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# Design and challenges for a randomized, multi-site clinical trial comparing the use of service dogs and emotional support dogs in Veterans with post-traumatic stress disorder (PTSD)

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ABSTRACT

Posttraumatic stress disorder (PTSD) is a leading cause of impairments in quality of life and functioning among Veterans. Service dogs have been promoted as an effective adjunctive intervention for PTSD, however published research is limited and design and implementation flaws in published studies limit validated conclusions. This paper describes the rationale for the study design, a detailed methodological description, and implementation challenges of a multisite randomized clinical trial examining the impact of service dogs on the on the functioning and quality of life of Veterans with PTSD. Trial design considerations prioritized participant and intervention (dog) safety, selection of an intervention comparison group that would optimize enrollment in all treatment arms, pragmatic methods to ensure healthy well-trained dogs, and the selection of outcomes for achieving scientific and clinical validity in a Veteran PTSD population. Since there is no blueprint for conducting a randomized clinical trial examining the impact of dogs on PTSD of this size and scope, it is our primary intent that the successful completion of this trial will set a benchmark for future trial design and scientific rigor, as well as guiding researchers aiming to better understand the role that dogs can have in the management of Veterans experiencing mental health conditions such as PTSD.

## 1. Introduction

According to the National Health and Resilience in Veterans Study, the weighted lifetime prevalence of probable posttraumatic stress disorder (PTSD) among U.S. Veterans is about 8.0% [1], while estimates of lifetime prevalence of PTSD in era-specific cohorts of Veterans range

*Abbreviations:* ADA, Americans with Disabilities Act; ADI, Assistance Dogs International; AE, adverse event; AKC, American Kennel Club; CGC test, Canine Good Citizen test; CAPS, Clinician Administered PTSD Scale; CSSRS, Columbia Suicide Severity Rating Scale; DAR, Dimensions of Anger Reactions; DSM-V, Diagnostic and Statistical Manual of Mental Disorders version 5; HERC, Health Economics Research Center; HRQoL, health-related quality of life; IACUC, Institutional Animal Care and Use Committee; IRB, Institutional Review Board; ITTRS, Interactive Touch Tone Randomization System; MCS, mental component score; MINI, Mini International Neuropsychiatric Interview; PCL-5, 5-item PTSD Checklist; PCS, physical component score; PHQ-9, 9 item Patient Health Questionnaire; PSQI, Pittsburgh Sleep Quality Index; PTSD, posttraumatic stress disorder; QoL, quality of life; RCT, Randomized controlled trial; SAE, serious adverse events; VA, U.S. Department of Veterans Affairs; VR-12, Veterans Rand 12 Item Health Survey; WHO-DAS II, World Health Organization Disability Assessment Scale II; WPAI:GHP, Work Productivity and Activity Impairment Questionnaire: General Health Problem V2

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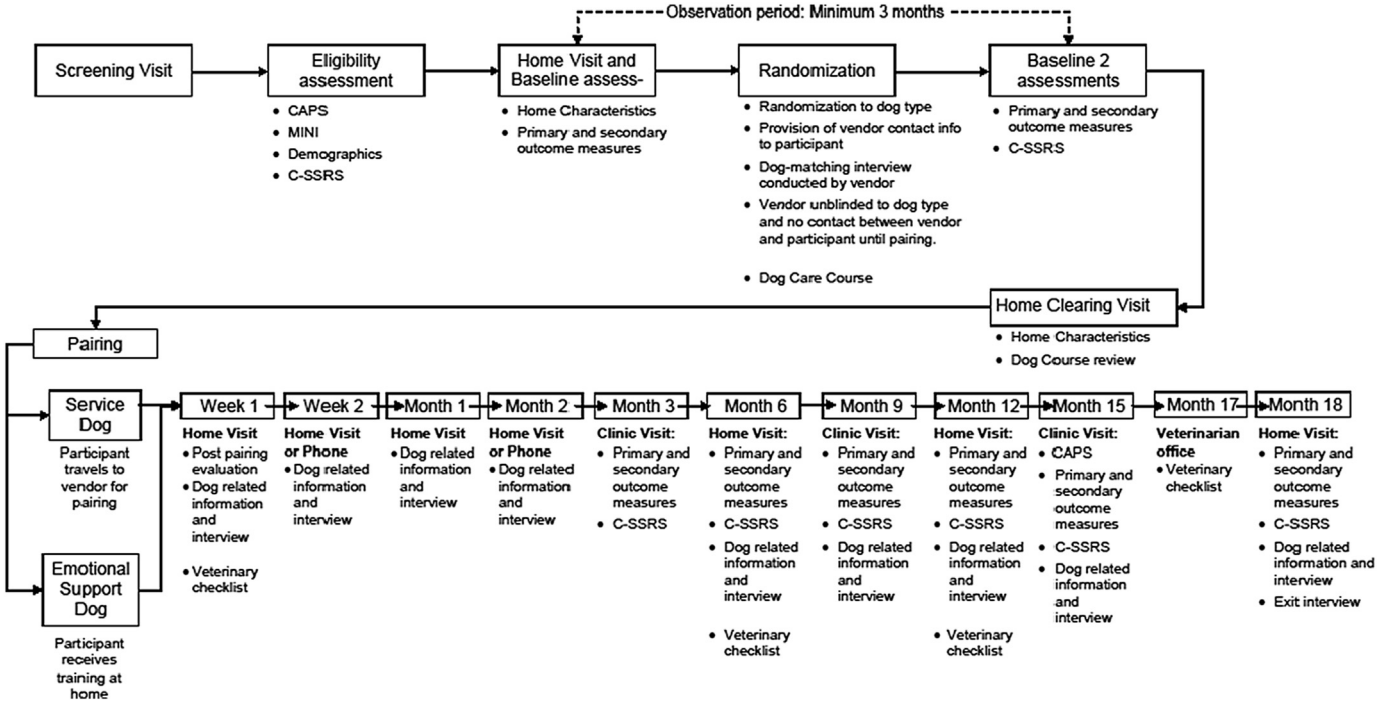


