiences of military personnel and veterans. The DRRI was developed and tested in three separate national samples of veterans of the first Gulf War. The selected scales were found to have good internal consistency reliability ($\alpha = 0.85$ to $0.89$) and to evidence significant associations with PTSD and other mental health outcomes.

**Department of Defense Survey of Health Related Behaviors Among Active Duty Military Personnel Survey.** We will use the Combat Exposure Scale from the Department of Defense Survey of Health Related Behaviors Among Active Duty Military Personnel Survey to assess high and low frequency combat experiences. The scale includes 17 combat experiences and asks respondents to quantify the number of times they have had each experience (never deployed, 0, 1-3, 4-12, 13-50, and 51+). We will use this scale to describe the study sample and assess comparability of intervention groups at baseline.

**National Comorbidity Study Replication (NCS-R) Survey - PTSD Scale.** We will use items from the PTSD scale (Section 18) of the NCS-R Survey to assess traumatic experiences, including non-military experiences. The scale includes 14 traumatic experiences and asks “how long ago did the traumatic event happen?” for each positively endorsed experience. We will use this scale to describe the study sample and assess comparability of intervention groups at baseline.

**Medical Outcomes Study (MOS) Social Support Survey Items.** We have selected four items from the MOS Social Support Survey that we believe are most relevant to our study population to assess the availability of social support (“none of the time” to “all of the time”).

**Traumatic Brain Injury (TBI) Questions.** Screening for traumatic brain injury is conducted using three items originating from the Land Combat Study, conducted by the Walter Reed Army Institute of Research. These items ask participants about injuries they may have sustained during deployment, as well as the results of those injuries. In addition, participants are asked to indicate any current symptoms that they believe might be related to a possible head injury. Participants who have not been deployed during their lifetime will not be asked these questions.

Primary Outcomes/PTSD and Depression Symptom Severity

**Posttraumatic Diagnostic Scale (PDS).** The PDS is a 49-item self-report measure that assesses both severity of PTSD symptoms related to a single identified traumatic event and
probable diagnosis of PTSD. In this study, we will replace the first section of the PDS with the other two trauma checklists and then ask respondents to identify the trauma that is currently bothering them the most, as in Part 2 of the PDS. This allows more thorough probing about military combat trauma experiences. Part 3 assesses the 17 PTSD symptoms during the prior 4 weeks. Respondents are asked to rate the severity of the symptom from 0 (“not at all or only one time”) to 3 (“5 or more times a week / almost always”). Part 4 assesses interference of the symptoms. The PDS yields a total severity score (ranging from 0 to 51) that largely reflects the frequency of the 17 symptoms of PTSD. A PDS Profile Report also provides a preliminary determination of DSM-IV PTSD diagnostic status, a count of the number of symptoms endorsed, a rating of symptom severity, and a rating of the level of impairment of functioning. The PDS shows high sensitivity (.89) and specificity (.75) as compared to the SCID-IV interview for PTSD, with a high degree of concordance in diagnosis (kappa=.65). It also shows high internal consistency (.92) and also high correlations with other related constructs and test-retest reliability over 2–3 weeks (.78–.84 for each symptom cluster).62

**Depression Symptom Severity: Hopkins Symptom Checklist Depression Scale-20 Item Version (HSCL-20).** The HSCL-20 is a self-report scale comprising the 13 items of the Hopkins Symptom Checklist Depression Scale plus 7 additional items from the Hopkins Symptom Checklist-90-Revised. The additional 7 items were added to better represent all diagnostic symptoms of major depression and improve the instrument’s sensitivity to clinical change.63 The HSCL-20 has been widely used as an outcome measure of depressive severity in large clinical trials.64-71

Secondary Outcomes

Several secondary outcomes will be assessed as well, including somatic symptom severity, alcohol use, health-related functional status, and work functioning to include assessments of absenteeism and presenteeism.

**Somatic Symptom Severity – Patient Health Questionnaire – 15 (PHQ-15).** Somatic symptom severity will be measured with the widely used and validated 15 item Patient Health Questionnaire (PHQ-15).72 Symptoms will be scored per established criteria as 0 (“not bothered at all”), 1 (“bothered a little”) or 2 (“bothered a lot”), except for sleep disturbance and fatigue, which were scored as 0 (“not at all”), 1 (“few or several days”), or 2 (“more than half the days or nearly every day”). A total sum of greater than or equal to 15 indicate a high somatic symptom severity based on data from primary care settings.72

**Alcohol Use Disorders Identification Test (AUDIT).** The AUDIT47 will be used to assess alcohol use, alcohol dependence symptoms, and alcohol-related problems, focused on the recent past. This 10-item scale is widely used and has been shown to be consistent with ICD-10 definitions for alcohol dependence and harmful alcohol use.48-50

**Health-Related Quality of Life and Functional Status – Medical Outcomes Study Short Form-12 (SF-12).** Compared to research on the mental and physical health effects of exposure to traumatic stressors, research on the social and economic consequences of trauma is still at an early stage of development.73 However, available data indicate that trauma exposure and PTSD can have deleterious effects on occupational and social functioning.73-78

Limitations in role functioning will be assessed using the SF-12.79 The SF-12 is a widely used measure of health-related quality of life and functioning with established reliability and validity.79 This measure will be used for the economic analysis as well as to measure functioning as an outcome.
**Numeric Rating Scale for Pain.** We will use a two-item numeric rating scale for pain adapted from the NRS and used in the University of Washington’s IMPACT studies. The first item asks patients to rate pain intensity on average using an 11-point, 0 (“no pain”) to 10 (“pain as bad as you can imagine”) numeric rating scale. The second item asks patients to rate how much the pain interferes with their daily activities on another 11-point, 0 (“no interference”) to 10 (“unable to carry on any activities”) numeric rating scale. The NRS has advantages over other pain intensity measures due to patient preference, lower amounts of missing or incomplete responses, ease of data recording, and the ability to administer the measure on the phone.

**WHO Health and Work Performance Questionnaire—Short Form (HPQ-SF).** The HPQ-SF will be used to assess work presenteeism and absenteeism. The self-report survey contains 11 items and assesses work in the prior 4 weeks. These items will be used both to assess work functioning and to estimate costs related to PTSD and associated conditions.

**Service Use Questionnaire.** We have developed this measure to assess how much health care each respondent has utilized over the past 6 months. The questions ask about all care, regardless of whether it was provided in a military or non-military setting. Although active duty service members receive the majority of their care through the military, some may seek mental health services from external sources (e.g. through a spouse's health insurance plan) due to fear that mental health treatment could jeopardize career advancement. To accurately assign costs, the questions separate utilization by modality of service, including hospital inpatient, hospital outpatient, office visits, and emergency department visits. Where applicable, we also assess type of provider, including mental health specialists, primary care providers, and other specialists.

The aforementioned outcomes and schedule for administration of these measures can be seen in the following table:

### 6.3.5 Study Data Collection Schedule

<table>
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<tr>
<th>Construct &amp; Variables</th>
<th>Measure(s)</th>
<th>Eligibility Determination</th>
<th>Eligibility</th>
<th>Baseline</th>
<th>3-mo</th>
<th>6-mo</th>
<th>12-mo</th>
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<tr>
<td>Depressive symptoms</td>
<td>HSCL-20</td>
<td>X X X X</td>
<td></td>
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<tr>
<td><strong>Secondary Outcomes</strong></td>
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<tr>
<td>Somatic symptoms</td>
<td>PHQ-15</td>
<td>X X X X</td>
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<td></td>
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<tr>
<td>Alcohol abuse</td>
<td>AUDIT</td>
<td>X X X X</td>
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<tr>
<td>Health-related functioning</td>
<td>SF-12</td>
<td>X X X X</td>
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<tr>
<td>Work presenteeism and absenteeism</td>
<td>WHO Health &amp; Work Performance Questionnaire (HPQ) Short Form</td>
<td>X X X X</td>
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<tr>
<td>Pain</td>
<td>Adapted Numeric Rating Scale for Pain</td>
<td>X X X X</td>
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<td><strong>Treatment Modifiers and Costs</strong></td>
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<tr>
<td>PTSD pharmacotherapy</td>
<td>Adapted from referenced PTSD treatment trial</td>
<td>X X X X</td>
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<tr>
<td>Care Manager Contacts</td>
<td>Chart review</td>
<td>X X X</td>
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<td>Intensified PTSD Treatment</td>
<td>New diagnoses of PTSD, new mental health specialty referral, from chart review</td>
<td>X X X</td>
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<tr>
<td>Cost-related utilization variables</td>
<td>Utilization of hospital inpatient, outpatient, and emergency department services; office-based medical and mental health visits, counseling, and telephonic care</td>
<td>X X X</td>
<td></td>
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<tr>
<td><strong>TIME ESTIMATE (in minutes)</strong></td>
<td>30 60 60 60 60</td>
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<td><strong>Intervention Assessments</strong></td>
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<td>PTSD symptom severity</td>
<td>PCL-C</td>
<td>Used as intervention tool to monitor symptoms and assess treatment progress</td>
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<tr>
<td>Depression symptom severity</td>
<td>PHQ-9</td>
<td>Used as intervention tool to monitor symptoms and assess treatment progress</td>
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<tr>
<td><strong>Qualitative Information</strong></td>
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<tr>
<td>Acceptability, Satisfaction, and Perceived Effectiveness</td>
<td>Qualitative interviews with providers, patients, and care managers</td>
<td>Rolling qualitative assessments for randomly selected enrolled patients, one time interviews with subset of providers and care managers</td>
<td></td>
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</table>

**Data Storage & Management**

*Web-based data.* We will employ a wide range of data capture and data management systems using the STEPS UP portal that will be hosted by RTI as a data coordinating center. These include monitoring and assessing study activities, results, and outcomes; managing and tracking study materials; and supporting and managing the conduct of the proposed research. We envision providing Web-based support systems that can (a) track and monitor study activities such as IRB submissions and training, (b) facilitate adverse event reporting, (c) provide project management aids such as timelines and contact lists, (d) track respondents for our longitudinal
study, and (e) manage documents. As part of the coordinating center’s general support to the individual longitudinal protocols for study-wide follow-up requirements, we envision providing a Web-based tracking system that will aid in registration, tracking, and reporting of participant accrual.

Our data coordinating center will implement QA/QC plans to ensure that data are high quality, reliable, and verifiable. Our research team will define requirements and clarify expectations for all aspects of the project. In addition, we will follow strict QA procedures to ensure that projects adhere to quality management plans. Of course, any system of this type requires appropriate data security to ensure protection of sensitive information. The section below on “Information Security” describes our approach for ensuring data security for the STEPS UP study.

Data Collected by Phone Interviews and Mail. To protect the confidentiality of service members and study data only appropriate study staff will have access to participant identities. On all study forms and materials, service members will be identified by a subject number only, and a master list linking identity to subject number will be kept on the secure web portal with access only available to the on-call behavioral health specialist team and the PI.

Quality Control
Study Monitoring and User Support
To ensure that all members of our research team remains informed of the study progress and problems, we will develop reports and tools to monitor data flow in real time. Periodic reports on topics such as participant enrollment, data collection activities, and protocol- and site-specific performance will be developed and posted in secure locations on the Web portal. Reports will also be generated to ensure data quality. In addition, we will produce routine, automated reports that are sent directly to site personnel and prepare reports summarizing the quality of the data collection and measurement process.

For most multicenter projects, user support is an important function that the data coordinating center performs. It includes hardcopy documentation (manuals and answers to frequently asked questions on the project Web portal) as well as technical support from staff trained to help the users. During the course of the research, coordinating center personnel will be available by telephone or e-mail to answer questions as they arise. Problems may arise that necessitate revisions to the study materials or systems, and the coordinating center will bring these issues before the study investigators for resolution. The coordinating center will issue field memoranda to document any changes in protocol and follow this with any necessary changes in operating procedures, data collection forms, or computer software. All documentation and software revisions will be managed in accordance with the change control procedures specified as part of the project management plan.

