

Protocol # 13-51

Self-management to Improve Function Following Amputation

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Abstract

Lower extremity amputations in the Veterans Administration Health Care System are a significant cause of morbidity, mortality, loss of function, and reduced quality of life. Adaptation to limb loss is a long-term and complex process. Recent research suggests that patients benefit from ongoing partnerships with healthcare providers to help improve overall health and reduce disability. One important piece of this partnership is self-management, which is the process where a patient adopts an active role in managing the symptoms, treatment, physical and psychosocial consequences, and lifestyle changes that are inherent in living with a chronic condition, such as an amputation. The primary purpose of this study is to evaluate the effectiveness of a 5-week group-based self-management intervention for Veterans with lower extremity limb loss (VETPALS). VETPALS is an adaption of an empirically supported self-management program, PALS (Promoting Amputee Life Skills). The PALS program demonstrated improved physical and psychosocial functioning when delivered in community-based support groups for amputees, but this program has not been adapted for the needs of Veterans and implemented in the VA healthcare system.

This study is a two-arm randomized controlled trial (RCT) to determine the efficacy of VETPALS. Study staff will screen and enroll Veterans with recent lower extremity limb loss within the last 2 years. Each participant will complete a baseline interview and then is sequentially placed into a cohort of 6-10 participants; each cohort will be randomized to the VETPALS group based self-management program (intervention) or an individual education support program (control). Once participants complete the randomized arm and follow-up assessments, they are free to participate in the other group. This ensures participants are offered both programs and are not deprived of a potentially valuable healthcare service.

All participants will complete outcome interview assessments at baseline, 6 weeks (coinciding with the end of the VETPALS or individual program) and 6 months. The assessments evaluate the efficacy of the intervention by examining depression, physical function, self-efficacy, patient activation, problem solving, quality of life, and positive affect. This study is one of the only prospective randomized controlled trials of a behavioral intervention for individuals with limb loss. Up to 750 patients will be enrolled in the study across 5 VA sites. The VA Puget Sound Health Care System (Seattle, WA) will oversee this study at five VA sites: Seattle, Houston, Cleveland, Tampa, and Minneapolis. Target enrollment between the five VA sites is 472 participants. Additionally, these five VA sites will partner with other VA facilities to enroll additional participants in the study who can participate in the study via video telehealth and telephone interviews. At the end of the study, we expect that results of the study will be used to integrate a self-management intervention into the VA Amputation System of Care.

List of Abbreviations

AE	Adverse Event
AUDIT-C	Alcohol Use Disorders Identification Test
CHQOER	Center for Health Quality, Outcomes, and Economic Research
COWAT	Controlled Oral Word Association Test
CPG	Chronic Pain Grade questionnaire
CRF	Case Report Form
DCF	Data Clarification Form
DOD	Department of Defense
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FCI	Functional Comorbidity Index
JAHVH	James A. Haley Veterans' Hospital (Tampa, FL)
LSCVAMC	Louis Stokes Cleveland VA Medical Center (Cleveland, OH)
MEDVAMC	Michael E. DeBakey VA Medical Center (Houston, TX)
MFA-SF	Musculoskeletal Function Assessment Short Form
MSES	Modified Self-Efficacy Scale
MSPSS	Multidimensional Scale of Perceived Social Support
MVAHCS	Minneapolis VA Health Care System (Minneapolis, MN)
OHSU	Oregon Health & Science University
PALS	Promoting Amputee Life Skills
PAM	Patient Activation Measure
PANAS	Positive and Negative Affect Schedule
PANS	Polytrauma Amputation Network Sites
PAVE	Prevention of Amputations in Veterans Everywhere
PI/SC	Principal Investigator/Study Chair

PHQ-9	Patient Health Questionnaire Depression Module
PTCS	Psychosocial Treatment Compliance Scale
RAC	Regional Amputation Centers
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
RCT	Randomized Controlled Trial
SAE	Serious Adverse Event
SPMSQ	Short Portable Mental Status Questionnaire
SPSI-R	Social Problem-Solving Inventory-Revised
UAE	Unanticipated Adverse Event
UAP	Unanticipated Problem Involving Risks to Participants or Others
VAPSHCS	VA Puget Sound Health Care System (Seattle, WA)
VETPALS	Modified intervention of PALS for the Veteran population
VSSC	VHA Support Service Center
WAIS-III	Weschler Adult Intelligence Scale – Third Edition
WHOQOL-BREF	World Health Organization Quality of Life Scale

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Rehabilitation R&D Project #D1143-R