**Fig. 1.** Study flow and test measures.

from 18.7% to 37.3% [2–4]. Symptoms of PTSD include persistent intrusion symptoms, avoidance of stimuli associated with the traumatic event, negative mood or cognitive changes associated with the trauma, and increased arousal causing impairment or distress [5]. Additionally, individuals with PTSD typically have comorbid mental health conditions such as personality, mood, anxiety, and nicotine, drug, and alcohol use disorders [6]. The resultant impacts are disability, decreased mental health functioning, poor quality of life, and an inability to reintegrate fully into society [2,7,8].

Evidence-based treatments for PTSD include eye movement desensitization and reprocessing, exposure, cognitive, cognitive restructuring, cognitive processing, trauma-focused cognitive behavioral, stress management therapies, and pharmaceutical interventions [9,10]. It has been proposed that service dogs can provide adjunctive treatment to manage PTSD, however, there is limited published research on its effectiveness, and much of it is anecdotal. It has been reported that dogs help individuals with panic disorders [11], and can help individuals with PTSD overcome flashbacks, nightmares, and anxiety, and enhance medication adherence [12–14].

Conducting well-controlled studies that use animals is complex because of the many sources of animal-human interaction bias and the difficulty of controlling training and animal behavior across study participants. While there are studies that show the positive consequences of pet ownership on global psychological and social well-being [15–17], the benefits of animal-assisted therapy for specific conditions are not well established because published studies are of relatively low quality and have many flaws [18–20]. These flaws include the lack of, or inability to, incorporate several critical elements to enable valid conclusions including: non-treatment groups, controls for novel experiences with animals, written documentation of treatment procedures, blind observations, long-term follow-up, as well as underpowered studies, reliance on self-report, placing a 'positive spin' on negative results, and selective reporting of data. Stern and Chur-Hansen [20] and Kamioka et al. [19] made recommendations for designing future studies. They suggest researchers should carefully consider how they select study animals, and should design studies with multiple data collection sites and time points. When publishing the results, authors should provide detailed descriptions of the methodology and the intervention, record reasons participants withdrew, describe all adverse events, and specify the cost of the intervention.

The purpose of this paper is to describe the design and methodological considerations in an ongoing VA-randomized controlled trial (RCT) aimed at determining the impact of provision of service dogs on the functioning and quality of life of Veterans with PTSD.

## 2. Methods

### 2.1. Aims

The primary aim of this RCT is to determine whether overall functioning and quality of life of Veterans with PTSD are improved by the provision of service dogs relative to provision of emotional support dogs. It was hypothesized that given the special training of service dogs to handle tasks that may benefit Veterans with PTSD, they would provide greater improvements than emotional support dogs. Secondary aims are to compare the impact of service and emotional support dogs on mental health outcomes, health care utilization and costs, and employment and productivity.

### 2.2. Design overview

The study aims are being achieved through the conduct of a longitudinal, randomized, intent-to-treat, two-arm, parallel design, multicenter clinical trial. Veteran participants diagnosed with PTSD, are being recruited from three VA sites: Atlanta VA Medical Center, Iowa City Veterans Affairs Health Care System and VA Portland Health Care System. Following enrollment and screening, participants are randomly assigned to receive either a service dog or an emotional support dog. There is then an observation period lasting a minimum of 3 months, during which both the study team and the participants are blinded to the type of dog to which the participant has been randomized. On completion of the observation period, participants are paired with a dog and followed over an 18-month period, during which they are assessed at multiple time points via a combination of clinic and home visits. Fig. 1 shows the study timeline and assessment schedule.

### 2.3. Design considerations

The use of dogs as an intervention raises some design considerations atypical of a RCT. These include the need for safety oversight of both participants and dogs, recognizing the fact that the human-dog interaction results in changes to both over the course of the study, and finally, how this and other factors influenced the choice of control intervention.

#### 2.3.1. Human and animal safety

Participant safety was optimized by vetting of the dog suppliers (referred to henceforth as 'vendors') to ensure they provide well-trained healthy and physically sound dogs, not permitting vendors to use rescue dogs, and proofing all dogs to ensure each meets stringent standards (see Section 2.8.3). Dog safety was optimized by having strict participant inclusion/exclusion criteria, such as exclusion of individuals with a history of violence or animal cruelty or who do not have a stable home environment, inspecting each participant's home on a regular basis to ensure it is safe for a dog, providing veterinary insurance and mandating four veterinarian visits during the intervention period, and thoroughly training participants in dog handling and care. Further, for the combined safety of the participant and dog, the human-dog bonding process was monitored throughout the study and a member of the study team was available for enquiries and emergency home-visits as needed. These issues are all discussed in greater detail below.

#### 2.3.2. Implications of an interactive relationship between participant and intervention

Unlike a pill or prosthesis, the "intervention" can also be affected by interactions with the participant. Consequently, changes to both that go beyond physiological or biomechanical mechanisms – that are not typically considered in other studies – had to be considered in this study. An example of this is the necessity to ensure that participants bond well with their dogs, and that the dog-human bond remains intact throughout the study. Further, participants must take responsibility for ensuring their dog maintains its trained behaviors, since a change in dog behavior could impact the potential effectiveness of the intervention. To this end, several processes are in place: (1) vendors conduct an in depth interview with each participant in order to match dog-participant temperament and life style (see Section 2.9.2), (2) local dog trainers closely monitor the dog-participant bond throughout the study, (3) the possibility of providing a replacement dog if the participant-dog bond is not adequate is included in the protocol, and (4) dog trainers are available to retrain the dogs and participants on handling their dogs as needed.