Programming and Data Delivery Quality Control Procedures
We understand that the maintenance of databases and tools requires a high standard of quality that is only achievable with a high standard of software development, testing, documentation and quality control processes. For this project, the RTI-operated STEPS UP Trial Coordinating Center will employ a System Development Life Cycle (SDLC) that is appropriately planned, controlled, and documented as defined in RTI Standard Operating Procedures (SOPs).
Our SDLC is developed using guidelines from the Software Engineering Institute’s (SEI) Capability Maturity Model Integration (CMMI) guidelines. In addition to following the guidelines included in the SDLC, we will implement a Quality Assurance (QA) process to ensure that the data generated are of high quality, reliable, and verifiable. We will work to define requirements and clarify expectations for all aspects of the project. We will

- objectively evaluate the performance of our processes, the systems and documentation we produce, and the services we provide against our process descriptions, standards, and procedures;
- identify and document all noncompliance issues discovered in the evaluations;
- provide feedback to the project staff and Project Director on the results of all quality assurance activities; and
- ensure that all identified noncompliance issues are addressed.

Quality control processes during data collection contribute to the value of the delivered data. RTI project staff ensures quality through several means:

- review of instrument specifications by survey and programming staff; and
- preprogrammed validity checks on entry fields in the instrumentation, such as dates and some types of numeric answers

RTI suggests taking proactive measures to produce clean data with as few missing values as possible. Assessment instruments will be specified with range checks, valid value checks, confirmation of key preload information, careful formulation of multiple choice responses, and other programmed approaches to ensure complete and clean data. Items can be required to have a response, by specifying keys for “don’t know,” “refused,” “not applicable,” or other form of nonresponse. These techniques prevent concerns over missing data values in the delivered files.

Telephone Contact & Data Collection

The vast majority of data collection for the project will occur through the previously described web-based data entry. However, telephone contact may be required to obtain follow-up data for after non-response to initial web-based data collection efforts. We will also use very similar methods to those below to insure fidelity of the telephone care management efforts employed in our PTSD intervention package.

There are three main components to ensuring quality control during the study. These include interviewer monitoring, feedback to interviewers from call center staff, and Quality Control (QC) meetings. Each of these components is described below.

- Caller Monitoring. This monitoring plays a key role in determining whether the training modules are effective and if procedures are being followed properly. Call center staff monitor approximately 10% of the production hours, which is the industry standard. Monitors use silent audio and video monitoring to follow along with the interviewers while they work. This type of monitoring allows notation of any coding errors, instrument malfunctions, or inadequate probing by interviewers. Feedback forms are used to record any infractions, as well as positive feedback for interviewers. As necessary, interviewers can receive retraining on items that are problematic. Project staff will also monitor interviewers, particularly at the beginning of the data collection period. If there are systematic problems, project staff can then discuss these issues during QC meetings. Project staff can also monitor interviewers remotely through our silent audio and video monitoring system.

- Caller Feedback. It is important for callers to receive feedback on their performance throughout the data collection period. Call center staff give weekly updates to each caller on
several performance measures. This includes measures such as the number of completed calls/interviews, the calls to refusal/noncontact ratio (higher is better), the time the caller spends in a case compared to time out of production (more is better), and the caller’s average hours per completed case (lower is better).

- Quality Control (QC) Meetings. Project staff will hold QC meetings with interviewers and supervisors as needed to discuss data collection issues. Our experience has shown that these sessions build rapport and enthusiasm among interviewers and project staff, assist in the refinement of the instrument, and provide ongoing training for staff. Such meetings have identified previously unrecognized problems with the instrument, such as questions that the respondent does not understand, questions that are difficult to administer, and software problems. These sessions also provide feedback on the data collection procedures and CATI-related software (such as the CATI call scheduler).

Qualitative Study

In the qualitative study, we will interview a variety of participants in the intervention (patient, provider, care manager) to understand the experience including acceptability, satisfaction, and effectiveness. The interview protocols and consent scripts are included in Appendix Q.

**Patient Perceptions of Acceptability of, Satisfaction with and Effectiveness of Intervention.** To gather data and information on the effectiveness of the stepped care approach, web-based resources, and centralized telephonic stepped care management we will carry out a series of in-depth interviews with a randomly selected subset of patients (soldiers with war-related PTSD and associated disorders) within both arms of the randomized trial to complement the main evaluation study. The purpose of these interviews will be to assess patients’ experience with and perceptions of the services they have received, specifically the centralized telephone care management and associated tools.

At three points in the study enrollment, early (months 1-3), mid-study (months 8-11) and late (months 15-18), RTI will randomly select every 5th patient enrolled into each arm of the study, for a total of 15 patients in each arm and will send names, site, and contact information to RAND. RAND staff will contact these participants directly to invite their participation in the interviews; those interested in participating will be verbally consented prior to beginning the interview. RAND will recruit from the sample until the target of 10 interviews is achieved (5 from each arm) at each phase of the study (early, mid, and late), for a total of 30 interviews overall. Interviews will last 1 hour each and be scheduled to occur at regular time points during the trial, time points are anchored to the participants study enrollment date: 1 month following enrollment, 4 months following enrollment, and 10 months following enrollment. Interviewers will follow well-established procedures for conducting semi-structured interviews.\(^{87-89}\) Topics to be covered in the interviews include perceptions of and satisfaction with care, experience with and perceptions of the telephonic care management, self-report information on utilization of informal and formal services, and adherence to care (see protocols in Appendix Q).

**Provider Perceptions of Telephone Care Management** To gather data and information on the perceived effectiveness of stepped care and care management we will carry out a series of interviews with health care providers, care managers, and administrators working within the study sites. Interviews will be designed to also gain insights into whether and how care
management may be facilitating their care and management of their patients with war-related post traumatic stress and depression.

To this end, we will recruit 30 health care providers (from among those providers treating patients in each arm) to participate in two, 90 minute semi-structured open ended interview about their experience treating and managing patients with war-related PTSD and associated disorders. We will invite all health care providers involved in the study to participate, assuming that we can recruit and schedule about this number (30) of participants. The first wave of provider interviews will occur between months 8-11 (mid study) of the trial and the second wave of provider interviews in months 15-18 (late study) of the trial. Working through the site PIs, we will identify primary (physicians, physician assistants, nurse practitioners) and behavioral health care providers treating study participants at each site. We will select a mix of providers by site and invite up to 5 providers per site to participate in these interviews (ensuring a balance of provider type within and across sites). Providers will be sent an email about the qualitative evaluation of the program and inviting them to participate in a semi-structured interview. Providers interested in participating will be verbally consented prior to beginning the interviews, and will be informed that participation is voluntary and confidential and that the data will be used only for the purpose of informing the qualitative evaluation of the intervention. For these provider interviews, we will use chart-assisted recall methods to ask each provider to recall and discuss the care provided to a set of up to three specific, identified patients with war-related PTSD. We will ask the provider to provide feedback on various decisions made about the clinical treatment for the patient, referrals, and patient adherence, as well as potential barriers and facilitators (at the individual provider, patient, and system levels) to guideline concordant care and experience with the telephone care management capability (applies only to the providers treating patients in this arm). As part of our qualitative assessment, we will ask about any additional burden that providers in the trial encountered beyond scheduled appointments and phone interviews. This additional burden could stem from added paperwork, e-mail traffic, preparation time, or other activities. To assess this information, we will include a set of 5 questions that assess 1) whether providers spent time outside of scheduled in-person and telephone appointments on activities related to RCT patients or RCT protocols, 2) the nature of these activities, 3) the time spent on these activities, 4) whether the time spent on these activities exceeded the typical preparation and paperwork time for non-RCT patients. The data that we collect from this set of questions will support our cost analyses, discussed in the section titled “Cost Effectiveness Data Collection” below.

In addition, within the centralized telephone care management arm, we will interview up to 12 nurse care managers about their experiences with and perceptions of the stepped care approach and utility of the telephone care management capability. We will invite the 6 study on-site nurse care managers as well as 6 nurse care managers working in the centralized care management facility to participate in the one hour interviews. Invitations will be sent by email and include a description of the qualitative evaluation. Care managers interested in participating will be verbally consented prior to beginning the interviews, and will be assured that participation in the interviews is voluntary and confidential. Data from the interviews will be used only for the purposes of the qualitative evaluation. For each of these nurse care managers, we will conduct interviews at two different time points in the trial. These time points will be site dependent and focus on conducting the first interview in the early part of the study, and once near the conclusion of the study. Copies of the semi-structured interview discussion guides are included in Appendix Q.
Qualitative analyses will be performed to assess patient and provider perceptions of the intervention’s feasibility, effectiveness, and costs. We believe our use of multiple data collection methods will yield high-quality results\textsuperscript{90, 91} that can be triangulated to increase the reliability and validity of the findings.\textsuperscript{92} Semi-structured interviews will produce 1) narrative descriptions, 2) short answers and lists, and 3) close-ended (quantitative) responses. To analyze narrative data, we will first review the texts to identify key themes. Themes are abstract constructs that investigators identify before, during, and after data collection. They come from literature reviews, investigators’ \textit{a priori} understandings, and the text itself. For example, we anticipate coding for “potential barriers” and “potential quality improvement” and other topical areas of interest. To deduce themes from the texts, the research team will read a sample of interview notes and look for examples that suggest processes, actions, assumptions, and consequences\textsuperscript{93, 94} and will also look for metaphors, repetitions across informants, and shifts in content that may indicate relevant themes.\textsuperscript{95\textendash}97

After separately examining portions of the coded notes, the research team will reach consensus about which themes to examine in detail. For example, we anticipate including themes related to barriers to care, potential interventions, continuity of care, follow-up, adherence, and positive aspects of care. We will then develop a codebook using standard procedures.\textsuperscript{90, 98} We will use text management software (e.g., Atlas/ti) to mark instances where each theme occurs in our data.\textsuperscript{99} To increase the confidence of identifying all instances of a theme, we will have two coders read over the material and mark codes independently.\textsuperscript{100} Coders will be blind to the characteristics of the interviewee. Once the themes have been marked, we will pull all relevant text. For each theme, we will describe the range, central tendency, and distribution. We will do this by presenting segments of text—paraphrases of cases and verbatim quotes from informants—as exemplars of concepts. Since coders will be blind to whose text they are reading, we can describe how themes are distributed across types of informants and stakeholders (e.g., military personnel, veterans, family members, type of care providers).

As mentioned in Appendix Q, providers will be asked to talk about 3 patients. These patients will be randomly selected by RTI. The research associate will then provide the name of the patients to be discussed to the provider. The providers will be told not to disclose identifying information to the RAND interviewer.

\textbf{Cost Effectiveness Study}

We will assess costs using a societal perspective, taking into account all treatment costs (e.g. medications, nurse and physician salaries, building rents and maintenance, equipment costs) as well as costs that accrue to the participant. Specifically, we will include questions related to the number and type of medical and mental health services, including telephone care and use of internet resources, at each wave of data collection. To supplement the data collected during the qualitative assessments (see section above), we will also gather information from providers to assess whether participation in the RCT created additional burden beyond time spent with patients. Finally, we will conduct semi-structured interviews with office managers to inquire about other costs that may have been associated with the program, such as maintenance costs and supplies (see section above, Qualitative Assessments). Exhibit 1 lists the cost components that we will consider in the analysis, as well as data sources for assessing those costs.
### Exhibit 1. Data Sources for Cost Analysis

<table>
<thead>
<tr>
<th>Cost component</th>
<th>Data source(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personnel costs</td>
<td>Provider and clinic information</td>
</tr>
<tr>
<td>Training costs</td>
<td>Training program protocol, invoices for trainers and other training materials, DoD Pay tables</td>
</tr>
<tr>
<td>Participant opportunity costs</td>
<td>Participant survey, telephone bills, DoD pay tables</td>
</tr>
<tr>
<td>Facilities costs</td>
<td>Local market rental rates</td>
</tr>
<tr>
<td>Costs of Internet-based tools</td>
<td>Invoices (e.g. for licensing fees, server space)</td>
</tr>
<tr>
<td>Maintenance costs and supplies</td>
<td>Information from office managers, program invoices</td>
</tr>
</tbody>
</table>

### 6.4 Statistical Consideration

#### 6.4.1 The primary endpoints (i.e., primary outcome variables) and the secondary endpoints

The primary outcomes will be PTSD symptoms (as measured by PDS) and depression symptoms (HSCL-20). Secondary outcomes will include alcohol use (AUDIT), general anxiety (GAD-7), somatic symptom severity (PHQ-15), and functional status (SF-36), including work function (HPQ short form).