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2.0

3.0 Introduction

Scientific Background

Dysvascular lower extremity amputation is a significant health care concern. Lower extremity amputations are a significant cause of morbidity, mortality and loss of function. Every year, over 150,000 individuals undergo amputation related to dysvascular disease or diabetes.¹ Over the period of 1988 to 1996, rates of lower limb amputation in the United States complicated by these chronic illnesses increased over 27%,² and annual Medicare and Medicaid costs exceeded 4.3 billion dollars annually.¹ In 2005, it was estimated that there were over 806,000 individuals living with lower limb loss related to dysvascular disease or diabetes in the US, and because of the rising prevalence of diabetes, future increases between the years 2020 and 2050 are expected to be highest in this group.³

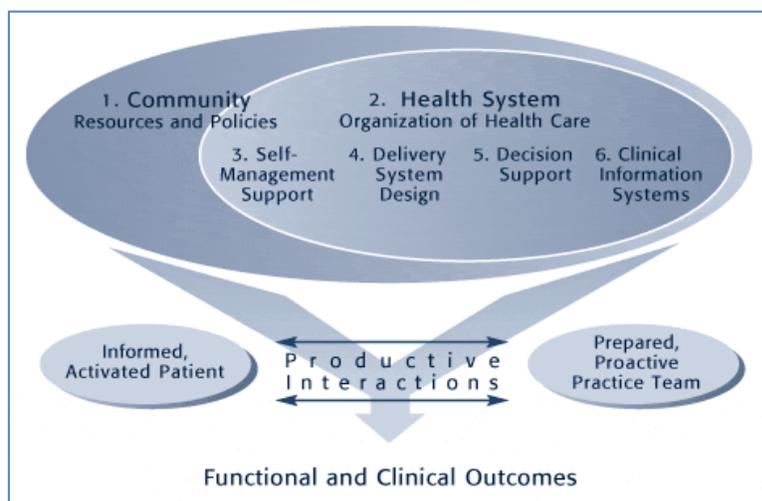


Figure 1

We need to improve the long term care of Veterans with an amputation. Models of chronic illness are well suited to amputation care. Over the last two decades, there has been increasing recognition that the challenges posed by chronic illness and disability differ substantially from those brought by acute illnesses, and that health

care delivery should be adapted and tailored to these specific longer-term needs. One prominent example is the Wagner Model of Chronic Illness Care.⁴ The Wagner Model proposes that for individuals with chronic illness, health care resources and practices should be re-aligned so as to focus less on discrete, acute intervention and more on sustainable, long-term management.⁵ The ultimate goal is an ongoing partnership between "informed active patients and a prepared proactive team" (Figure 1).^{4, 6-7} Thus, building patients' investment and involvement in their own care is an essential component of this process. The specific mechanism for doing this is the promotion and facilitation of self- management. This increased emphasis upon patient participation is also highly consistent with the Institute of Medicine's charge to the US health care system to become more patient and family centered.⁸

Self-management has been defined as a dynamic and continuous process⁹ that encompasses the tasks that individuals must undertake to live well with one or more chronic conditions.¹⁰ More specifically this entails the "ability to manage the symptoms, treatment, physical and psychosocial consequences, and lifestyle changes inherent in living with a chronic condition."⁹ This last statement includes the important notion that individuals with limb loss have opportunities to impact their health in three domains by 1) impacting their primary disease process (e.g., properly managing diabetes, hypertension), 2) managing secondary

complications and symptoms (e.g., skin care, pain management, depression), and 3) proactively engaging in activities that may or may not be directly related to limb loss, but bolster health, well-being and quality of life (e.g., stress management, social support).

Self-management interventions have been successful in improving outcomes across a broad variety of chronic illnesses including arthritis^{11, 12, 13, 14} asthma,^{15, 16} diabetes,^{17, 18, 19} and hypertension²⁰. They have been effectively utilized to treat depression in individual^{21, 22} and group-based formats²³, and have been implemented as a key component of collaborative care for comorbid depression and chronic illness²⁴. They have been shown to reduce health care utilization in the form of ER visits, hospital admissions, and bed days of care.^{15,25} Multiple studies have demonstrated that self-management programs are cost effective over the life of an illness, and bring noticeable improvements in quality adjusted life years.^{26,27,28}

Self-management interventions improve outcomes by promoting self-efficacy, patient activation and problem solving. Self-efficacy is "the belief in one's capabilities to organize and execute the courses of action required to manage prospective situations."²⁹ In a health care setting, this may include such things as monitoring blood sugar, learning transfer techniques, interacting with health providers, and reducing stress. This belief is based upon a history of behavior-specific learning, and can be both taught and improved.³⁰ Existing literature suggests that self-management programs result in improvements in self-efficacy that can be retained over many years.^{31,14} In turn, self-efficacy is associated with better health maintenance, as well as greater physical and psychosocial functioning. For example, among diabetics, greater self-efficacy is associated with more frequent blood glucose testing, less frequent skipping of medication and binge eating, and closer adherence to an ideal diet.³² Self-efficacy has also been associated with lower levels of depression as well as better global health status.²⁵