#### 2.3.3. Selection of a control intervention

As described further in Section 2.8 below, a service dog is a dog that is individually trained to do work or perform tasks for people with disabilities, whereas an emotional support dog is the term for a pet that provides therapeutic benefit to its owner with a disability through companionship and affection [21]. While a standard-of-care control group may be scientifically justified, the control intervention selected was provision of an emotional support dog. This was chosen because the study aims to determine whether provision of a service dog, and the specific tasks it can perform, is beneficial to Veterans with PTSD. This is a significant challenge because it is not known whether and to what degree, the benefits of a service dog arise from factors other than performing the tasks it is trained to provide; the dynamics of a living animal need to be considered. Therefore, one necessary control involves the impacts of pet ownership, which as noted above, have been shown to enhance psychological and social well-being ([17,15]). A secondary reason for use of an emotional support dog control intervention relates to potential study participants wanting to be paired with a dog. During a pilot study, it was learned that very few potential participants were willing to enroll in the study when they knew there was a possibility that they would not receive a dog for participating (see Appendix A for more details).

### 2.4. Study oversight

Another unique aspect of this clinical trial is the oversight required. The study received approval from the VA Central Institutional Review Board (IRB, protocol #13-54) for the human subjects' protections elements, as well as from the Institutional Animal Care and Use Committees at Atlanta (protocol #V001-14) and Iowa City (protocol #1490201) for the animal welfare oversight. The VA Portland Health Care System local IACUC determined that their input was not necessary. A Data Monitoring Committee provides ongoing monitoring. The study is registered on ClinicalTrials.gov (ID: NCT02039843).

### 2.5. Study personnel

Due to the complexity of the study, multiple teams of individuals are involved. There is a central leadership team (Study Chair, Coordinating Center team, Executive Committee, VA Chief Veterinary Medical Officer) which oversees the study and is responsible for making protocol-related and dog-related decisions and for managing and analyzing data. There is a local study team at each participating medical center comprised of a study investigator, and at least one study coordinator, research assistant, and dog trainers. Together, this team is responsible for local data collection. VA veterinarians are responsible for oversight of dog-related matters (dog medical record and training standards, dog purchase contracts, dog delivery schedules, and interactions with dog vendors). Finally, a senior dog trainer is responsible for proofing all dogs against contract standards before VA acceptance, and ensuring that the local dog trainers provide consistent support with dog obedience or training problems to participants in the study.

### 2.6. Participants

Participants are Veterans diagnosed with PTSD who are enrolled in the mental health clinic at one of the participating VA medical centers and who have received a referral to the study by their mental health provider. This criterion was included because the aim is to evaluate the effect of the interventions as adjuncts to – not replacements for – standard VA mental health care for PTSD. Other inclusion and exclusion criteria are described in Table 1).

These criteria were selected to maximize participant and dog safety, and to increase the likelihood that a participant would complete the study. Specifically, exclusion criteria 1, 3, 4 and 8 are included to increase the likelihood that participants can care for a dog over the study duration; exclusion criteria 2, 5 and 6 are included to maximize dog safety; exclusion criterion 9 is included to maximize participant/family safety, and criteria 7 and 10 are included to maintain integrity of the research design.

### 2.7. Power analysis and sample size

The study will compare changes in functioning and quality of life over the 18-month intervention period, relative to baseline, for participants randomized to two treatment groups: those receiving an emotional support dog and those receiving a service dog. Table 2 shows group differences, variability estimates, and corresponding sample sizes required to obtain a power of 85% assuming a statistical significance level of 0.05 (two-tailed test) for the outcome variables of interest (World Health Organization Disability Assessment Scale II [WHO-DAS II] and Veterans Rand 12 Item Health Survey [VR-12] Physical Component Score [PCS] and Mental Component Score [MCS]). Assuming the largest of the three sample sizes, 82 participants per group, and a maximum of 25% participant loss or dropout rate, a sample size of 110 participants per treatment is required for this study.

**Table 1**
Inclusion and exclusion criteria.

| *Inclusion criterion* |
|---|
| 1. Age 18 or older |
| 2. PTSD defined by Clinician Administered PTSD Scale for DSM-V (CAPS, [22]) |
| 3. Is enrolled in VA mental health services and agrees to remain in mental health treatment throughout the duration of the study and has attended at least one mental health visit in the 90 days prior to consent |
| 4. Can adequately care for a dog |
| 5. Home environment is accessible to study staff and is suitable for a dog |
| 6. Others in the home are agreeable to having a dog in the home |
| 7. Has someone to care for the dog in a long-term absence and is willing to provide contact information of that individual |
| 8. Is willing to accept the randomization outcome |
| 9. Is willing to travel to training site for pairing |
| 10. Is able and willing to provide informed consent to participate |
| *Exclusion criterion* |
| 1. Has been hospitalized for mental health reasons in the past 6 months |
| 2. Has shown aggressive behavior that would make it unsafe for a dog |
| 3. Has been diagnosed with a psychosis, delusions, or dementia as determined by responses to the Mini International Neuropsychiatric Interview version 7.0.0 (MINI) |
| 4. Has signs of active suicidal intent as determined by endorsement of 'active suicidal ideation with specific plan and intent' on the Columbia Suicide Severity Rating Scale (C-SSRS; [23]) or a suicide flag in the VA medical record |
| 5. Has shown past or current homicidal intent or cognitive disability |
| 6. Has a VA medical record chart note for violent/disruptive behavior |
| 7. Owns a cat, dog or other household pet that would threaten bonding with the study dog |
| 8. Has a current diagnosis of moderate or severe substance (alcohol) use disorder using DSM-V criteria (score > 4) |
| 9. Is pregnant, has a partner that is pregnant, or has children younger than 5 year in the household for > 8 h/day, one or more days/week |
| 10. Is participating in other research that would interfere with study participation |