#### 6.4.2 Data analysis

**Randomization**

Participants will be stratified by clinic and randomly assigned to condition using a random permuted block scheme with block sizes of 4 and 6 within each clinic. This approach will be used to prevent study staff from anticipating the assignment of the next study participant and to achieve balance of treatment assignment within each clinic. As a first step, the randomization program will randomly select a block size. Suppose that a block size of 4 is selected. Participant A is randomly assigned to STEPS-UP or Respect-Mil as is participant B. Suppose that participant A is assigned to STEPS-UP. If participant B is randomized to STEPS-UP, participants C and D will automatically be assigned to Respect-Mil, in order to balance the distribution of study conditions within the block. If participant B was randomized to Respect-Mil (so there is now one participant in each condition), participant C will be randomly allocated to STEPS-UP or Respect-Mil. In this scenario, participant D will be assigned to the opposite of participant C, again to balance out the distribution of conditions within the block. Following this completion of a block of 4 randomized participants, the computer system will randomly select the next block size, and the allocation repeats as described.

**Comparisons at Baseline**

Baseline comparisons of the two treatment arms will focus on gender, race/ethnicity (white, African American, or other), age, branch of service, as well as baseline values of primary and secondary trial outcome variables. Chi-square tests will be used for comparisons of categorical variables and t tests will be used for continuous variables. The goal is to determine if randomization successfully balanced the study with respect to the variables in question. We are aware that a statistically significant imbalance does not necessarily imply a biased measure of the treatment effect and that the absence of a statistically significant difference does not imply
absence of bias.\textsuperscript{101, 102} The goal here is to describe the study population. The issue of potential bias will be explored in secondary analyses of the primary outcome as described below.

Analysis of the Primary Outcomes

The study will evaluate differences across the two study arms with regard to change in two primary outcomes, the PDS (PTSD symptom severity) and the HSCL-20 (depression symptom severity). A critical p-value of 0.025 will be used to adjust for having two primary outcomes in the study. A linear model will be employed for the primary analysis of the depression and PTSD outcomes if the data fit the assumptions of linear models reasonably well, perhaps after transformation to logarithms or another scale. Two forms of the linear model will be considered: a mixed linear model and a repeated measures model.\textsuperscript{103} Under the mixed linear model, the scale score is a linear function of time. Fixed effects in the model include time as a continuous variable, an indicator for treatment arm, and the interaction between time and treatment arm. Random effects for slope and intercept are included to capture inter-subject variation in changes in score over time within treatment arm. The fixed effect interaction term measures the difference between average changes over time in the two treatment arms; this is the treatment effect.

If the assumption that scores vary linearly in time is untenable in one or both treatment arms, then a repeated measures model will be considered. This is a model for the vector of time-specific means in the two treatment arms with no specific assumption about the shape of trends over time in either arm. Predictors include time as an ordered categorical variable, an indicator for treatment arm, and the interaction between time and treatment arm. The interaction is again the treatment effect. Error terms, which measure each individual’s departure from the treatment arm mean at the five time points, are assumed to be correlated within individuals over time.

By assuming a specific shape for the trends over time, the fixed effects under the linear mixed model form a special case of the more general effects under the repeated measures model. Thus, a likelihood ratio test can be used to compare the fit of the two models to the data. The mixed model conveys greater statistical power for the treatment effect when the assumption that scores vary linearly in time is acceptable. Otherwise, the repeated measures model is preferred.

If neither linear model proves appropriate, given the distributional properties of the scores, then treatment arms will be compared using a permutation test.\textsuperscript{104} The test is straightforward. First calculate the test statistic for the interaction term under the mixed linear model or repeated measures model, depending on the shape of the trends in scores over time. Then, create 10,000 permutations of the data and calculate the test statistic for each permutation. Determine the p-value for the observed test statistic from the frequency distribution of the test statistics in the permutations. If the permutation test is employed, then the treatment effect will be expressed as the difference between median changes of score in the two arms. The inter-quartile range will replace the standard deviation as a measure of dispersion.

Secondary Analyses for the Primary Outcomes – Proportion Responding to Treatment

A comparison of the proportion of subjects experiencing a clinically significant change on the PDS and HSCL in the two treatment groups is also of interest. Therefore, the proportions in the two arms will be compared using a chi-square statistic as a secondary analysis.
Secondary Analyses for the Primary Outcome – the Effect of Covariates and Subgroup Analyses

The analyses described above will be extended to determine if the treatment effect varies over subgroups of interest in this study by adding appropriate interactions to the model. For example, an indicator for gender could be added to both a linear model along with two-way interactions of gender with time and treatment arm, and a three-way interaction of time, treatment arm and gender. A statistically significant three-way term would indicate that the treatment effect differs in men and women. Extension of the permutation test is accomplished by adding the specified interactions and permuting subjects within categories of the covariate. Variation of the treatment effect among study sites will be examined using the same approach. Study site will be treated as a fixed effect, rather than a random effect because the study sites constitute a large fraction of total available sites but are not a random sample of available sites. It should be noted that the study will have less statistical power to detect subgroup differences and covariate effects than it will have for the main treatment effect.

The comparison of proportions responding will be expanded to a logistic regression to explore the effects of covariates and subgroups on this aspect of the outcome.

Secondary Outcomes

The statistical methods outlined above will also be employed for secondary outcomes that are represented by severity scale scores like the PHQ-15 (somatic symptom), AUDIT (alcohol use), etc.). The choice between a linear model and a permutation test will be made separately for each outcome. Outcomes of other forms will require other methods. For example interval use of pharmacotherapies for PTSD could be modeled as a repeated binary outcome using presence/absence of use of current pharmacotherapies for PTSD between 3-month assessments as the outcome. Comparison of treatment arms using generalized estimating equations (GEE) would be appropriate. However, it is also possible that the probability of using these treatments may change over time, which would mean that the time intervals are not true repeated measures of the same outcome probability. This can be accommodated by adding time interval to the model as an ordinal predictor. The interaction between time interval and treatment arm would provide a test for changes in the odds ratio for treatment arm over the course of the study. The same considerations apply to any outcome that can be modeled as a repeated binary measure. We will also compare the occurrence of suicidality between the two treatment arms as a secondary outcome; however, we anticipate suicidality to be a fairly rare event.

Cost Effectiveness Analysis

We will assess the cost-effectiveness of STEPS UP relative to optimized usual care using standard methodologies described by Gold and colleagues and Haddix et al. Data for this analysis will be gathered by a variety of means, as noted above. Cost-effectiveness analysis (CEA) is a method of comparing the economic desirability of alternative health interventions by calculating the marginal cost of a unit of improved health. Our measure of cost-effectiveness will be the incremental cost-effectiveness ratio (ICER), defined as the difference in the per capita cost of the treatment and control groups divided by the difference in the average effectiveness of the interventions. In our case, the “control” refers to optimized usual care, and the “treatment” is STEPS UP. Specifically,
(1) \[
\text{ICER} = \left( \frac{\mu_{c2} - \mu_{c1}}{\delta_{e2} - \delta_{e1}} \right)
\]

where \( \mu_{c2} \) is the per-capita cost of the treatment, \( \mu_{c1} \) is the per-capita cost of optimized usual care, \( \delta_{e1} \) is a measure of effectiveness, such as the health-related quality of life measured over 1 year for participants in the treatment group, and \( \delta_{e2} \) is the same measure of effectiveness for participants in the control group. Following Simon et al.,\(^{108}\) we will estimate confidence intervals for our CERs using bootstrap methods.

Policy makers can use ICERs to determine if an intervention is a worthwhile investment in terms of public dollars. Hoch and Smith\(^{109}\) state that health care decisions without cost considerations assume that there are no alternative uses for the resources consumed and that outcomes and costs both be considered at population level. Within a DoD setting, where decisions about funding post-injury health care interventions may be weighed against supporting new technology that may prevent injury altogether, it is important that even effective interventions are cost-effective.

**Exhibit 1** illustrates four potential outcomes from a cost-effectiveness analysis. Interventions that improve health and decrease costs relative to the alternative (quadrant 1) should be prioritized, while interventions that increase costs and harm health (quadrant 4) should not be implemented. We hypothesize that telephonic care management will be both more expensive and more effective than optimized usual care (quadrant 2). Such a result would suggest that the telephonic care management should be prioritized in terms of resource allocation if the ICER were relatively low.\(^{110}\) In the United States, Braithwaite et al.\(^{111}\) state that an intervention that improves health at a cost less than $183,000 to $264,000 per quality adjusted life year (QALY) would be a worthwhile use of resources.

**Primary Cost-Effectiveness Endpoints.** Our primary outcome for calculating the ICER will be health-related quality of life. A U.S. Public Health Service expert panel recommended that cost-effectiveness analyses use QALY’s as the primary endpoint.\(^{36}\) QALYs are a combination of morbidity (e.g., health-related quality of life) and mortality. Here, health-related quality of life is used to adjust length of life by quality, such that a year in perfect health is 1 QALY and death is 0 QALYs. Unlike clinical outcomes, the health-related quality of life dimension is weighted by the amount of time a patient is experiencing the problem. Moreover, health-related quality of life is a preference-based metric, such that the severity of a disease state not only reflects a description of functioning, but also society’s preference for how desirable or
undesirable that disease state is. For example, Kibert and Lawson\textsuperscript{112} measured the preference of a Type-I diabetes mellitus (DM) with comorbid blindness and end stage renal disease (ESRD; requiring dialysis) health state from patients with DM and ESRD. In a separate study, Revicki et al.\textsuperscript{113} measured the preference of a severe depression health state from patients being pharmacologically treated for depression. Average preference for the severe depression health state was less desirable than was average preference for DM with comorbidities. Thus, a health state like DM with comorbidities, which requires frequent life-saving medical treatment, is more desirable than severe depression, which is theoretically treatable with medication and/or psychotherapy. This example demonstrates that non-preference-based measures of health status and clinical symptom focused measures are predominantly clinician tools, not health policy tools per se.\textsuperscript{114-117}

We will determine preference-based health-related quality of life using a method derived by Brazier et al.\textsuperscript{118} These researchers developed a transformation formula, using data from the to-be-administered SF-12. They isolated 249 health states from the measure, and asked a community sample to provide their preference for these health states using standard econometric disease valuation techniques. This method has been supported by the work of our team members. Specifically, the preference-based health-related quality of life of veterans (using the Brazier et al. SF-12 score transformation method) was estimated for PTSD, other anxiety, mood, and substance use diagnoses.\textsuperscript{119, 120} We will then multiply the preference-based health-related quality of life by time and sum over one year. This calculation will give us an estimate of the QALY for each patient, which will then be used as the primary outcome in the ICER. As with other clinical outcomes, we expect that the QALY for patients randomized to the enhanced care will be more favorable than QALY for patients randomized to usual care. We will therefore measure, “in a comprehensive and valid way the total improvement in health that could be expected from each of a number of alternative treatments, programs, or courses of action.”\textsuperscript{121}

Supplementary Cost-Effectiveness Endpoints. The cost-effectiveness methodology has the drawback that it can only be used to evaluate the incremental effectiveness of an intervention with respect to a single outcome. In reality, an intervention aimed at reducing PTSD and depression may influence many outcomes. To address this issue, we will calculate cost-effectiveness ratios with respect to several alternative outcomes in addition to QALYs. First, we will use the number of PTSD-free and depression-free days over 1 year. Although the number of PTSD or depression free days is not a comprehensive measure of health-related quality of life, it has the advantage of being straightforward to interpret. In addition, several prior studies\textsuperscript{23, 108, 122} have used number of PTSD or depression free days as their primary outcome. To capture the notion that reductions in PTSD symptoms could have broad impacts that effect not only mental-health symptoms but also productivity and utilization of general medical care, we will consider days spent at work over 1 year, as well as overall medical care utilization. Utilization of medical services is relevant given the high degree of somatization associated with mental health illness.\textsuperscript{123, 124} We will measure medical care use by considering inpatient visits, outpatient visits, and visits to the emergency room.

Finally, in addition to calculating CERs for several outcomes, we will also assign dollar value on relevant outcomes (productivity increases, reduced medical care utilization, and changes in health related quality of life), to calculate the benefit of the intervention. We will then compare this benefit to the cost of the intervention, recognizing that there may be additional benefits (such as reduced alcohol use or improved relationships with family members) that are not captured in this analysis.
General Statistical Approach. We perform three ordinary least square regressions: Effect, Cost, and Net Benefit. A strength of the following regression models is that we can test for significance of using CBT over LT in terms of cost, effectiveness, and the net benefit. The equations are as follows and adapted from (Hoch & Smith, 2006). For demonstration purposes we keep these models simple, but we intend to add parameters in efforts to determine any differential effects of treatment (e.g., demographic differences).