Significance of the Proposed Work

In 2008 VA Patient Care Services established a National Amputation System of Care to meet the needs of Veterans with limb loss. The stated mission of this program is to enhance the environment of care for persons with amputation receiving services in the VA by incorporating the latest practice in medical rehabilitation management, rehabilitation therapies, and prosthetic componentry.³³ With a series of regional centers, network sites, and clinic teams, the amputation system of care is charged with providing services that are comprehensive, holistic, and "coordinate lifelong rehabilitation... for service members and veterans as they progress from the acute care setting to their home environments."³⁴ One essential component of this service is the promotion of a partnership between patients and providers such that new amputees receive the knowledge and skills to become active participants in their own long-term health care.

The VA Amputation System of Care recognizes the value of self-management in long-term amputation care and intends to disseminate self-management interventions. Given the demonstrated value of self-management programs, the VA Amputation System of Care is in the process of actively establishing self-management groups at RACs (Regional Amputee Centers) and PANS (Polytrauma Amputation Network Sites) locations throughout the United States. Based upon the initial data reported by members of the current study team, the PALS program has been selected as the intervention for national VA dissemination. In fact, in 2011 staff

members at each RAC and PANS location were trained to deliver the original PALS intervention in anticipation of the implementation of this program. Nonetheless, very important questions remain as to how best to translate the intervention in terms of duration, content, and delivery (i.e., partially by video conferencing) to achieve maximum benefit in the VA. The proposed project is both well poised and well timed to provide meaningful information to inform the development of health care practice and policy for Veterans with amputation.

Limitations of current data and research

Initial evidence of the effectiveness of self-management following limb loss is promising, but limited. Only one published trial to date has examined self-management for amputees. The Promoting Amputee Life Skills (PALS) project,³⁵ conducted by members of the current study team, designed and implemented an 8-week group-based intervention to improve self-management following limb loss. The intervention was implemented within a network of existing support groups maintained nationally by the Amputee Coalition, a prominent non-profit consumer group. The PALS project demonstrated that group-based self-management could effectively improve physical and psychosocial functioning following limb loss, and was well received by participants. The current proposal builds upon previous research that has demonstrated the efficacy of the PALS self-management intervention, but addresses important next questions: 1) Is the PALS self-management intervention appropriate for Veterans, specifically considering the very high prevalence of diabetes and vascular disease, 2) Can it be housed and delivered within a health care system as opposed to existing community support groups 3) Will the intervention be more effective for individuals who are new amputees and 4) Will a shorter format that also incorporates an option for video conferencing retain the efficacy of the original PALS intervention?

Limitations of the initial PALS trial

Despite the important groundwork laid by the initial PALS trial, the applicability of this intervention to the VA Health Care System remains unknown. Several important questions remain unanswered:

1. The original PALS intervention made use of existing community-based support groups. PALS was implemented in a network of established support groups maintained by the Amputee Coalition, a national consumer organization. Groups were composed of individuals who had already expressed an interest in, and dedication to, support group attendance. Although this study design had obvious strengths in terms of its ability to capitalize upon existing programs, it also had challenges, as the casual settings and strong emphasis upon socialization sometimes undermined the ability to cover formal content. As a part of its ongoing quality improvement processes, the Amputee Coalition has recommended that PALS be implemented in a structured medical setting. The efficacy of PALS in such a setting has not been established. This is one of the primary goals of this current study.
2. The original PALS intervention made use of a heterogeneous patient population that is not typical of new amputees within the VA Healthcare System. Original PALS participants reported a range of etiologies of limb loss. Roughly one third (37.1%) reported their

amputation was due to dysvascular disease or diabetes, one third reported a traumatic amputation (39.3%) and the remaining third reported amputation due to cancer, limb deficiency, or other cause (23.6%). In contrast, nearly 98% of amputations within the VA are due to dysvascular disease or diabetes.³⁶ This observation suggests that the content and skills presented in PALS should be tailored more specifically to the needs of Veterans with limb loss due to medical comorbidities such as dysvascular disease and diabetes. This project aims to maintain much of the original content and structure of PALS, but alter class examples, support materials, and peer modeling for VETPALS to more heavily emphasize challenges experienced by Veterans with limb loss.