**Table 2**
Information for sample size calculations.

| Outcome measure | Between-group difference | Variability estimate (SD) | Sample size (per group) |
|---|---|---|---|
| WHO-DAS II[a] | 10 points | 13.0 | 32 |
| VR-12 PCS[b] | 15% from 39.8 | 10.8 | 60 |
| VR-12 MCS[c] | 15% from 33.2 | 10.6 | 82 |

[a] World Health Organization Disability Assessment Scale II.
[b] Veterans Rand 12 Item Health Survey Physical Component Score.
[c] Veterans Rand 12 Item Health Survey Mental Component Score.

### 2.8. Interventions

There are two intervention groups, as described below.

#### 2.8.1. Provision of a PTSD service dog

A service dog is a dog that is individually trained to do work or perform tasks for people with disabilities. Examples of such work or tasks include guiding people who are blind, alerting people who are deaf, pulling a wheelchair, reminding a person with mental illness to take prescribed medications, and calming a person with PTSD during an anxiety attack [21]. Service animals are working animals, not pets. The work or task a dog has been trained to provide must be directly related to the person's disability [21]. Under the Americans with Disabilities Act, service dogs are entitled to enter public buildings and cannot be asked to leave unless the animal is misbehaving [21]. Further, a handler can be asked what tasks the dog performs but not about his/her disability. For this study, the Service Dogs are required to pass the Assistance Dogs International (ADI) Public Access Test [24] and are taught to perform five tasks specific to PTSD that were selected by a team of mental health professionals with expertise in PTSD:

1. Locate and turn on a light in a dark room – task command is "Lights"
2. Enter a room and sweep perimeter – task command is "Sweep"
3. Retrieve an object at the handler's (here the participant's) request – task command is "Bring"
4. Stand in front of the handler to provide a physical barrier between the participant and the person approaching – task command is "block"
5. Stand behind the handler to provide a physical barrier between the participant and a person approaching from behind – task command is "Behind"

#### 2.8.2. Provision of an emotional support dog

An emotional support dog is the term for a pet that provides therapeutic benefit to its owner with a disability through companionship and affection [21]. Emotional support dogs must be well-behaved at all times, and well-socialized to people and other animals, however, they are not taught specific tasks that address a particular disability.

#### 2.8.3. Dog proofing, and skills and behaviors common to service dogs and emotional support dogs

In order to ensure all dogs in this study are exceptionally well-behaved and well-trained, they must all pass the American Kennel Club (AKC) Canine Good Citizen (CGC) test, which requires the dog to demonstrate that it has been trained to and indeed does, respond to the handler's commands, allows a stranger to approach and speak to the handler, allows a stranger to touch or pet it while in an everyday situation with its handler, remains calm when being groomed by a veterinarian/groomer, moves politely through pedestrian traffic and is under control in public places, is well-behaved around other dogs, and can be left with a trusted person. In addition, as noted above, all service dogs must pass the Assistance Dogs International (ADI) Public Access Test and emotional support dogs must pass the AKC Community Canine Test (an advanced version of the AKC CGC). The vendor is responsible for training the dogs. Every dog is then proofed (tested against contract standards) by the Senior VA Dog Trainer prior to being provided to a participant. Proofing requires that each service dog successfully completes the ADI Public Access Test and the five tasks specific to PTSD outlined above, while every emotional support dog must successfully complete the AKC CGC. Only dogs meeting these standards are considered for placement with a participant. A dog that shows any signs of aggressive behavior such as growling, snapping, biting, attacking, or attempting to attack is never placed with a participant.

### 2.9. Outcome measures

There are two primary and six secondary outcome measures. The selection of the outcome measures underwent much deliberation because of the absence of evidence regarding the mechanism(s) by which service animals might improve PTSD. While it was believed that PSTD symptoms could improve with a service dog, the ability to interpret results in a way that would be biologically plausible would be difficult [25]. Furthermore, the (in)ability to specify the effect size for symptom changes would have made power calculations difficult. Therefore, the research team decided that outcomes should be assessed in terms of impacts on overall mental, social and psychosocial function, as well as on health care utilization and costs, and employment and productivity. That is, primary consideration was given to the importance of reintegrating Veterans with PTSD into society and effectiveness of a service animal at facilitating this.

#### 2.9.1. Primary outcome measures

- *World Health Organization Disability Assessment Scale II* (*WHO-DAS II*; [26]). The WHODAS II is a 36-item questionnaire that assesses functioning in six activity domains during the prior 30 days: 1) Understanding and communicating; 2) Getting around; 3) Self-care; 4) Interpersonal interactions; 5) Life activities, including household

and school/work, and 6) Participation in society. For each item the participant rates the difficulty they have conducting a task. They respond on a 5-item scale: 'None,' 'Mild,' 'Moderate,' 'Severe' or 'Extreme/cannot do.' Domain scores and a total disability score are obtained. Scores can range from 0 to 100 where 0 = no disability; 100 = full disability, thus lower scores indicate better functioning.