1) \[ QALY = \alpha_0 + \alpha \text{Treatment}_\text{type} + \varepsilon \]
2) \[ \text{Cost} = \beta_0 + \beta \text{Treatment}_\text{type} + \nu \]
3) \[ \text{NB} = \gamma_0 + \gamma \text{Treatment}_\text{type} + \omega \]

Here, the regressions measure the association between treatment type (STEPS-UP or OUC) and outcomes including QALYs, costs, and the net benefit of the program (NB, defined below). Treatment type is a dummy variable equal to 1 if the individual received STEPS-UP, zero otherwise. Thus \( \alpha_0 \) & \( \beta_0 \) are the average QALYs (our measure of effectiveness) and cost for OUC. Models 1 and 2 are important, because the ICER alone plus its sign (positive or negative) can provide the detail necessary to determine which quadrant the treatment falls in (Exhibit 1, above). For example, if the difference in cost is negative but the difference in effectiveness is positive, then the ICER would be negative. But without greater detail, a reader would be unable to discern whether the negative ICER was due to a lower cost (and greater effectiveness) or higher cost and (less effectiveness).

\( \text{NB} \) integrates the Effect and Cost models by using a willingness to pay threshold. Here, \( \text{NB} = [\text{willingness to pay} \times QALYs \text{ Gained}] - \text{Cost} \). Willingness to pay is the pre-determined threshold. Similar to Models 1 and 2, we can perform inferential tests on the regression coefficients to determine if the net benefit of CBT versus LT is significant.

6.4.3. Safety Monitoring and Analysis Plan

Continuing a clinical trial when interim results demonstrate overwhelming evidence of benefit or harm to one treatment group raises ethical concerns. We plan to monitor the trial for patient safety including adverse events (AEs) involving clinically significant worsening of PTSD or associated symptoms and serious adverse events (SAEs) involving potential issues of patient safety. All patients will be asked to report adverse events to study personnel as soon as possible. At the time of consent, the site research associate will explain what constitutes an AE/SAE and will give each patient a card containing contact information to report an AE (see Appendix U). This information will also be posted on the STEPS UP web portal. We will record and report SAEs to the chair of the DSMB in accordance with IRB reporting guidelines, focusing study related and unrelated suicide attempts, suicide completions, and psychiatric and medical hospitalizations. Based on considerable previous experience, we expect very low event rates and a very low probability of observing a statistically significant difference between the treatment arms. Additionally, given the greater emphasis on longitudinal case management in the intervention group, we might expect to see a higher rate of SAE and AE detection in the intervention group compared to those receiving optimized usual care. Therefore, we have not proposed formal interim analyses to compare these rates across the two arms while the study remains in progress. We will, however, provide the DSMB with monthly reports in which any new events will be listed and the event histories of the two arms to date will be summarized.
Data Safety Monitoring Board (DSMB)

The proposed study will constitute a greater-than-minimal-risk protocol. As is customary for multisite, randomized clinical trials, we will institute a Data Safety Monitoring Board (DSMB). The DSMB will comprise of 3 independent clinicians and researchers not connected to the research to ensure DSMB integrity, independence, and unencumbered decision making. The DSMB includes Thomas R. Ten Have, Ph.D., M.P.H., Senior Scholar in Biostatistics at the Center for Clinical Epidemiology and Biostatistics and Professor of Biostatistics at the University of Pennsylvania School of Medicine; John R. Freedy, M.D., Ph.D., Program Director of Trident/Medical University of South Carolina (MUSC) Transitional Year Residency program, Director of Behavioral Science Curriculum at Trident/MUSC Family Medicine Residency, and Medical Director, Skilled Nursing Facility at Trident Regional Medical Center; and Linda Ganzini, M.D., M.P.H., Professor of Psychiatry and Medicine Senior Scholar at the Center for Ethics in Health Care at Oregon Health & Science University (OHSU), Staff Psychiatrist at Consult-Liaison Psychiatry Service and Outpatient Mental Health, Director of the Interprofessional Fellowship Program in Palliative Care at Portland VA Medical Center (PVAMC), and Director of Geriatric Psychiatry Fellowship Program at PVAMC. The Initiating PI (Dr Engel), aided by the STEPS UP Clinical Research Programs Director (Dr. Freed), will work closely with the DSMB to ensure the board has all the information it needs to monitor trial progress, adverse events, and overall safety. We will also provide the DSMB with unblinded data from the randomized trial at periodic intervals of DSMB choosing to review findings and study procedures and determine if any changes to the study are needed.

The DSMB will review the progress of the study and monitor patient intake and enrollment, outcomes, adverse events, and other issues related to patient safety. The DSMB will make recommendations to the Human Research Protection Office (HRPO) at USAMRMC and local IRBs about whether the study should continue or be stopped. The DSMB can consider patient safety, ethical issues, or other circumstances as grounds for early study termination, including either compelling internal or external evidence of treatment differences or unfeasibility of addressing the study hypotheses (e.g., poor patient intake, poor adherence to protocol). The study biostatistician will provide data to the DSMB at intervals specified by the DSMB or in response to requests from the HRPO or local IRBs. The DSMB will meet at least annually during the course of the study to begin at the time of initial participant recruitment. In the interim, the DSMB can decide or be asked to convene if there is any serious event requiring its attention. Members of the DSMB can also decide to visit one or more study sites for participant safety, patient rights, or other study related reasons.

The DSMB is required to review all unanticipated problems involving risk to volunteers or others, serious adverse events, and all deaths associated with the protocol, and provide an unbiased written report of the event to the USAMRMC Office of Research Protections (ORP) Human Research Protections Office (HRPO). At a minimum, the DSMB should comment on the outcomes of the event or problem, and in the case of a serious adverse event or death comment on the relationship to participation in the study. The DSMB chair (appointed by the board members), with the assistance of the DSMB as requested or otherwise appropriate will indicate whether he or she concurs with the details of the report provided by the study investigator. Reports for events determined by the site investigator, the DSMB, or the DSMB chair to be possibly or definitely related to participation and reports of events resulting in death will be promptly forwarded to the HRPO.
6.4.4 Sample Size Estimation

Given the uncertainty about the type of linear model — linear mixed model or repeated measures model — that will be used to analyze the data, we take a conservative approach to determining the sample size for the trial. Specifically, the sample size required to compare 12-month changes in the outcome was determined ignoring both the data collected at intervening time points and assuming zero correlation between measurements on the same subjects at baseline and 12 months. This assumption is conservative in the sense that a positive correlation would produce a smaller standard deviation for change over 12 months.

The variable of interest in the calculations is $D = (\bar{X}_{22} - \bar{X}_{21}) - (\bar{X}_{12} - \bar{X}_{11})$ where $\bar{X}_{ij}$ is mean score in treatment arm $i$ at time $j$. The expected value of $D$ is $\Delta = (\mu_{22} - \mu_{21}) - (\mu_{12} - \mu_{11})$. Sample size calculations were based on the effect size, $\Delta/\tau$, where $\tau$ is the within-group standard deviation. In this case, $\tau$ is the within-group standard deviation of change in score.

Assuming a sample size of 600 subjects per arm and a Type I error rate of 0.025, the study will have power=0.80 to detect an effect size of 0.178 standard deviations. This is very close to the values obtained in previous studies, as we demonstrate below. Given that we anticipate 20% participant attrition over the 12 month study 750 patients will be recruited in each arm of the study (1500 patients total) will be recruited to attain 600 participants in each of the intervention and control groups at the 12 month study outcome.

Under the assumptions that $\sigma_1 = \sigma_2 = \sigma$ and $\rho = 0$, the effect size can be also be expressed in terms of the within-group standard deviation at baseline. Note first that $\tau = \sqrt{\sigma_1^2 + \sigma_2^2 - 2\rho\sigma_1\sigma_2}$ where $\sigma_1$ and $\sigma_2$ are the standard deviations at the two time points between which change is measured and $\rho$ is the correlation between the measurements on a subject at the two. Under the assumed conditions, $\tau = \sigma\sqrt{2}$, which implies that $\Delta/\tau = 0.252$. In other words, the study will have power=0.80 to detect a difference between changes in the two groups that amounts to only one quarter of the within group standard deviation.

To put this in perspective, note that Gilbody and his colleagues$^{14}$ obtained a standardized mean difference of 0.25 for the difference between depression scores at six months in a meta-analysis of 37 randomized trials of therapy to treat depression. They defined the standardized mean difference to be the difference between the means in two treatment groups divided by the within-group standard deviation. In terms of the notation used here, this is $(\bar{X}_{22} - \bar{X}_{12})/s$ where $s$ is an estimate of $\sigma$. Now, if randomization is successful, then the treatment difference $D$ will be approximately $(\bar{X}_{22} - \bar{X}_{12})$ because the baseline difference $(\bar{X}_{21} - \bar{X}_{11})$ will be close to zero. Therefore, $(\bar{X}_{22} - \bar{X}_{12})/s$ is an estimate of $\Delta/\sigma$. Thus, the value of $\Delta/\sigma$ that can be detected with power=0.80 is very close to the average value obtained in the studies analyzed by Gilbody and colleagues.$^{14}$

Foa and colleagues reported a mean PDS score of 33.59 and a standard deviation of 9.96 in 128 study subjects with PTSD and a mean of 12.54 with a standard deviation of 10.54 in 120 subjects who were not diagnosed with PTSD.$^{62}$ Assuming $\Delta/\sigma = 0.252$, the standard deviation of 9.96 gives us $\Delta = 2.51$, which is only 12% of the difference between the means in subjects with and without PTSD. Thus the study will have power=0.80 to detect a difference in treatment
response that is small relative to the mean for those with PTSD and relative to the difference between mean scores in those with and without PTSD.

We note, finally, that assuming zero correlation between baseline and follow-up scores is likely unrealistic. A positive correlation is more likely than zero correlation. A positive correlation will reduce the value of \( \tau \). For example at \( \rho = 0 \) we had \( \tau = \sigma \sqrt{2} \) but at \( \rho = 0.5 \) we have \( \tau = \sigma \). Thus, a positive correlation will reduce the size of the treatment effect that can be detected at a specified level of power. The planned sample size should therefore be adequate for this study.

In summary, with 750 patients in each arm of the study the investigation will have ample sample size to detect statistically and clinically meaningful differences between the intervention and control groups on the two study primary outcomes PTSD and depression.

**6.5 Reporting Adverse Events**

**6.5.1 Expected Adverse Events from Research Risks and Reporting**

We anticipate that the risk of study participation will be relatively small and includes exacerbation of general distress or PTSD symptoms, unexpected disruption of an established effective provider-patient relationship, or compromised confidentiality of medical information. The treatment approaches included in the STEPS UP package are non-experimental and evidence-based; however, the risks of these approaches in combination are unknown. Although we expect the program to be relatively safe, it is possible that STEPS UP will pose greater risk than routine care for PTSD and associated conditions.

Participants in both groups will receive at least an optimized version of usual and customary care for PTSD and associated depression and all participants will sign an informed consent form prior to initial study evaluation explaining the potential risks. We will notify the patient’s primary care doctor of any volunteers that are ultimately consented but excluded from the research study. We will also work with local military mental health providers and volunteers to ensure appropriate care for any volunteer who is ultimately excluded from the study or who is enrolled but is subsequently terminated from further study participation for any reason. Examples of ways we will facilitate appropriate care may include return to previous provider care, appropriate clinical referral to a mental health specialist, and urgent or emergent medical or psychiatric care as necessary and indicated.

Data will be obtained from patients recruited specifically for this protocol. Demographic and diagnostic data, monitoring clinician assessments and ratings, and patient self-report questionnaires will be collected and used for information related to study participation and treatment efficacy. Only the PI, site investigators, and care manager will have access to participant identities. On all study forms and materials, participants will be identified by a subject number only, and at each site a master list linking identity to subject number for that site’s participants will be kept double locked in the site PI’s office.