3. The original PALS intervention enlisted individuals who frequently had experienced limb loss several years prior. The median number of years since amputation was 4. Although PALS demonstrated that self-management could be introduced at any point in the life of an individual living with chronic illness, there is a strong rationale for providing education, skills, and support early in the process of adapting to amputation. To provide just one example, good early knowledge of, and investment in, self-management strategies to promote skin care could prevent complications leading to additional amputation. As previously mentioned, subgroup analyses of PALS outcomes indicated it was more effective for individuals less than 3 years following limb loss and, when asked, most participants in PALS reported it should be offered during the first 6 months after amputation as we propose in this project.
4. The original PALS intervention consisted of 8 consecutive weeks of group attendance and a follow-up visit. While this format encouraged the ongoing development of group cohesion, it also represented a barrier to participation. Notably, the project defined treatment completers as individuals who attended at least 75% of the scheduled sessions. Within the intervention condition receiving PALS, only 64.7% achieved this level of compliance. Based upon the experience from this previous trial, the proposed VETPALS intervention has altered the session structure so that the initial session in which skills are presented is longer, but the total number of sessions is reduced to 5. There is good evidence that chronic disease self-management skills can be effectively taught in 5 weeks.
5. The original PALS intervention required in person attendance, which also represented a barrier to participation. The VA has demonstrated an increasing investment in expanding the use of telehealth services to overcome obstacles related to distance and physical limitations, as well as costs associated with medical care. In fact, the VA Amputation System of Care is specifically mandated to implement and sustain tele-rehabilitation programs "to assure consistency of amputation rehabilitation across the VA."³⁷ The proposed VETPALS intervention allows Veterans to participate via video teleconferencing. To date there is no evidence of the effectiveness of amputation self-management that utilizes telehealth technology to facilitate participation.
6. The original PALS intervention was more effective for individuals endorsing difficulties with an outcome the intervention was designed to address. Individuals who reported depression or low self-efficacy at baseline were more likely to experience improvements in physical functioning, depression, and self-efficacy as a result of the intervention. Although this finding

is not surprising, and is not a specific limitation of PALS, it raises an important question for an intervention that is directed globally at Veterans with limb loss, namely "Do the identified outcomes of this intervention actually reflect important challenges faced by Veterans?"

Despite promising early evidence, the applicability of PALS to the VA remains unknown. Specifically, little is known about the efficacy of PALS 1) when implemented in medical settings, 2) for Veterans with dysvascular disease and diabetes, 3) who are new amputees, 4) using a shortened format incorporating video teleconferencing to improve participation. The proposed study, using the adapted intervention, VETPALS, addresses these issues and represents the next logical step in research on the application of this clinical program to the VA.

4.0 Objectives

Aim 1: Randomized Controlled Trial – Primary Outcomes

Determine the impact of a group-based self-management intervention for Veterans with limb loss (VETPALS) upon physical and psychosocial functioning

Hypothesis 1a: Individuals randomized to VETPALS will display greater improvements from baseline in physical functioning as measured by the Musculoskeletal Function Assessment Short Form (MFA-SF) than Veterans in the individual education support (control) condition post-intervention and at 6-month follow-up.

Hypothesis 1b: Individuals randomized to VETPALS will display greater improvements from baseline in psychosocial functioning as measured by the Patient Health Questionnaire Depression Module (PHQ-9) than Veterans in the individual education support condition post-intervention and at 6-month follow-up.

Aim 2: Randomized Controlled Trial – Secondary Outcomes

Determine the impact of a group-based self-management intervention (VETPALS) upon self-efficacy, patient activation, problem solving, quality of life, and positive affect.

Hypothesis 2a-e: Individuals randomized to VETPALS will display greater improvements from baseline in self-efficacy, patient activation, problem solving, quality of life and positive affect than Veterans in the individual education support condition post-intervention and at 6-month follow-up.

Hypothesis 2f: Changes in the intermediate outcomes of self-efficacy, patient activation, and problem solving, thought to be core components of effective self-management, will correlate strongly with changes in the primary outcomes of physical and psychosocial functioning.

Aim 3: Implementation Evaluation

We will evaluate the implementation of the VETPALS intervention into the VA health care system by examining 1) actual versus planned participation (recruitment, retention, treatment engagement, treatment fidelity), 2) barriers and facilitators to implementation, and 3) participant perceptions of the treatment.

Our evaluation is directly informed by, and reflective of, the RE-AIM framework³⁸, which proposes dimensions for consideration in the translation of research into real-world practice. RE-AIM incorporates the following: Reach (participation within intended population and characteristics of participants), Efficacy (the impact of an intervention when implemented as intended), Adoption (the percentage and representativeness of organizations that will adopt the intervention), Implementation (intervention integrity, quality, and consistency), and Maintenance (the degree to which intervention impacts are maintained at the individual and organizational level). Our particular implementation and strategies questions are tailored primarily to provide qualitative information about Reach (by gathering qualitative information about characteristics of participants and non-participants using focus groups) and Implementation (via fidelity monitoring as well as focused interviews to assess qualitative aspects of intervention integrity). Information about Efficacy and Maintenance (at an individual level) will be assessed in Aims 1 and 2. Our combined use of survey measures and qualitative, semi-structured interviews is a well-established methodology in the health services literature,³⁹⁻⁴⁰ and several of our questions were modeled after the semi-structured interview items provided in Curran et al. (2011).