- *Veterans Rand 12 Item Health Survey* (*VR-12*; [27]). The VR-12 is a 12-item self-administered health survey that assesses health-related quality of life (HRQoL). The VR-12 is a modification of the VR-36. It yields two subscores: a Physical Component Score (PCS) and a Mental Component Score (MCS). The PCS score reflects general health, physical functioning and role playing and bodily pain. The MCS reflects emotional, vitality/mental health and social functioning. Scores on each scale are standardized using t-scores normed to data from 877,775 Veteran respondents in the 1999 Large Health Survey of Veteran Enrollees (Veterans Health Study; [28]). Standardized to a mean of 50 and standard deviation of 10, scales typically range from 0 to 100, with higher scores reflecting better quality of life.

#### 2.9.2. Secondary outcome measures

- *PTSD checklist* (*PCL-5*, [29]). The PCL-5 is a 20-item self-report measure that assesses the 20 DSM-V symptoms of PTSD. For each item, participants select a response to indicate the extent to which they have been bothered by a particular problem in the past month. Responses are given in a 5-item scale – 'Not at all,' 'A little bit,' 'Moderately,' Quite a bit,' or 'Extremely.' Scores range from 0 to 80 with higher scores indicating more problems.
- *Pittsburgh Sleep Quality Index* (*PSQI*; [30]). The PSQI is a 19-item survey used to assess sleep-related problems during the prior 30-day period in seven components: 1) Subjective sleep quality; 2) Sleep latency (i.e., how long it takes to fall asleep); 3) Sleep duration; 4) Habitual sleep efficiency (i.e., the percentage of time in bed that one is asleep); 5) Sleep disturbances; 6) Use of sleeping medication; and 7) Daytime dysfunction from which a global score is computed. Individual items are scored on a weighted 3-point scale and then summed across components yielding a score range of 0 to 21, with higher scores indicating poorer sleep quality.
- *Patient Health Questionnaire* (*PHQ-9*; [31]). The PHQ-9 is a 9-item instrument for assessing severity of depression. Items address mood, anxiety, eating habits, and somatoform symptoms. Participants answer how often in the prior 2 weeks they have been bothered by a specified problem on a 4-item scale: 'Not at all,' 'Several days,' 'More than half of the days,' or 'Nearly every day.' Scores range from 0 to 27, with higher scores indicating more severe depression.
- *Dimensions of Anger Reactions* (*DAR*; [32]). The DAR is a seven-item scale that assesses anger disposition directed to others. Participants are asked to indicate the degree to which each statement describes their feelings and behavior on an 8-point scale ranging from 0 (not at all) to 8 (exactly so). Scores are totaled yielding a range of 0–56, with higher scores indicating greater anger disposition.
- *Non-VA healthcare utilization: non-VA inpatient care and non-VA outpatient care* (*Health Economics Research Center [HERC] non-VA utilization survey*; [33]). The HERC non-VA utilization survey is used to assess non-VA healthcare utilization. It documents outpatient, inpatient and Emergency Department visits to non-VA providers. Participants are asked to specify their use of healthcare services over the prior 3 months so that use of non-VA healthcare can be documented.
- *Work Productivity and Activity Impairment Questionnaire: General Health Problem V2.0* (*WPAI:GHP*, [34]). The WPIA:GHP is a 6-item survey that assesses employment and productivity. It documents work missed due to health and other problems, as well as the effect of the health problems on productivity while at work. Participants provide information about the number of hours worked and missed due to health problems, as well as the extent to which health problems impacted their ability to work and to conduct other daily activities. WPAI outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity.
- *Medication log.* A log of all non-VA medications and sleep aids used by participants is maintained throughout the study.

### 2.10. Randomization and blinding

#### 2.10.1. Participant randomization and blinding

Randomization is conducted centrally by the study coordinating center using an Interactive Touch Tone Randomization System (ITTRS). Random assignments to the intervention groups were generated by SAS 9.3 using a random block scheme stratified by site. Once eligibility for a Veteran has been confirmed, a member of the study team calls the ITTRS which then generates the randomization assignment. The local study team and the participant remain blinded to the group assignment during the study observation period. Only the coordinating site and members of the contract management team are informed of the assigned intervention. This is necessary so that a dog vendor can be assigned and training of a dog can begin.

#### 2.10.2. Assignment of dog vendor and blinding

Three vendors are providing dogs for the study. Each vendor provides both service dogs and emotional support dogs. Following randomization, a vendor is assigned based on dog availability. The vendor then conducts a dog-matching interview with the participant. The vendor is blinded to dog type until the dog-matching interview is completed.

### 2.11. Procedures

#### 2.11.1. Recruitment

Participants are being recruited using three primary strategies: 1) IRB-approved presentations about the study given to mental health providers at each VA site during which the study is described and providers are encouraged to refer potentially eligible Veterans; 2) Emails with IRB-approved study recruitment fliers sent to mental health providers at each VA site asking them to encourage potentially eligible Veterans to inquire about the study; and 3) IRB-approved flyers and brochures distributed directly to potential participants following mental health visits and placed in mental health clinic waiting areas and at meeting locations of Veteran-centric interest groups and organizations. The study fliers provide contact information for the local study team.