Some participants may feel uncomfortable thinking about past traumatic events and responding to questionnaires and interviews about symptoms and levels of functioning. They may also have concerns about security and confidentiality of personal information provided online. Participants will be informed about these risks and told that they may withdraw from the study at any time, may refuse to complete any treatment procedures they find too uncomfortable, and that doing so will not in any way affect their health benefits.
A detailed consent form will be signed by each patient following an additional discussion about the study with Q&A by the trained research associate prior to assessment and randomization. All procedures and protocols will be reviewed and approved by applicable IRBs for approval prior to initiation of the study. For participants requiring psychotrophic medications for treatment of PTSD and depression symptoms, paroxetine has been used extensively and has an excellent safety record. It is an FDA-approved treatment for PTSD. Although paroxetine is generally well tolerated, it has been associated with a number of common side effects, including gastrointestinal (GI [anorexia, constipation, diarrhea, flatulence, nausea]), sexual dysfunction (anorgasmia, abnormal ejaculation, erectile difficulties), dry mouth, anxiety, dizziness, nervousness, somnolence, tremor, asthenia, sweating, yawning, and blurred vision.

6.5.2 Reporting Serious and Unexpected Adverse Events to the IRB

The best interests, health, and well-being of participants will be maintained throughout the study. For the purposes of this study an unexpected adverse event (AE) will be defined as clinical worsening of depression, PTSD, or emotional or physical distress. Serious adverse events (SAEs) are new onset of suicidal ideation or a significant worsening in previous suicidal ideation, other behavior that is a danger to self or others, and other adverse physical reaction requiring urgent or immediate medical attention (e.g., inpatient hospitalization, emergency room visit). SAEs and AEs will be monitored by study care managers with whom study participants interact on a regular basis. Participants will also have ongoing health care access and access to their primary care provider in the event new medical opinions or services are needed. If an SAE occurs, the site investigators and initiating PI will follow the policy and procedures established by local IRBs and by HRPO. SAEs are rated as either study related or non-study related, based on a site-level review of clinical details surrounding the event. SAEs will be reported by telephone to the site’s IRB within 24 hours and a report will immediately follow to all IRBs with jurisdiction, to the initiating PI, and to the DSMB. Unexpected or serious adverse events occurring in subjects enrolled at non-study facilities will be reported to relevant IRBs, the DSMB, and the initiating PI within 10 working days of site investigator notification of the event. Reporting of the event must be reported even if the PI believes that the event is unrelated to the study protocol. Expected adverse events, (i.e., those events included as potential risks in the consent form) which are not serious, will be reported yearly on the Annual Continuing Review (CR). A pre-planned procedure is established to ensure a rapid and appropriate response if an adverse event does arise. Study care managers are notified if a study participant endorses significant distress while completing weekly homework and other assignments. In the event that a study participant reports a suicidal or homicidal behavior or other significantly distressing thought(s) and/or behavior(s) to their study care manager or a research team member, that individual will contact the site investigator. If not available, the PI will be contacted. The site investigator is responsible for ensuring participant safety and needed medical services are delivered as clinically safe, indicated, and appropriate. The study DSMB will review study SAEs and AEs and use the pattern of SAEs and AEs among other study information and data to make periodic recommendations regarding study safety and continuation.

A summary of all serious or unexpected side effects also will be included in the annual continuing report (CR).

6.6 Human Biological Specimens/Tissue (HBS/tissue)

Not applicable. The proposed research involves no laboratory evaluations or biologic sampling.
6.7 Subject Confidentiality Protection
Source documents will be kept by each study site for their own subjects. Source documents will be kept separately from case report forms in locked filing cabinets in locked offices. Study records will be kept separate from the subject’s medical record. Coded information from the case report forms will be entered into the study database at each respective study site. Only personnel having the correct user name, password, and signing on from a computer with the appropriate IP address will have access. The link between study code and identifying information will be kept by each study site’s PI in a locked file and on a computer with password protection and will only be available to members of that site’s research team, the initiating and partnering PIs and the data collection coordinators.

Only the investigators and the research staff will have access to the original research data. Deidentified and encrypted data will be transmitted between investigators via the web portal maintained by RTI International as discussed above in the Information Security section. Appropriate regulatory agencies (OHRP, USAMRMC, local IRBs) may view records which contain identifying information. Data will not be revealed to insurance companies or other individuals or organizations.

6.7.1 Certificate of Confidentiality
In response to DCI’s Administrative Review on 23 September 2010, we are no longer seeking a Certificate of Confidentiality, as it does not apply to active duty subjects as it pertains to military command authorities.

6.7.2 HIPAA Authorization
Your answers to the following questions will assist compliance with the requirements of the Health Insurance Portability and Accountability Act (HIPAA). The DOD HIPAA regulations 6025.LL-R and other guidance can be found on the DCI website.

If your research will collect Protected Health Information (PHI) such as, physical, clinical, psychological well-being, behavioral and genetic data (e.g., blood pressure, type of cancer, disease stage, ADL, PSA, urine protein, use of alcohol, depression, etc.) along with any of the following 18 personal identifiers, a HIPAA authorization is required. The research data collected in such format is referred to as “Identifiable Protected Health Information”

i. Are you intending to collect subject’s Protected Health Information (PHI) and any of the following 18 personal identifiers?
___ No – HIPAA does not apply – go to question #iv
_X Yes – please check which ones:

_X_ 1. Names
_X_ 2. Street address, city, county, 5-digit zip code
_X_ 3. Months and dates (years are OK) and ages >89 (unless all persons over 89 years are aggregated into a single category)
_X_ 4. Telephone numbers
__ 5. Fax numbers
_X_ 6. E-mail addresses
_X_ 7. Social security number
X_ 8. Medical record number  
__ 9. Health plan beneficiary number  
__ 10. Account number  
__ 11. Certificate/license number  
__ 12. Vehicle identification number (VIN) and/or license plate number  
__ 13. Device identifiers and serial numbers  
__ 14. URLs (Uniform Resource Locators)  
__ 15. Internet protocol address number  
__ 16. Biometric identifiers, such as finger and voice prints  
X_ 17. Full face photographic images or any comparable images  
X_ 18. Any other unique identifying number, characteristic, or code such as patient initials

ii. Can you limit your collection of personal identifiers to just dates, city/state/zip, and/or “other unique identifier” (#18 of the above)?  
__ Yes – then your dataset may qualify as a Limited Data Set – please complete a Data Use Agreement and attach to your protocol. Then go to question #iv.  
X_ No – Go to question #iii.

iii. Is obtaining patient Authorization “impracticable”?  
__ Yes – Authorization may qualify to be waived by the IRB. Go to Section 6.7.3 HIPAA Authorization Waiver for the application.  
X_ No – Research subjects will need to sign a HIPAA Authorization. Complete the HIPAA Authorization and attach to this protocol.

iv. What precautions will you take to protect the confidentiality of research source documents (Case Report Forms, questionnaires, etc.), the research data file, and the master code (if any)?

All case report forms will be labeled with study code number only and will not have any of the previous 18 identifiers recorded on them. The study code number will be randomly generated and assigned to each participant and will contain no identifying characteristics, such as date of birth or social security number. Case report forms from all study sites will be kept on the secure web portal. The link between subject identifiers and the study list will be stored on a password-protected file on a password-protected limited access and encrypted drive on the study site computer network. A hard copy of the list (for backup purposes) for a site’s participants will be kept in a locked file in the office of the site Principal Investigator.

A similar procedure will be used for identifying information stored at RAND for the subset of individuals who will be recruited to participate in qualitative interviews (after secure transfer of that information from RTI to RAND). A separate identification number will be used for the purposes of the qualitative interviews.

v. When will you destroy the research source documents, data file, and the master code?

The investigators and study staff will keep the research data, HIPPA information and consent forms for up to six years after the end of the study. Then, the master list that connects identifying information to the data will be destroyed. The data will be kept indefinitely but there will be no identifying information on the data forms.
vi. Will research data including Identifiable Protected Health Information be sent outside of WRAMC?

__ X __ Yes – Please explain assurances you have received from the outside party that they will appropriately follow confidentiality protections, follow the HIPAA requirements, and abide by the provisions of your Authorization. Data use agreements will be in place among all collaborating agencies.

___ No

Deidentified and encrypted data will be transmitted between investigators via the web portal maintained by RTI International as discussed in the Information Security section. Copies of the consent forms may be sent to the RTI International and RAND Corporation IRBs, as fully engaged collaborating organizations, upon request. Additionally, RAND will be given the names and contact information of participants selected for invitation to participate in the qualitative study. Boston and University of Washington may have access to identifying information outside of the military facility as part of supervision of study procedures. Appropriate regulatory agencies (OHRP, USAMRMC, local IRBs) may view records which contain identifying information. Data will not be revealed to insurance companies or other individuals or organizations.

6.7.3 HIPAA Authorization Waiver
Not applicable

6.8 Reporting Protocol Deviations
Any protocol deviations during the course of the study will be promptly reported to the WRAMC IRB (which will be the IRB of record) via WRAMC DCI and the local IRB for the deviation site, by the Project Director in coordination with the DSMB. Examples of deviations include, but are not limited to, variances from the treatment schedule for an individual patient, failure to use the most current consent form, and/or incomplete or lost records.

Reporting a protocol deviation will be accomplished by submitting a protocol deviation memorandum to the IRB via DCI. The memo will contain a summary of the deviation, an assessment of the situation and possible change in risk level to the participants, and a plan to correct/resolve the deviation. The study PI, Medical Monitor, and site PI (or all site PIs, if applicable) will be made aware of any deviations.

6.9 Other Reporting Requirements
The following are reporting requirements and responsibilities of the Principal Investigator to the United States Army Medical Research and Materiel Command’s (USAMRMC) Office of Research Protections (ORP), Human Research Protection Office (HRPO).

(1) The protocol will be conducted in accordance with the protocol submitted to and approved by the USAMRMC ORP HRPO and will not be initiated until written notification of approval of the research project is issued by the USAMRMC ORP HRPO.

(2) Accurate and complete study records will be maintained and made available to representatives of the U.S. Army Medical Research and Materiel Command as a part of their responsibility to protect human subjects in research. Research records will be stored in a
confidential manner so as to protect the confidentiality of subject information.

(3) All unanticipated problems involving risk to subjects or others, serious adverse events related to participation in the study and subject deaths related to participation in the study will be promptly reported by phone (301-619-2165), by email (hsrrb@amedd.army.mil), or by facsimile (301-619-7803) to the USAMRMC, Office of Research Protections, Human Research Protection Office. A complete written report will follow the initial notification. In addition to the methods above, the complete report will be sent to the U.S. Army Medical Research and Materiel Command, ATTN: MCMR-RP, 504 Scott Street, Fort Detrick, Maryland 21702-5012.

(4) Suspensions, clinical holds (voluntary or involuntary), or terminations of this research by the IRB, the institution, the Sponsor, or regulatory agencies will be promptly reported to the USAMRMC ORP HRPO.

(5) Any deviation to the protocol that may have an adverse effect on the safety or rights of the subject or the integrity of the study will be reported to the USAMRMC ORP HRPO as soon as the deviation is identified.

(6) Major modifications to the research protocol and any modifications that could potentially increase risk to subjects will be submitted to the USAMRMC ORP HRPO for approval prior to implementation. All other amendments will be submitted with the continuing review report to the USAMRMC ORP HRPO for acceptance.

(7) A copy of the approved continuing review report and the local IRB approval notification will be submitted to the USAMRMC ORP HRPO as soon as these documents become available. A copy of the approved final study report and local IRB approval notification will be submitted to the USAMRMC ORP HRPO as soon as these documents become available.

(8) The knowledge of any pending compliance inspection/visit by the FDA, OHRP, or other government agency concerning this clinical investigation or research, the issuance of Inspection Reports, FDA Form 483, warning letters or actions taken by any Regulatory Agencies including legal or medical actions and any instances of serious or continuing noncompliance with the regulations or requirements that relate to this clinical investigation or research will be reported immediately to USAMRMC ORP HRPO.

7. REFERENCES


8. FACILITIES/ORGANIZATIONS TO BE USED

RAND Corporation
1200 South Hayes Street
Arlington, VA 22202
FWA00003425

RTI International
3040 Cornwallis Road
P.O. Box 12194
Research Triangle Park, NC 27709-2194
FWA3331

Walter Reed Army Medical Center
6900 Georgia Avenue NW
Building 2, Room 3E01
Washington, DC 20307
FWA00000477

Fort Bragg
Womack Army Medical Center
2132 Reilly Street
Fort Bragg, NC 28310
FWA00012834

Fort Bliss
William Beaumont Army Medical Center
5005 North Piedras Street
El Paso, Texas 79920-5001
FWA00005646

Fort Campbell
Blanchfield Army Community Hospital
650 Joel Drive
Fort Campbell, Kentucky 42333
FWA00005646
9. ROLE AND RESPONSIBILITIES OF EACH INVESTIGATOR AND COLLABORATOR

Partnering PIs, their institutions, and coinvestigators and their roles are described below. In addition to the partnering PIs, several institutions will include coinvestigators or other substantive and support staff for the project to ensure use of a broad range of talent to address the key issues related to the planned studies (see biosketches).