To assess actual versus planned intervention participation in the VA context, which reflects the RE-AIM dimensions of Reach and Implementation, we will measure several aspects of participation (proportion of appropriate population who participates, characteristics of participants and non-participants, retention, treatment engagement/adherence, other therapy exposures) and implementation (treatment fidelity, leader perceptions of the intervention) on an ongoing basis and at the time of treatment completion. Study coordinators will maintain detailed logs of all potentially eligible participants, so that reach can be assessed. For participants, group leaders will maintain a weekly log documenting attendance and modality of participation (in-person vs. video teleconference), tardiness or early departures from each session, and whether or not homework assignments were completed in the previous week. Additionally, to assess overall treatment engagement and adherence, we will have both group leaders complete the Psychosocial Treatment Compliance Scale (PTCS)⁴¹ for each participant upon treatment completion. The combination of these two data sources (weekly logs and PTCS) will allow us to examine differences in participation by delivery modality (in-person vs. video teleconference), understand retention, and quantify treatment exposure.

For participants in both the control and intervention conditions we will also administer a brief survey at the end of the intervention that measures utilization of supplementary project resources, including the recommended websites and participation in concurrent therapeutic/clinical activities (e.g., therapies, locally available programs such as peer visits, utilization of Amputee Coalition resources). This brief survey will also assess several potential factors in engagement, including perceived credibility of the treatment and perceived self-reported engagement in the treatment.

Treatment fidelity will be computed on an ongoing basis. The overall fidelity of the therapists to the treatment will be computed as a percentage of essential treatment elements adhered to out of the total number of essential elements (using the checklists). Treatment fidelity will be

reported in the final manuscript submitted for publication. Inter-rater reliability for the fidelity checks will also be computed and reported.

To describe and understand barriers and facilitators to implementation in the VA context and to further assess Reach and Implementation dimensions, we will assess for any systematic differences in recruitment and retention due to age, gender, ethnicity, geographic distance from the medical center, amputation level, or marital status. Additionally, investigator-level study staff (Drs. Turner, Williams, Norvell) will conduct structured interviews with the site coordinators and each of the VETPALS facilitators in the program at the study conclusion to assess the time commitment required to lead each group, the administrative procedures used (i.e., clinic and procedure codes, scheduling strategies), and any local clinical or organizational factors that facilitated or hindered recruitment, scheduling, retention, or delivery of the intervention. To understand better any barriers and facilitators to implementation from the Veteran's perspective, we will conduct 2-4 focus groups in the final year of the study. Participants in the focus groups will be non-randomly selected to ensure good representation of participant demographics, health status, geographic distribution, and varying levels of intervention engagement and attendance. Focus groups will be facilitated by Investigator level staff using guided questions to ascertain treatment, psychological, organizational and logistical factors that may have affected participation.

To understand the causal events leading to change and the specific components of the intervention that most influenced it, we will solicit feedback from the intervention participants, control participants, and leaders via the focus groups described above. All participants, including those participating via telehealth, may be invited. We will conduct in-person focus groups which may include participants via telehealth. We will also ask all intervention participants to complete a questionnaire via pencil-and-paper to formally assess treatment satisfaction (the same satisfaction items used in the original PALS study).

5.0 Resources and Personnel

Roles and responsibilities

The **Principal Investigator/Study Chair** (Aaron P. Turner, PhD) and **Co-Principal** (Joseph M. Czerniecki, MD), will assume responsibility for all aspects of the conduct of this research study and supervise all Seattle-based personnel. They, along with the site PIs, will be responsible for training research staff, including the VETPALS facilitators, peer facilitators, and site study coordinators. They will also develop the study protocol, operations manual, monitoring plan and have oversight on study monitoring and study steering committee meetings.

Site Principal Investigators (Drs. Heckman, Henson, Kelly, Latief, and Hansen) are responsible for operations, data collection, and data integrity at their sites which involves oversight of the site study coordinators and regular meetings to discuss data and operations. They are also responsible for training the research staff at their site, including the VETPALS facilitator, peer facilitator, and site study coordinator. Site PIs, along with VETPALS facilitators,

will contact the data manager to obtain random assignment for participants. Site Principal Investigators may also assist with screening and enrollment as needed at their site.