#### 2.11.2. Screening

Screening takes place in four stages. First, potential participants undergo a telephone screening using an IRB-approved script. They are asked about their PTSD symptoms, whether they are enrolled in VA mental health services, whether they own dogs, cats or other household pets, whether they have children < 5 years in their home and about their current living arrangement. Second, a member of the study team examines the potential participant's electronic medical record chart notes to review applicable eligibility requirements (see Table 1 above). Individuals who meet the inclusion/exclusion criteria at this point and who remain interested in the study are asked to obtain a referral letter from their VA mental health provider to be shared with the study team at or prior to a scheduled in-person screening visit. Third, potential participants attend an in-person screening visit at the local VA test site. At the start of the screening visit, participants provide written informed consent and sign a HIPAA authorization form. Participants are also sent a hard copy of the informed consent form by mail in advance of the visit so they can come to the visit prepared with questions. Following informed consent, the referral letter from the individual's mental health

provider is collected, a short demographic interview is administered, and the CAPS (to confirm the presence of PTSD) is completed. If the CAPS criteria are met, measures to assess exclusionary symptoms are completed. These are the MINI to assess active psychosis, delusions, or dementia, and the C-SSRS to assess active suicidal ideation. If the participant meets all eligibility requirements, a home visit (stage 4 of the screening process) is scheduled. During this home visit, the potential participant's home is assessed to determine whether it is accessible and safe for both the study team and a dog. Factors examined include accessibility to outdoor space, fencing around a yard (if one is present), evidence that all doors from the home to the outside close securely, and assurance that all household chemicals and materials that are potentially harmful if ingested can be kept way from the dog. If the home is accessible to the study team but does not meet all suitability criteria, potential participants are given up to 3 months to fix the issues, at which time a further home visit takes place.

#### 2.11.3. Baseline 1 testing

If all criteria above are met, then during the same visit, baseline outcomes assessments are completed in the following order: WHODAS II, PCL-5, PSQI, VR-12, PHQ-9, DAR, HERC non-VA utilization survey, WPAI:GHP, and medication log. All but the HERC non-VA utilization survey, WPAI:GHP and medication log are completed in pen and paper form by the participant. The HERC non-VA utilization survey, WPAI:GHP and medication log are completed in interview format with a qualified member of the study team. On completion of baseline testing, a member of the study team calls the ITTRS to randomize the participant to a dog type (service dog or emotional support dog); however, the participant, study team, and dog vendor remain blinded to the assignment until later in the protocol (see Section 2.11.5).

#### 2.11.4. Observation period

There is a three-month minimum observation period that begins immediately following baseline testing and ends once a dog becomes available. As noted above, during this period the Veteran and local study team are blinded to the intervention group to which the participant in randomized. At the start of the observation period, the participant is provided with contact information for the vendor from which they are to receive a dog so they can set up a dog-matching interview. Following the dog-matching interview the vendor (only) is unblinded to the type of dog the participant is to receive, so that selection and training of the dog can begin. Also during the observation period, the participant completes a dog care course. The course was specially designed for this study. It includes information about dog health issues and when to seek medical attention, general care and feeding of dogs, recognition and prevention of dog aggression, financial burden associated with having a dog both during and after the study, the differences between service dogs and emotional support dogs, and legal rights of service dogs and emotional support dogs.

#### 2.11.5. Baseline 2 testing and unblinding

Once the assigned dog has been proofed and is ready for the participant, a clinic visit takes place during which a second set of baseline assessments is completed using identical measures and procedures as previously described, and the participant completes a Dog Knowledge test to ensure he/she understands and recalls the content of the dog care course. Participants who score $< 80\%$ correct on the test receive additional education from the study team dog trainer. Following the completion of the clinic visit, a second home visit is conducted to reconfirm that the home is still suitable for a dog. If all criteria have been met, the participant and local study team are unblinded to the type of dog the participant will be receiving.

#### 2.11.6. Pairing

The dog-pairing process varies, dependent upon the type of dog. Participants who receive a service dog are provided transportation and accommodation to spend about 1 week at the vendor's facility, during which they receive training on handling a service dog. Participants who receive an emotional support dog receive at-home training over a single day from the local dog trainer on how to manage their emotional support dog.

#### 2.11.7. Follow-up

- One week after pairing the study team dog trainer conducts a home visit to check that the pairing has been successful. At this visit the study team dog trainer collects data regarding dog health and behavior and interviews the participant to determine whether he/she has any concerns and challenges that must be addressed.
- Two weeks after pairing the participant is contacted for a second time by the study team dog trainer. If there were no concerns at the one-week follow-up and there are no children under age 10 years living in the home, this contact is by telephone. If there were concerns at the one-week follow-up, or if the participant has a child/children under age 10 years living in the home, this contact is in-person at the participant's home. Once again, data regarding dog health and behavior, and participant concerns and challenges are collected.
- One month and two months after pairing the study team dog trainer conducts another home visit/contacts the participant using the same protocols as described for the one-week and two-week follow-ups, respectively. Once again, if there is a child/children under age 10 years living with the participant, then home visits will take place.
- At 3, 9, and 15 months after pairing, participants attend a study appointment at the local VA study site. During these visits, the primary and secondary outcome assessments are administered using the order and protocol described in Section 2.11.3. In addition, the C-SSRS is administered in interview format at each visit to monitor for suicidal intent, and the CAPS is completed at the 15-month visit.
- At 6, 12, and 18 months after pairing, a home visit is conducted by the local study team at which the primary and secondary outcome assessments are administered using the order and protocol described in Section 2.11.3. Data regarding dog health and behavior, and participant concerns and challenges are also collected. In addition, the C-SSRS is administered in interview format at each visit to monitor for suicidal intent, and, at the 18-month visit, an exit interview is conducted by trained interviewer during which the participant is asked whether he/she wants to keep the dog, the reasons why, the positive and negative aspects of having a dog, the ways in which the dog helped with symptoms of PTSD, the specific service dog tasks used and the frequency with which each was used, what other tasks participants would have liked the dog to be trained to do, the ways in which the dog has impacted HRQoL, ways in which the dog has influenced interpersonal relationships and whether the participant thinks others would say their dog has helped them. There are two versions of these interviews because questions are tailored to either service dogs or emotional support dogs.