Deployment Health Clinical Center, Walter Reed Army Medical Center – Initiating Institution

Charles C. Engel, MD, MPH, Initiating Principal Investigator, is a psychiatrist, clinical epidemiologist, and expert health services researcher with 20 years’ experience working in and completing research to identify evidence-based practices for improving military mental health care quality for active-duty and VA beneficiaries with war-related mental health problems and concerns. Dr. Engel runs the DoD-chartered Deployment Health Clinical Center (DHCC) with a staff of 35–40 tasked with improving mental health services for recently deployed troops and their families using service delivery, services research, and educational outreach strategies to providers and beneficiaries. Dr. Engel also directs a 15-site, 43-clinic effort to improve and evaluate PTSD and depression care in military primary care using an evidence-based systems approach called “RESPECT-Mil.” Dr. Engel’s vision, organizational skills, clinical and research experience, and extensive knowledge of the military health service system ideally positions him to lead the proposed research. As Principal Investigator and Project Director, Dr. Engel will be responsible for study oversight and management of study team members, as well as project communication among team members, advisory groups, and the Data and Safety Monitoring Board.

Michael C. Freed, PhD, Director & Coinvestigator, is a licensed Clinical Research Psychologist at the DHCC. He holds an appointment as a Research Assistant Professor in the Department of Psychiatry and is a CSTS Scientist, both at Uniformed Services University of the Health Sciences. Dr. Freed is a health services researcher with clinical and research expertise in
Dr. Freed will serve as the Clinical Research Program Director, with responsibility for coordinating and guiding the protocol through multiple IRBs associated with the different study sites and investigator institutions, HRPO, and other regulatory approvals. He will also interface with the DSMB to ensure that their information and coordination needs are fully addressed. Dr. Freed will be responsible for coordinating with study personnel at partnering and collaborating sites, including RTI International, RAND Corporation, University of Washington, Boston VA, as well as coordination of efforts with the Care Management Center. He will oversee the development of operations manuals for study personnel and facilitate the development of standardized study forms for use across data collection sites.

Dr. Freed will also help supervise study personnel at the Deployment Health Clinical Center site and establish plans for communication with study investigators and personnel to ensure efficient and effective flow of information and documentation. He will oversee the report writing and report submission for all protocol addenda, protocol deviations, adverse events, and continuing reviews and ensure strict confidentiality procedures are followed in the handling of all research data and personal health information. He will ensure compliance with Good Clinical Practices (GCP), the international ethical and scientific quality standard for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical trials that involve human subjects. Compliance with GCP assures that data and collated results are credible and accurate, and that the rights, safety, confidentiality, and well-being of trial subjects are protected.

Kristie Gore, PhD, Director of Research, DHCC, is a clinical research psychologist and the Associate Director of Research at the DHCC. She has nearly a decade of experience with the conduct and management of multi-site clinical trials. Her research experience involves clinical interventions for anxiety disorders, including randomized clinical trials for panic disorder, and for PTSD, and her roles have ranged from study psychotherapist to program director. Dr. Gore has conducted research within the military system and she understands the IRB, contracting, and regulatory compliance needs of a large clinical trial. Her role in the current study will be oversight of all activities completed at WRAMC, to include the development, submission, and maintenance of regulatory documents and hiring of study-related personnel.

21.2 RTI International – Partnering Institution

Robert M. Bray, PhD, Partnering PI, Director of Research Coordinating Center, is a social psychologist, substance abuse researcher, and senior program director of military behavioral health at RTI. He has over 25 years’ experience conducting comprehensive multisite worldwide military health surveys and coordinating multisite population health research. Since 1982 he has been PI on DoD’s flagship survey of health-related behaviors, which has driven numerous policy decisions. His long history of conducting complex large scale studies (many in
challenging military populations) provides the needed breadth to oversee coordinating center activities. Under his direction, RTI will also provide a cadre of additional personnel with expertise in statistics, substance abuse, mental health, family support, health services, health promotion, and communications. Dr. Bray will oversee all activities conducted by RTI associated with the clinical trial and coordinating center. He will communicate directly with Dr. Engel and Dr. Jaycox (RAND Partnering PI).

**Donald Brambilla, PhD**, is a statistician with 24 years’ experience in epidemiological investigations, and 17 years of experience in the design and execution of clinical trials, including 8 multi-center Phase III trials and several Phase II trials. Dr. Brambilla’s clinical trial background/experience makes him an ideal candidate to lead sample selection, data weighting, and data analysis activities. Dr. Brambilla will serve as lead statistician on this project. He will have primary responsibility for statistical aspects of study design and analysis, particularly for the primary endpoint. He will oversee and coordinate the work of the statistical team to ensure that planned analyses are completed in a timely fashion.

**Becky Lane, PhD, Coinvestigator**, a research psychologist with extensive experience designing research studies and survey instruments, collecting data, and performing quantitative and qualitative data analysis, will serve as research coordinator to oversee quality control and supervision of enrollment and assessment activities by project staff at participating study sites. She will oversee the recruiting, hiring, and training of the eight onsite research associates for participating installations, and will monitor the progress of these research associates as they recruit volunteers to participate in the study. Dr. Lane has served in project director and task leadership roles on military survey projects including the DoD Lifestyle Assessment Program (DLAP) surveys and the Naval Health Research Center (NHRC) Status of Transitioning Military Personnel study. Her experience includes managing staff and monetary resources, managing data collection and reporting activities, monitoring budgets and project timelines, and interacting with team members and external clients to discuss project needs and to deliver easily utilizable results.

### 21.3 RAND – Partnering Institution

**Lisa Jaycox, PhD, Partnering PI**, is a clinical psychologist and Senior Behavioral Scientist at RAND with 15 years of combined research and clinical experience focused on PTSD and its treatment. Her PTSD research prior to joining RAND included conducting clinical trials of Prolonged Exposure and psychosocial prevention programs for female assault survivors with Dr. Edna Foa. At RAND, she has extended this work to develop a trauma-focused school program for children exposed to trauma that draws on cognitive-behavioral techniques. Her work has included treatment development as well as effectiveness research in schools, and resulted in a program that is now being used nationally. In addition, Dr. Jaycox has been involved in several projects aimed at improving depression care within primary care settings, including the Partners in Care study and the Youth Partners in Care study. Here Dr. Jaycox was again involved in both the intervention protocol development effort as well as overall conduct of the quality improvement effectiveness trials. Recently Dr. Jaycox co-led the Invisible Wounds study, which examined mental health among previously deployed service members and veterans, along with the systems of care available for their treatment. Thus, Dr. Jaycox brings a combination of experience with clinical trials, PTSD, veterans, and primary care work that will be invaluable to this proposed work. As Partnering PI, Dr. Jaycox will oversee all activities conducted by RAND. This includes collaborative work associated with the clinical trial (design, instruments, intervention elements), qualitative assessments (protocol development, interviews, and analysis),
and cost of care analyses (consideration of key assumptions, interpretation of findings). She will communicate directly with Dr. Engel and Dr. Bray (RTI Partnering PI).

**Terri Tanielian, MA**, is a Senior Social Research Analyst at the RAND Corporation who specializes in health care and military studies using qualitative and quantitative research strategies. Most recently, she co-led an assessment of the prevalence of PTSD, depression, and TBI among troops who had been deployed to Operations Enduring Freedom and Iraqi Freedom, the costs and consequences associated with these conditions, and the systems of care available to address these issues among our nation’s veterans. She has conducted several studies involving focus groups and semi-structured interviews with military populations to include providers as well as beneficiaries. Her recent work in the military health system makes her a valuable asset to this project. Ms. Tanielian will take the lead in designing and conducting the qualitative data collection and analyses as outlined in the proposal. She will supervise the other RAND research staff working on these tasks, oversee the development of interview protocols, coordinate the participant selection and recruitment, train the interviewers and data coders, as well as direct the qualitative analyses. She will work closely with Dr. Jaycox, Dr. Engel, and Dr. Bray to ensure that the findings from the qualitative studies are appropriately incorporated into the overall findings from the trial.

**Christine Eibner, PhD**, is an economist at RAND and recently served on the management team for the RAND report entitled *Invisible Wounds of War: Psychological and Cognitive Injuries, Their Consequences, and Services to Assist Recovery* (eds. Tanielian and Jaycox). In addition, she was the lead author and study co-leader for the economic analysis chapter included in this report. Since coming to RAND in 2003, Eibner has been involved in numerous studies related to military medical policy, including a survey of health insurance enrollment and utilization for military retirees, and an assessment of a new paradigm for maintaining military medical readiness during peacetime. She is currently involved in several projects related to micro-simulation modeling and economic cost projections, including an analysis of health care cost containment strategies in Massachusetts, a simulation model projecting the economic costs of substance abuse in the United States, and a simulation model predicting the cost and coverage implications of national health care reform proposals. Prior to joining RAND, she was an intern at the Agency for Health Care Policy and Research (now the Agency for Healthcare Research and Quality), and a post-doctoral research associate at Princeton University. She will lead the economic analyses on costs for this project.

### 21.4 Collaborating Investigators

**Douglas Zatzick, MD, MPH** is currently Associate Professor in the Department of Psychiatry and Behavioral Science at the University of Washington School of Medicine and a member of the Core Research Faculty at the Harborview Injury Prevention and Research Center. Dr. Zatzick’s research focuses on clinical epidemiological and intervention studies of trauma exposed youth, and adults who are treated in acute care medical and emergency department settings and other non-specialty mental health settings. Dr. Zatzick is currently the principal investigator on an NIMH R01 investigation that is delivering stepped collaborative care interventions targeting PTSD for injured trauma survivors treated in acute care medical settings. As a coinvestigator on the project Dr. Zatzick will provide consultation around the development and implementation of the stepped collaborative care procedure. This includes assistance with drafting the grant application, travel to coinvestigator meetings, expert consultation on protocol implementation issues, and participation in the development and submission of manuscripts and subsequent grant applications.
Brett Litz, PhD, is a Professor of Psychiatry in Boston University School of Medicine and a Professor of Psychology in Boston University’s School of Arts and Sciences. He is also a staff clinical psychologist and former Associate Director of the Behavioral Sciences Division (BSD) of the National Center for PTSD at VA Boston Healthcare System (VBHS) and the Director of the Mental Health Core of the Massachusetts Veterans Epidemiological Research and Information Center (MAVERIC), also located at the VBHS. Dr. Litz has extensive experience in developing and implementing Web-based and telehealth interventions for PTSD and other mental health problems implicated by exposure to combat and operational stress and trauma. For example, Dr. Litz developed the self-management CBT model that is used in the DE-STRESS program. Dr. Litz and Dr. Engel have collaborated on several research projects, including a successful pilot trial of the DE-STRESS program. As a coinvestigator, Dr. Litz will take responsibility for the development, implementation, and oversight of both the Web-based and phone-based self-management CBT interventions for deployment-related PTSD in active-duty OIF/OEF veterans. Dr. Litz will oversee all aspects of the Web-based and phone-based interventions including modifications to the interventions and development of related documentation (including the training manuals for the care managers). Dr. Litz will also conduct trainings for care managers and provide clinical supervision for the interventions. Additionally, Dr. Litz will provide input on study design while collaborating with many consortium members. During subsequent years of the project, Dr. Litz will continue to oversee all aspects of the Web-based and phone-based interventions and will assist in data analysis, report and manuscript preparation, and conference presentations. Dr. Litz will supervise the Boston VA post-doc who will assist him with the above tasks. Throughout the study period, Dr. Litz will maintain regular contact with Dr. Engel and other project staff and will participate in regularly scheduled team conference calls. The Boston VA Research Institute, Inc. (BVARI) facilitates research at the BHS, a Department of Veterans Affairs Medical Center in Boston. The percentage of effort in this application represents the professional effort for Boston University. Dr. Litz’s overall specific effort on this project during all five project periods will be 20% or 2.4 calendar months of this University effort.