Co-Investigators (Rhonda Williams, PhD and Dawn Ehde, PhD) will oversee VETPALS facilitator ratings on an ongoing basis to provide corrective feedback to facilitators in real-time along with the PI/SC. They will also lead weekly meetings with the study facilitators to provide ongoing supervision and discuss delivery of the treatment, including the prevention of facilitator drift in the manuals. The Co-Investigators will also assist with tasks as requested by the PI/SC, which include but are not limited to: finalizing the study protocol, overseeing progress at all sites, developing the operations manual and other study SOPs, monitor treatment fidelity by reviewing audio files, running steering committee meetings, and training VETPALS facilitators and peer facilitators.

Co-Investigator Stephen T. Wegener, PhD was a Co-PI for the original PALS program on which VETPALS is based. He will assist with tasks as requested by the PI/SC and Co-Investigators, which include but are not limited to: training VETPALS facilitators and peer facilitators, revising the treatment manual/participant workbook, interpretation of statistical analysis, and writing manuscripts for publication at the end of the study.

Co-Investigator and Consultant Dr. Daniel Norvell is responsible for all pre-study tasks and training of research staff. This includes oversight of all baseline and follow-up assessments, database development for data entry and analysis, and assistance in IRB submission. The VA Puget Sound will act as the lead study site and will host an investigators' meeting, which study site PIs, coordinators and VETPALS facilitators will attend to receive appropriate pre-study training. During this training session, the core investigators will ensure that all study materials (surveys, protocol, inclusion/exclusion criteria) are discussed, ensure that the study coordinator fully understands the study procedures and SOPs, and that all regulatory documents are approved and appropriately filed in regulatory binders. Initial training for VETPALS group facilitators will happen at this time and is described in more detail in the next section. He will also be a consultant on study operations. He will also monitor subject recruitment and follow-up rates at all sites and will monitor all adverse events.

Dr. Norvell will also oversee the database manager at Spectrum Research and all database operations, including but not limited to, data queries, data analysis, data export as requested by the PI/SC. He will have primary responsibility for ensuring the safety and secure storage of all electronic study data. Dr. Norvell and Spectrum Research will only have access to coded data.

Site study coordinators are primarily responsible for day to day study operations, which include recruiting participants and ensuring that all enrolled participants are adhering to the study protocol. These tasks include: ensuring all potential participants are identified through screening procedures, appropriately obtaining informed consent and HIPAA authorization, maintaining an updated screening and enrollment log, contacting participants regularly to schedule and remind them of study visits, and collecting baseline and follow-up data through the electronic data capture (EDC) system using an eCRF. The Seattle site study coordinator may also conduct study interviews by telephone for other sites in the event a site study coordinator is

unavailable. The site study coordinator will have regular contact with Dr. Norvell and the site PI. The site study coordinators remain blind to treatment group.

The study **project coordinator** is based at the Seattle site, and is primarily responsible for oversight of daily study operations at the five participating sites. The project coordinator also has regular contact with Dr. Norvell, the PI (Dr. Turner) and Co-PI (Dr. Czerniecki) to assist in study troubleshooting with the site PIs and study coordinators as needed. The study project coordinator, with oversight from the PI and Co-PI, is responsible for submitting IRB materials to the VA Central IRB, including but not limited to: initial applications, protocol modifications, site correspondence, protocol deviations, and SAE reports. The project coordinator, along with Dr. Norvell, also monitors the site study coordinators and communicates with investigators to ensure efficient day-to-day study operations. The project coordinator will organize monthly teleconferences with site PIs and study coordinators to discuss progress, operations, and answer group operational questions as they arise.

Additionally, VAPSHCS project staff will conduct periodic site monitoring and quality assurance of each site to ensure that informed consent, training requirements, and adverse event monitoring are being routinely performed in strict accordance with the research protocol, requirements of the Central IRB, and local VA R&D committees. During the first 6 months of enrollment at each site, the project coordinator and/or Drs. Turner and Norvell will conduct a virtual internal audit using the regulatory audit template from VAPSHCS. We will encourage each site to conduct an internal audit that adheres to their facility audit process to confirm both project wide and local facility compliance. We will also work to request a formal R&D audit during year 1, if possible, regardless of the local policy at each site.

VETPALS facilitators are allied health professionals who are responsible for implementing the VETPALS intervention group sessions. VETPALS facilitators will be trained by the core group of investigators to deliver a modified version of PALS which reflects changes in content, delivery modalities (e.g. telehealth, video teleconferencing), and participants (Veterans with dysvascular disease/diabetes). VETPALS facilitators will receive training during a two-day group-based training that includes didactics, supervised practice, discussion, and home study. Notably, all VETPALS facilitators have already received initial training the PALS protocol and have advanced Department of Defense (DOD) training and certification in amputation care. VETPALS facilitators are primarily responsible for contacting the data manager to randomize a group of participants, maintaining an accurate randomization log, and conducting the 5 intervention sessions per group of 8 ± 2 participants. The intervention sessions will take place in a private conference room with video teleconferencing capabilities at each VA site. All VETPALS facilitators will participate in ongoing group supervision as part of fidelity monitoring of the intervention, and additional focused instruction will be provided on an individual basis as needed when identified during a review of audio-recorded sessions. VETPALS facilitators may assist with screening and enrollment at their site.