#### 2.11.8. Veterinarian checks

In order to ensure that the dogs begin and remain healthy throughout the study, participants are required to take the dog to a veterinarian for a thorough health check at 1-week, 6-months, 12-months, and 17-months post-pairing.

#### 2.11.9. Payment

Participants are compensated $25 for each clinic visit and $10 for each home visit completed. In addition, after being paired with a dog, they receive a stipend of $75 per month for dog care (food, toys, bedding, etc.), a coupon for dog food, and an insurance policy to cover the costs of veterinary care for the dog for the duration of time they are enrolled in the study.

### 2.12. Data and safety monitoring and adverse event definitions and reporting

#### 2.12.1. Data and safety monitoring

A data safety monitoring committee that is comprised of individuals with expertise in statistics, veterinary medicine, and PTSD, monitors study progress. The committee is tasked with monitoring study progress, recruitment, trial safety, protocol adherence, and data quality. The committee decided that study safety data, rather than results of interim analyses, would be used to determine whether the study should be terminated at any point.

#### 2.12.2. Adverse event definitions and reporting

The study uses the International Conference on Harmonization definitions of adverse event (AE) and Serious Adverse Events (SAE) as follows. An AE is defined as "*any untoward medical occurrence in a clinical investigation subject that is subjected to one of the study treatments that does not necessarily have to have a causal relationship with the treatments*" while a SAE is defined as "*any event that results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, is a congenital anomaly/birth defect, or any other condition that, based upon medical judgment, may jeopardize the subject and require medical, surgical, behavioral, social or other intervention to prevent such an outcome*." The study involves both humans and dogs, thus AEs and SAEs can pertain to either.

Reporting of adverse events is conducted in accordance with the Office for Human Research Protections guidelines. AE reporting begins at the time of pairing and ends 30 days after the participant ends study participation. All SAEs are reported to the IRB. Further, SAEs involving dog deaths, dog bites, or participant deaths are reported to the study leadership team within 12 h of the site investigator becoming aware of the event.

If a dog were to die, was injured or became very sick during the study, the participant will receive support from the study team's mental health professional and his/her own mental health provider will be informed. If the participant wants a replacement dog, the study will provide one. It will be the same type of dog (service or emotional support) as previously, and data collection will continue.

## 3. Data analysis

Analyses of all outcome measures will use an intent-to-treat (ITT) population as well as a per protocol population (PP) which is defined as the population of participants who are paired with a dog using their initial randomization assignment. All statistical tests will be 2-sided and at 5% level of significance. SAS 9.2 or higher will be used to conduct all statistical analyses.

### 3.1. Primary analyses

There are two primary outcomes in this study: (1) improvement in overall functioning as assessed by the total WHODAS II score, and (2) improvement in quality of life as assessed by the PCS and MCS of the VR-12. Two hypotheses will be tested: (1) Compared to Veterans who receive an Emotional Support Dog, Veterans who receive Service Dogs will have improved ability to fully engage in important life domains over time as measured by the WHO-DAS 2.0 domain scores and the WHO-DAS 2.0 total score. (2) Compared to Veterans who receive an Emotional Support Dog, Veterans who receive Service Dogs will have improved quality of life, as measured by the global mental and physical health component scores of the VR-12.

In some instances, simple descriptive statistics will be the primary statistics of interest, describing change from baseline (screening home visit) to the 18-month follow-up visit. For the primary outcomes, a linear repeated measures mixed model will be used to determine changes over time between groups. Gender and site will be used as covariates in the models. Other variables will also be examined, including demographic factors such as age, education level and service history, to determine if any significant outcome differences exist. If they do, these potential confounders will also be included in the models as covariates.

### 3.2. Secondary analyses

Secondary continuous variable analyses will include linear repeated mixed model analysis on PTSD Symptom Severity using PCL-5, depression, and sleep. Variables found to be potential confounders will be included in the model as deemed appropriate based on clinical reasoning and statistical inference. Suicidality will be examined using logistic regression methods.

### 3.3. Missing data

Data are collected in-person though interviews and home visits resulting in minimal missing data. If encountered, a detailed sensitivity analysis can be conducted of the effects of various assumptions about the missing data and/or missing data will be imputed using standard multiple imputation techniques.

## 4. Discussion

This is a congressionally mandated study examining the impact on activity and quality of life of providing Veterans with PTSD either a service dog or emotional support dog [35]. The study has been designed to address many of the weaknesses noted by Stern and Chur-Hansen [20], Kamioka et al. [19], and Herzog [18] in prior studies in which the impacts of service and emotional support animals have been evaluated. Unlike in prior studies, the dogs selected for this study must meet contract-defined health, behavioral, and training standards. Service dogs must pass the ADI Public Access Test and emotional support dogs must pass the AKC Community Canine test administered by the VA Senior Dog Trainer prior to being provided to a participant. Further, the study is appropriately powered with 220 participants to be paired with a dog and it is taking place at three different VA test sites across the US (Atlanta, GA, Iowa City, IA, and Portland, OR). Also, the intervention period is long (18 months in duration), and outcomes data are being collected at multiple time points: twice prior to pairing, and then at months 3, 6, 9, 12, 15, and 18 during the intervention period. Finally, most of the outcome measures are self-report, there are 'objective' measures of economic impact regarding the impact of the dogs on healthcare utilization.

Studies that involve the interaction between humans and animals raise logistical hurdles that must be considered when designing and conducting future studies. Unlike a medication or prosthetic which can be manufactured in accordance with demand, there are limited supplies of high quality healthy well-trained service dogs and emotional support dogs. Likewise, dog training is a specialized skill and the availability of qualified dog trainers across the country is limited. Finally, the general public requires education regarding the regulations around public access for service dogs, and the differentiation of service dogs from emotional support dogs.