Wayne J. Katon, MD, University of Washington, Coinvestigator, is Professor and Vice Chair in the Department of Psychiatry and Chief of the Division of Psychiatric Epidemiology and Health Services. Dr. Katon is internationally renowned for his research in three major areas: developing population-based primary care disease management models that potentiate the ability of the primary care medical system to treat major depression; improving the recognition and treatment of DSM-IV psychiatric disorders in primary care and medical specialty patients with medically unexplained symptoms such as pelvic pain or fatigue; and demonstrating the impact of effectively treating major depression in patients with chronic medical illness in reducing amplification of aversive symptoms of chronic medical illness and improving social and vocational functioning. Dr. Katon and his research group are considered one of the preeminent research groups in the United States in studying interventions to improve the care of mental illness in the primary care system of the United States. Dr. Katon will serve on the planning and oversight committee.

Jurgen Unützer, MD, MPH, University of Washington, Coinvestigator, is Professor and Vice-Chair of Psychiatry at the University of Washington and an Adjunct Associate Professor in the Department of Psychiatry and Biobehavioral Sciences at UCLA. A geriatric psychiatrist and health services researcher, Dr. Unützer is also an affiliate investigator at the Center for Health Studies, Group Health Cooperative of Puget Sound and a consultant in mental health services.
research at RAND. He recently served as senior scientific advisor to the World Health Organization and as an advisor to the President’s Commission on Mental Health. His research focuses on improving the care of older adults with depression and comorbid medical disorders. He is the principal investigator of project IMPACT, a multi-site study to improve care for late-life depression funded by the John A. Hartford Foundation and the California HealthCare Foundation. Dr. Unützer has participated in several large multicenter trials of collaborative care for depression and has led the largest multisite trial of collaborative care for depression. For the proposed study, Dr. Unützer will serve on the planning and oversight committee.

21.5 Site Principal Investigators
Dr. Molina (Ft. Bliss), MAJ Guirand (Ft. Bragg), Dr. Swan (Ft. Stewart), Dr. Hanley (Ft. Campbell), COL Reeves (Ft. Carson), and COL Peterson (Ft. Lewis). We have designated one person at each data collection site to serve as the Site PI. These individuals are primary care or behavioral care providers at their respective sites, and most also serve roles in the RESPECT-Mil program. Site PIs will be responsible for the oversight of all study procedures conducted at their site and will be available to troubleshoot any logistical problems. They will also be responsible for supervising site personnel and ensuring regulatory compliance.

External Advisory Committees
Our research team will be fortunate to receive additional input and advice from two external advisory committees. The Scientific Advisory Committee will be composed of respected researchers and experts who will contribute input on the design, analyses, and data interpretation of the intervention. The Consumer Stakeholder Advisory Committee will include a retired Army Ranger, a representative for a soldier advocacy group, an active duty soldier, a chaplain, a female reserve officer, and spouses of service members who received serious injuries in Iraq. One of their most valuable functions will be to help us gain the perspective of families/military members who have experienced firsthand the challenges associated with PTSD or related mental health issues and to assist in disseminating our findings.

We will hold annual meetings with the External Advisory Committees in Washington, D.C. The purpose of these meetings will be to gain insight on both the scientific implementation of the program as well as opinions on the acceptability and preference from a representative group of stakeholders. We also plan to hold semi-annual conference calls with the External Advisory Committees to ensure that they are regular participants in the consortium research process helping us shape the direction of our research.

Scientific Advisory Committee
Our research team will be fortunate to receive additional input and advice from an external advisory committee of highly respected researchers and consumer stakeholders. We will meet annually with our advisory committee. Kurt Kroenke, MD (retired Army Colonel), Regenstrief Institute, Inc., is widely respected as a primary care and mental health services researcher who has completed clinical trials, and quality-of-care research and is published in somatic symptoms including post-war syndromes such as the 1991 “Gulf War syndrome,” depression, pain, and other physical symptoms. He leads two randomized trials comparing care management vs. usual care, one in the treatment of primary care patients with depression and comorbid pain and the other comparing centralized care management coupled with automated symptom monitoring vs. usual care in cancer patients. He has also codeveloped widely used
primary care-mental health screening and measurement tools (e.g., PRIME-MD, Patient Health Questionnaire, GAD-7). Dr. Kroenke will serve on the planning and oversight committee, and will bring his experience to bear on the measurement and instrumentation tools to be used in the study. Allen Dietrich, MD, Professor of Family Medicine, Dartmouth Medical Center, has devoted his academic career to developing and testing systems of care that help primary care clinicians provide evidence-based practices within the busy context of their practices. He is a member of the IoM and President of North American Primary Care Research Group. He was the Principal Investigator in the MacArthur Foundation’s Initiative on Depression/Primary care which developed/tested the three component model (3CM), a precursor to the model we propose to test in the current research. Dr. Dietrich will serve on the planning and oversight committee and provide advisement to the study design and intervention, based on his previous experience with the 3CM. Charles W. Hoge, MD is a Neuropsychiatry Research Consultant for the Office of the Surgeon General and Senior Scientist at the Walter Reed Army Institute of Research. COL Hoge trained at the CDC’s Epidemic Intelligence Service and is the lead investigator on a series of landmark studies into the mental health consequences of the conflicts in Iraq and Afghanistan. He and his research team have also been instrumental in completing the four Mental Health Assessment Team reports that have characterized the mental health status of U.S. troops in the theater of operations. Dr. Hoge’s work represents the first time that important real-time data on PTSD and other mental disorders have been available while war is still ongoing. Kathryn Magruder, PhD, MPH is an experienced epidemiologist who brings expertise in conducting clinical trials in a primary care military setting. She is experienced in PTSD health services research and is a leader in the study of PTSD in primary care. Dr. Magruder is an epidemiologist and mental health services researcher, with joint appointments at both Medical University of South Carolina (MUSC) and the Ralph H. Johnson VA Medical Center. John Williams, MD, MHS is a professor in the Department of Internal Medicine and psychiatry at the Duke University School of Medicine, who is an expert on mental health services delivery in the VA, and brings a background in primary care mental health services research and clinical trials. Dr. Williams has done extensive primary care psychiatry work and is a collaborator in the RESPECT-Mil implementation study. He developed a decision aide for depression and will be leading the development of a similar aide for PTSD as part of the proposed intervention study. He is also a VA doctor who is attempting to modify policy in the VA to implement collaborative care/care management in primary care as a matter of routine.

Consumer Stakeholder Advisory Committee

Steve Robinson is a retired Army Ranger who is a veteran of Operations Desert Storm and Provide Comfort. He has served on the DVA Research Advisory Committee on Gulf War Illnesses and is a spokesman for the care of returning veterans from the present wars in Iraq and Afghanistan. He has testified before the House and Senate on matters pertaining to Force Health Protection and returning war veterans. LTC O. Wayne Boyd is an Army Chaplain assigned at the US Army Center for Health Promotion and Preventive Medicine with expertise in mental health issues and suicide prevention. He is a keen advocate for soldiers with a special interest in complementary and alternative medicine modalities and their role in reducing distress and mental illness after combat deployment. Ms. Tonia Sargent is the wife of a Marine who survived a serious gunshot wound to his head while serving in Iraq in 2004. She has firsthand experience with pathways to care and its challenges and is actively involved with Operation Home Front where she advocates for better systems and programs to help families of wounded personnel.
MAJ Jeffrey Hall, US Army, is stationed at Ft Polk, LA and has served two tours in Iraq, one in 2004 and one in 2006, and has 16 years of service. He is currently on orders to move to Ft Riley and deploy for the third time. Mrs. Sheri Hall has been married to MAJ Jeffrey Hall for 17 years and they have two teenage daughters. She has been a continuous advocate for MAJ Hall in his struggles through the military health care system.

10. **TIME REQUIRED TO COMPLETE THE RESEARCH (INCLUDING DATA ANALYSIS)**

Anticipated start date of participant enrollment - March 1, 2011  
Expected completion date - September 30, 2014

11. **BUDGET**

Will any outside organization provide funding or other resources? Yes (x)  No (    )

Funds are being provided by Congressionally Directed Medical Research Programs (CDMRP), award number DR080409, and are being managed by the Henry M. Jackson Foundation. For Award Notification Letter, please see Appendix R. For budget page, please see Appendix S.

12. **ENVIRONMENTAL IMPACT STATEMENT** (***May be revised IAW future DCI SOP)

Does any part of this protocol generate any of the following regulated waste?

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<thead>
<tr>
<th>Waste Type</th>
<th>Yes (x)</th>
<th>No (   )</th>
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<tbody>
<tr>
<td>a. Hazardous chemical waste</td>
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<td>b. Regulated Medical Waste</td>
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<tr>
<td>c. Radioactive Waste</td>
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</table>

If yes to any questions, please indicate at what stage and how much, and how it will be safely disposed to protect the environment and provide an Environmental Impact Statement signed by the appropriate official. If any or part of the protocol will be executed at the DCI Research Laboratories, an Environmental Impact Statement signed by the DCI Laboratory Chief will be required.

13. **INVESTIGATOR COMPLIANCE STATEMENT** (May be revised IAW DCI SOP)

a. I have read and understand the provisions of The Belmont Report, Ethical Principal and Guidelines for the Protection of Human Subjects of Research, April 18, 1979.

b. I have read and will comply with the NRMC DOD Assurance and WRAMC Federal-Wide Assurance for the protections of human subjects from research risks.

c. I have read and will comply with the institutional policies and guidelines as outlined in the Standard Operating Procedures (SOP) of the Department of Clinical Investigation and the Principal Investigator Guide. (See DCI web-site for a copy, http://www.wramc.amedd.army.mil/departments/dci/NCA_Web/NCA_WebPage.htm)

d. I have read and will comply with the “Potential Conflict of Interest in Clinical Research at WRAMC
as outlined in the DCI SOP.

e. I certified that any outside funds and/or other resources (other than requested from DCI) being provided for this study are listed above in this application under Section 11 - Budget.

14. RESPONSIBILITIES OF THE PRINCIPAL/ASSOCIATE INVESTIGATOR IN HUMAN SUBJECTS RESEARCH (**May be revised IAW future DCI SOP**)

The principal investigator is the individual who is primarily responsible for the actual execution of the clinical investigation. He/she is responsible for the conduct of the study, obtaining subjects' consent, providing necessary reports, and maintaining study documents. The Associate Investigator will assist the Principal Investigator for the responsibilities stated below.

As the Principal Investigator or Associate Investigator:

a. I will not enroll a subject into a study until the study has been approved by the appropriate authority and, when appropriate, the subject's primary care physician has granted approval for him/her to enter a study.

b. By signing this protocol, I warrant that any use of Protected Health Information (PHI) for reviews preparatory to research met the following requirements:
   i. The review of PHI was done solely to prepare a research protocol, or for similar purposes preparatory to research;
   ii. No PHI was taken outside the Military Health System; and
   iii. This review of PHI was necessary for research purposes

c. I am responsible for assuring that the prospective volunteer is not participating as a subject in other research that will significantly increase the research risks.

d. I am responsible for assuring the quality of each subject's consent in accordance with current federal regulations. This will include ensuring that any "designee" that obtains consent on my behalf is completely conversant with the protocol and is qualified to perform this responsibility.

e. I will obtain the WRAMC IRB approval for advertisements used to recruit research subjects.

f. I will not accept any outside personal remuneration for implementation of a study.

g. I will take all necessary precautions to ensure that the study does not generate hazardous chemical waste.

h. I will obtain the proper WRAMC clearance prior to all presentations, abstracts, and publications. The following require WRAMC approval:
   i. Reports involving WRAMC subjects and/or patients.
   ii. Reports that cite WRAMC in the title or byline.
   iii. Reports of WRAMC approved clinical investigation or research.
   iv. Reports of research performed at WRAMC.
   v. Reports of research conducted by WRAMC assigned personnel.

i. I must submit to the Department of Clinical Investigation (DCI):
   i. Any source of outside funding.
ii. An APR, due in the anniversary month of the protocol’s initial approval or due in the month as determined by the IRB for continuing review and approval.

iii. Reports of adverse effects occurring in subjects as a result of study participation or of any protocol deviations and submit these reports to Medical Monitor if there is one for the study.

iv. An Addendum, prior to any changes made to the study or a change in the funding status.

v. A Final Report within 30 days following termination of a study.

vi. Listing of presentations, abstracts, and publications arising from the study for inclusion in the APR.

j. I will maintain a Study File that must be kept for three years following completion of the study if no IND/IDE used (32 CFR 219.115(b). If IND medication or IDE appliances are used, the file must be kept for 2 years after FDA approval and can then be destroyed; or if no application is filed or approved, until 2 years after the study is discontinued and FDA notified (21CFR 312.62(c). The records should be kept in the Department/Service where the research took place (AR 40-38). If I am scheduled to PCS or ETS, these records will be given to a new WRAMC PI or the Department/Service Chief.