VETPALS peer facilitators are Veterans with limb loss. One peer facilitator at each site will be identified and trained by the VETPALS facilitator. Substitute or alternate peer facilitators may also receive training as needed at each site. The peer facilitator will help co-lead the VETPALS

sessions (as in the original PALS program). The peer mentor will only have study-related contact with participants in the context of the class. The peer will not access the medical record, or engage in other research-related activities. Thus, the peer mentor will not have access to any information about the participant that is not shared directly by the participant during class.

The **biostatistician** (David Yanez, PhD) will conduct periodic queries of the database to look for any discrepancies or inaccuracies in the data (e.g. missing and nonsensical values) that may not have picked up during the electronic data entry process. The biostatistician will primarily be responsible for statistical analysis as outlined in the original grant application and study protocol. The biostatistician will only have access to coded data.

6.0 Study Procedures

5.1 Study Design

Study Overview

All Veterans undergoing lower extremity amputation or receiving post-operative amputee care in the VA health care system during a 3 year period of prospective enrollment will be screened for study participation at all sites. Research staff at each site will identify potential participants who meet study eligibility criteria immediately following amputation surgery. All lower extremity amputees meeting study criteria who present to each study site will be invited to participate. All patients being considered or who have recently had lower extremity amputations are seen during the weekly amputee multidisciplinary rounds at each site. Study site coordinators and site PIs designated specifically for this study have established relationships with medical residents, fellows, physicians, and staff in various medical specialties (orthopaedics, vascular, podiatry, rehab, wound/skin) who have contact with potential participants. These personnel will refer patients to the study coordinator for evaluation of eligibility. Coordinators will also screen medical records of individuals receiving amputation in the 2 years prior to the start of the study to identify additional participants. Clinicians from one of these service lines will then introduce the study and the study coordinator to potentially eligible participants. Upon agreement from the patient, study site coordinators will approach patients individually and inquire about their interest and eligibility in volunteering for this study. Study coordinators will also mail an approach letter to patients who do not have an upcoming clinic appointment or who cannot be approached in person. Patients can call for more information or to opt-out of the study. Study coordinators will call patients who do not respond to the letter to see if they have questions or would like more information about the study.

The site study coordinator will conduct the screening interview, which includes a series of questions to confirm eligibility (screening questions), a description of the study, its importance in amputee patient care, the responsibilities of participating in the study, and the potential risks and benefits of participating. Upon patient agreement, the study coordinator will initiate the informed consent process and inform the patient of the timeline for completing the baseline questionnaire, and assign the patient a unique study ID.

Once 8±2 participants are enrolled or nearly enrolled at each site, study coordinators will schedule appointments to complete the baseline assessment, either in person or by phone. Data are collected via electronic Case Report Form (eCRF). Individual or groups of participants may attend an in-person appointment with the study coordinator either in a private room in the Clinical Research Unit or office, or in the VA library or computer lab. Participants will use computers to complete the eCRFs and study coordinators are available to help guide participants and answer any questions.

Enrolled participants are assigned on a rolling basis into successive cohorts of 8±2 individuals at each participating site. Each time 8±2 participants are enrolled, that cohort will be randomized 1:1 to receive either the VETPALS intervention or individual education support program (control condition). We will ensure that participants will not have completed a PALS program prior to study participation and will not be part of an existing PALS group during their study participation. Randomization will occur through an email exchange between the study sites (VETPALS facilitator or site PI) and the data manager at Spectrum Research. The data manager will maintain a randomization table that is stored locally on a server at Spectrum Research. When a cohort is ready for randomization, the facilitator or site PI will send an email to the data manager stating that a group of participants is ready for randomization. The email will also include a list of study ID numbers but will not contain any information that could identify participants. Within 12-24 hours of receiving the email, the data manager will verify the list of study IDs in the database to ensure all baseline assessments are complete, and then will obtain random assignment by accessing the randomization table. The data manager will respond via email to the facilitator or site PI with a value of 0 or 1 (0=individual education support program, 1=VETPALS). Both parties will retain a copy of the email for reference. The data manager will record the treatment assignment for the group in the randomization table, and the facilitator or site PI will record the treatment assignment in the randomization log. This method will ensure that treatment allocation is concealed during the recruitment of each cohort. A balanced number of groups will be randomly assigned to each site based on the projected enrollment at that site, which is a common randomization schedule used in group-based interventions. The randomization schedule and algorithm will not be shared with local sites to maintain concealment of treatment allocation. Additionally, the data manager will record a value of 0 or 1 to each study ID in the database which is linked to the study ID assigned at enrollment. Clinical research staff at each location (applicable investigators and VETPALS facilitators) will receive the treatment allocation and randomization ID in order to proceed with the treatment, intervention or control. Site study coordinators who conduct the baseline and follow-up assessments are blind to treatment.