There are at least two methodological challenges in the study that were accepted given resource and practical considerations. The first is the difficulty in recruiting a study population who possessed equipoise in context of a "living intervention". While classic designs suggest comparisons that can help show efficacy or effectiveness, the use of a such a group were non-ideal based on data from a pilot study (see Appendix A) showing that individuals were reluctant to participate if they were randomized to the no intervention arm. Thus, to strike an optimal balance between the need to have a standard-of-care control group with the anticipated strong desire of all potential subjects to

receive the intervention, the study includes a 3-month minimum observation period prior to the intervention period. Outcomes measures are assessed at the start and end of the observation period, providing data about the stability of each individual's pre-intervention responses, and thus in effect each individual is his/her own control. The second limitation is the inability to conduct post-pairing blinding of participants and study staff. It is clearly not possible to blind a participant to the type of dog they have received, and while it would have been possible to design a study in which study data collectors were blinded to the type of dog a participant has, this would substantially have increased staffing costs and would have complicated the logistics of an already highly complex study. Furthermore, because most of the outcome measures are self-report, blinding of study data collectors is less critical. It would have been advantageous to have included a measure to quantify the human-dog bond so we could examine whether it will differ between intervention groups. In lieu of this we will rely upon data such as the number of individuals in each group who choose to keep their dog at the end of the study. While this is not a direct measure of the strength of the dog-human bond it will provide some insight into this issue.

In sum, to our knowledge, this will be the first well-controlled RCT specifically designed to examine the impact of service dogs on the functioning of Veterans with PTSD. It is expected to fill a major knowledge gap and may inform future medical benefits policy on the use of service dogs for Veterans with mental health diagnoses, specifically PTSD.

## Authors' note

Aspects of the design of this study were determined by Section 1077 of Fiscal Year 2010 National Defense Authorization Act that required VA to 'conduct a scientifically valid research study of the costs and benefits associated with the use of service dogs for the treatment or rehabilitation of veterans with physical or mental injuries or disabilities.' Elsewhere in the bill it was specified that 'or mental injuries or disabilities' include post-traumatic stress disorder. The bill required that matters studied should include assessment of the therapeutic and economic benefits of using service dogs, specifically, quality of life benefits, savings on health care costs regarding hospitalization and use of prescription drugs, and gains in productivity and employment.

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The authors declare no financial or other conflicts of interests.

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## Appendix A. Summary of problems encountered and lessons learned from a pilot study to examine the impact of providing service dogs on quality of life to Veterans with PTSD.

To respond to the Congressional mandate, VA initiated a pilot study in July of 2011. A number of health and training problems with service dogs resulted in suspension of recruitment in January 2012 and again in August of 2012. A thorough analysis of design flaws in the pilot study was conducted thereafter, which resulted in the protocol described in the main paper.

The pilot study initially consisted of two experimental groups (1) Veterans receiving standard of care for PTSD and (2) Veterans receiving standard of care and a service dog. Only one participant agreed to be enrolled in the standard of care only study group because potential participants did not want to enroll in the study unless they were going to get a dog, therefore recruitment to this group was suspended. Going forward all participants completed standardized instruments to assess mental, physical, and psychosocial health as well as healthcare utilization before and after receiving a service dog.

Three service dog organizations (vendors) were engaged contractually to provide dogs for the study. Unfortunately, the study experienced some significant adverse events, and recruiting was ultimately suspended in August of 2012 after sixty participants had been enrolled, of these just 25 had received a dog. The principal adverse events were (i) dog bites experienced by children of two study participants, (ii) multiple study dogs with hip dysplasia, (iii) the death of a study dog likely due to an undisclosed coagulation disorder, and (iv) the need to euthanize a dog with an incurable spinal tumor.

In Table A, column 1 describes the study design feature that likely explains why an adverse event occurred, column 2 describes the adverse event itself, and column 3 describes how each study design feature has been changed to minimize the likelihood of adverse events in the ongoing study.

Table A
Study design features, adverse events encountered, and the approach used to address each in the ongoing study.

| Study design feature | Adverse event | Ongoing study approach |
|---|---|---|
| Vendors selected the dogs trained as service dogs without study team member oversight. Some vendors used rescue dogs whose health history was unknown. | Approximately 25% of the dogs developed clinical signs of hip dysplasia within 15 months of pairing; health problems identified by veterinarians during dog screening were not shared with VA. One rescue dog developed an incurable tumor. | Detailed health screening requirements were added to the dog procurement contract, using DoD working dog standards as the basis; medical records must be provided to VA veterinarians for review and approval and subsequently proofed prior to a dog being included in the study. Only purpose-bred dogs are used. |
| Vendors screened dogs for aggression and decided when each was fully trained and ready to be paired with a participant without study team member oversight. | Children of two study participants were bitten by the study dogs, and it was discovered that many dogs were poorly trained. | Detailed training standards were added to the procurement contract. The American Kennel Club (AKC) Canine Good Citizen test is used as the standard for good behavior for all study dogs; in addition, the Assistance Dogs International (ADI) Public Access Test and AKC Canine Good Citizen Test are used to |

| | | |
|---|---|---|
| | | evaluate the performance of service dogs and emotional dogs, respectively. The VA Senior Dog Trainer proofs the dogs against contract standards prior to purchase. |
| Vendors conducted post-pairing training with participants without study team member oversight. | Vendor staff discouraged participants from reporting problems to VA, and they provided input to participants that a dog would be helpful, thus biasing study outcomes. | VA dog trainers (not vendor staff) interact with participants post-pairing to ensure problems are identified quickly and to prevent biasing of data. |

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