This file may be inspected at any time by DCI, the Army Clinical Investigation Regulatory Office (CIRO), Department of the Defense (DOD), the Food and Drug Administration (FDA), and/or other regulatory agencies responsible for the oversight of research. This file will include:

i. The approved protocol and applicable addenda.

ii. The WRAMC Scientific Review Board and IRB minutes (as appropriate) and the DCI memorandum granting approval to begin the study.

iii. Other applicable committee minutes [e.g., Radioactive Drug Research Committee (RDRC); the Surgeon General’s Human Subjects Research Review Board].

iv. Each Volunteer Agreement Affidavit (i.e., consent form) signed by the subject.

v. APR or Final Report.

vi. Reports of adverse effects occurring in subjects as a result of study participation.

vii. Reports of any significant new findings found during the course of the study.

viii. All study documents generated from study date, e.g., patient enrollment log research records, data collection sheets, etc.

ix. Publications/abstracts/Presentations Clearance documents, and reprints from study data.

x. All information pertaining to an investigational drug or device.

xi. For HIV research studies, approval of the Chief, Infectious Disease Service.

k. I will be familiar with all applicable regulations governing research, and will adhere to all of the requirements outlined in the NRM’s DOD Assurance and WRAMC’s Federal-Wide Assurance granted by the Office for Human Research Protections, Department of Health and Human Services.

15. MEDICAL MONITOR RESPONSIBILITIES

(*May be revised IAW future DCI SOP*)

Duties as the Medical Monitor include:

• Monitoring the conduct of the protocol per the approval plan and ensuring protection of human subjects. This may involve periodic review of medical records of enrolled subjects and the research files being maintained by the PI.

• Reviewing and keeping abreast of adverse events and protocol deviations that occur during the researches (all adverse events, including deaths and serious or unexpected side effects, are reported to the Medical Monitor via the PI).
• If there is concern about the welfare of enrolled subjects, the Medical Monitor has the authority to stop a research study in progress, remove individual subject from a study, and take whatever steps necessary to protect the safety and well being of research subjects until the IRB can assess the Medical Monitor’s report. Notification of such actions must be forwarded to the DCI within one (1) working day of receipt of knowledge prompting human subject welfare concerns.

• Medical Monitors will be required to co-sign all adverse event reports, protocol deviation memoranda, APR, and addendum.

• The Medical Monitor must keep current the WRAMC required research ethics Human Subjects Training every 3 years.

• If the Medical Monitor is expected to be away for more than 14 days but less than 30, the PI or Medical Monitor must designate an acting Medical Monitor and document such action.

• If a Medical Monitor leaves WRAMC for greater than 30 days then the PI must be informed to designate a new Medical Monitor and report such change to the IRB via a memorandum for a change of Medical Monitor (see template).

16. **PRINCIPAL INVESTIGATOR SIGNATURE**

With my signature, I acknowledge that I have read and am accountable for the responsibilities under *Section 13* and *Section 14*. I understand that if I fail to comply with any of these responsibilities, all projects for which I am an investigator may be suspended. I also acknowledge the above Application for Clinical Investigation Project; Request for Approval of Clinical Investigation Study Proposal; Environmental Impact Statement; Investigator Compliance Statement; and Responsibilities of the Principal/Associate Investigator in Human Subject Research.

Charles C. Engel, MD, MPH
COL, MC, USA,
Director, DoD Deployment Health Clinical Center at Walter Reed
Associate Professor & Assist Chair (Research)
Senior Scientist, Center for the Study of Traumatic Stress
Department of Psychiatry
Uniformed Services University of the Health Sciences

17. **ASSOCIATE INVESTIGATOR SIGNATURE** (*Add as many associate signatures as necessary.*)

With my signature, I acknowledge that I have read the responsibilities under *Section 13* and *Section 14* and will comply with them.

Michael C. Freed, PhD
STEPS UP Clinical Research Programs Director &
Licensed Clinical Research Psychologist
Deployment Health Clinical Center
Walter Reed Army Medical Center
Kristie L. Gore, PhD  
Associate Director of Research  
Deployment Health Clinical Center  
Walter Reed Army Medical Center

18. MEDICAL MONITOR SIGNATURE (If a medical monitor is not required state NA to and delete the information below.)

(***(May be revised IAW future DCI SOP.)

With my signature, I acknowledge that I have read the responsibilities under Section 15 and agreed to serve as Medical Monitor for the above protocol. I understand that the Medical Monitor must be independent of the research study, i.e., not an investigator of the study and cannot be a subordinate in the PI’s rating scheme because of a potential for command influence type conflict of interest.

My PRD/PCS (Projected Rotation Date/Permanent Change of Station Date) is ____________________.

David M. Benedek, M.D.  
COL, MC, USA

19. DEPARTMENT CHIEF AND SERVICE CHIEF SIGNATURE

I concur with the submission of this proposal to the Clinical Investigation Committee and/or Human Use Committee for review and approval.

_________________________  
DEPARTMENT CHIEF  
COL John Bradley, MC  
Chief, Department of Psychiatry
20. APPENDICES
As appropriate include all relevant documents in the following sequences:

APPENDIX A – Figures / Graphs
N/A

APPENDIX B - Data collection sheets / Case Report Forms / Questionnaires

APPENDIX C – Signed General Impact Statement

APPENDIX D - All Other Impact Statements signed by applicable Departments, such as:
  Deployment Health Clinical Center

APPENDIX E – Signed Conflict of Interest Statement

APPENDIX F - Support Letters/Documents
  Letters of support from Collaborators and/or Consultants

APPENDIX G - Advertisement Brochure/Flyer

APPENDIX H - STEPS UP Questions and Answers Sheet

APPENDIX I – Site Standard Operating Procedures (SOPs) Ft. Bliss Example

APPENDIX J - Recruitment Phone Scripts

APPENDIX L – Cover Letter (to accompany consent forms)

APPENDIX M - DESTRESS-PC Materials

APPENDIX N - Beating the Blues Materials

APPENDIX O – DESTRESS-T Materials

APPENDIX P – Medication Guidance List

APPENDIX Q – Qualitative Study Materials

APPENDIX R – Award Notification Letter

APPENDIX S – STEPS UP Budget Page

APPENDIX T – Care Management Manual

APPENDIX U – Contact Information/Adverse Event Card

Please see the attached initial approved research protocol and summary of amendments. The research protocol is dated April 2011, prior to enrollment of participants. The summary of approved amendments and dates for the STEPS-UP study (Stumped Enhancement of PTSD Services Using Primary care) are provided below. More primary documentation related to the originally funded grant, this protocol and subsequent amendments can and will be made available in the event you wish to review them. Please note also that the study had an independent Data Safety and Monitoring Board that regularly reviewed study progress and reviewed key amendment decisions at regular intervals.

The protocol attached was approved by the Walter Reed National Military Medical Center (WRNMMC) Institutional Review Board (IRB) and the Human Research Protections Office, US Army Medical Research and Material Command. The WRNMMC IRB was the primary IRB for the study.

A description of subsequent protocol amendments listed by date of their approval follows:

1. 17 November 2011: This amendment updated study data collection forms, including revisions to the eligibility and baseline survey questionnaires in order to increase the efficiency of the data collection procedures and reduce the burden to participants.

2. 28 February 2012: This amendment added new Site Principal Investigators to four of the study sites, including Ft. Bragg, Ft. Campbell, Ft. Carson, and Joint Base Lewis McChord (JBLM; formerly Ft. Lewis).

3. 29 May 2012: This amendment removed “deployment to Iraq or Afghanistan” as an inclusion criterion into the study. The reason for the amendment was that the inclusion criterion requiring deployment to Iraq or Afghanistan would limit the generalizability of the study findings to those with PTSD or depression after deployment, when in fact many in the military have PTSD from non-war-related causes such as adverse childhood experiences, accidents, disasters, and physical and sexual assault. By removing the deployment criterion, the sample of service members enrolled in the STEPS-UP study would be more representative of the general service member population receiving care for PTSD and depression in military primary care settings. This amendment also revised study eligibility procedures so that patients undergoing a medical retirement were not automatically excluded from study participation. Finally, this amendment updated study data collection forms, including revisions to the eligibility and baseline survey questionnaires, and provided the 3-, 6-, and 12-month follow-up survey questionnaires for approval.

4. 26 September 2012: This amendment allowed the provision of incentives for study participation via electronic Amazon.com gift cards when participants completed the baseline, 3-, 6-, and 12-month follow-up questionnaires during off-duty hours. The amendment retroactively provided Amazon.com gift card incentives for participants who were already enrolled in the study prior to approval of this amendment and all subsequently enrolled participants. Second, the amendment updated the qualitative study materials to reflect the provision of Amazon.com gift card incentives for those healthcare providers and patients who participated in the qualitative interviews conducted during off-duty hours. Questions were
approved for addition to the qualitative interviews regarding the web-based self-management program for depression made available to participants in the intervention arm.

5. 11 December 2012: This amendment updated follow-up data collection procedures by allowing for text message reminders to be sent to participants who opted in to receiving text messages for study follow-up completion reminders and updated the follow-up reminder schedule. It also provided a paper/pencil form and telephone interview version of the follow-up survey questionnaires in order to provide more convenient opportunities for participants to complete the follow-up survey questionnaires rather than only being able to complete the questionnaires online. Furthermore, this amendment increased the number of participant qualitative interviews from 30 to 36 in order to recruit an even number of participants from each arm of the study from each of the six sites. The amendment also revised the adverse event reporting procedures described in the protocol to align with updated WRNMMC reporting procedures. It was originally planned for nurse care managers to deliver the telephone-based CBT option for participants in the STEPS-UP arm. The amendment changed this from nurse care managers to a centralized behavioral health specialist. This amendment also included an updated recruitment materials, personnel information, and consent form (minor formatting changes). Language was updated describing which personnel in each participating study clinic collected the RESPECT-Mil (usual integrated care) referral forms from providers to better align with current clinic procedures and better incorporate the study into the RESPECT-Mil referral process.

6. 13 December 2012: This amendment allowed for real time review of every eligibility determination prior to randomization, as well as a weekly pull of all eligibility data as a data quality check to prevent automated data collection error while the research team gained experience with and confidence in the automated study data collection system.

7. 01 March 2013: This amendment discontinued real time review of eligibility determinations prior to randomization.

8. 10 May 2013: This amendment revised the qualitative study materials in order to shorten and simplify the primary care provider qualitative interviews by removing the chart-review portion of the provider interview. Instead, the chart review portion of the interview was conducted with the nurse care managers during their qualitative interviews late in the study. These modifications were made in order to increase the feasibility of being able to conduct the chart review portions of the qualitative study.

9. 21 June 2013: This amendment revised the recruitment pamphlet with formatting changes to make it more visually appealing and added information about the Amazon.com gift card incentives provided for study participation.

10. 09 September 2013: This amendment updated consent form storage procedures for the study. Upon completion of the study, the electronic consent forms will be moved to a secure archived drive maintained by RTI International for the required six year retention period, at which time electronic consent forms will be destroyed. This amendment also updated personnel listed in the protocol.

11. 08 November 2013: This amendment changed the study Initiating Principal Investigator from Charles C. Engel, MD, MPH to Michael C. Freed, PhD and added Dr. Engel as a Collaborator. Due to Dr. Engel’s retirement from the military, he was advised to transition from Principal Investigator to Collaborator. Dr. Freed, who served as Study Director and Associate Investigator, was transitioned to Principal Investigator.
12. 24 January 2014: This amendment revised protocol language describing the data safeguarding plan developed for analyzing the study datasets maintained by RTI International.

13. 17 October 2014: This amendment revised language in the protocol and Data Safeguarding Plan to further describe the datasets that research staff may be able to access for data analysis, including removal of language about the Safe Harbor method for de-identification, as dates of medical encounters may be included in administrative medical service use datasets.

As the corresponding author for this submission, I offer the protocol and this summary of amendments as true and complete. Please contact me for any further questions.

Sincerely yours,

Charles C. Engel, MD, MPH
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