Additionally, each VA site will partner with another VA site treating Veteran amputee patients. Providers at the partner sites (e.g. Seattle partners with Tucson) will introduce the study to potentially eligible patients. Providers will give interested patients a study brochure so that patients can contact the VA site study coordinator. Patients will be screened via telephone script and those interested and eligible in participating will be consented by telephone and mail. Coordinators will mail a research study consent form using a USPS tracking number, establish telephone contact with the patient to answer questions during the informed consent process, and provide a postage-paid envelope for the patient to return the consent form. Patients participating in this study at partner sites will participate in the study via telephone assessments

with a site study coordinator. Patients from partner sites who are randomized to the intervention group can participate via telehealth (video teleconferencing). Similarly, patients randomized to the control group are contacted by telephone and receive post-amputation education materials by mail. Providers at the partner sites assist with scheduling the VETPALS classes as usual clinical care appointments, but are not involved in interacting with the participant for research purposes.

Cohorts allocated to the intervention will work with the VETPALS facilitator and 5 clinical appointments will be created in the participant’s medical record. Participants may receive reminder phone calls prior to each scheduled session. As in the original PALS intervention, participants will be encouraged to become members of the Amputee Coalition (free of charge) which allows access to publications and educational materials. Participants also receive copies of some educational materials from the Amputee Coalition, along with a VETPALS participant workbook. The VETPALS workbook is a modified version of the original PALS workbook. The PALS workbook is publicly available by request through the Amputee Coalition of America. The VETPALS workbook has been condensed as the original PALS program was 10 weeks, and VETPALS is 5 weeks. The VETPALS intervention occurs over 5 sessions and is co-led by an allied health professional (facilitator) and a peer who is an amputee. At all sites, the VETPALS facilitator is the Amputation Rehabilitation Coordinator (ARC) of each facility and are licensed physical therapists, with advanced DOD training and certification in amputation care. Additionally, one of the sites has a second facilitator who is a Clinical Health Psychologist with a focus in physical medicine and rehabilitation. Other research staff who are trained in VETPALS (e.g. Site PIs, Co-Is) who are trained in the VETPALS intervention may lead sessions in the event of a facilitator absence. Upon completion of the study protocol, all Veterans in the VETPALS program will be offered the individual education support program.

Outline of VETPALS intervention classes

<p>Session 1: 4 hour workshop</p>	<p>Self-management skills</p> <ul style="list-style-type: none"> -Knowledge of self-management -Problem-solving -Goal-setting -Self-monitoring -Skill focus: relaxation, calming mind & body <p>Tools for self-management</p> <ul style="list-style-type: none"> -Communication -Relaxation
<p>Session 2: 2 hour class</p>	<p>Managing Emotions</p> <ul style="list-style-type: none"> -Knowledge of behavioral activation -Skills: building resilience and positive mood

Session 3: 2 hour class	Health and Activity -Chronic disease management knowledge -Health behaviors
Session 4: 2 hour class	Interacting with family & friends
Session 5: 2 hour class	Maintenance of self-management behaviors -Set goals for the future -Maintaining everyday life/health self-management activities -Prevention relapse

The cohorts assigned to the individual education support program (control) will be informed of their treatment group by research personnel other than the study coordinator. Participants will have access to all of the medical and rehabilitation services they would typically receive in the normal course of amputation care (e.g. post-surgical follow-up, medical stabilization and wound healing, rehab for functional independence, prosthetic fit, gait training). This includes other VA Amputation System of Care resources such as caregiver and amputee support group. Participants will not receive the VETPALS or original PALS intervention during their time in the study. To enhance usual care and encourage study participation, participants in the control condition will be systematically contacted by a clinical member of the research team and provided with post-amputation education materials. We will use one or more of the following: *First Step – A Guide for Adapting to Limb Loss* and *SideStep – A Guide to Preventing and Managing Diabetes and Its Complications* published by the Amputee Coalition and *The Next Step – The Rehabilitation Journey After Lower Limb Amputation*, a VA/DOD publication. Participants will receive a subsequent call confirming receipt of the patient education materials, and inquiring about questions associated with the information. Individuals who express an interest in additional information will be referred to their amputation care team for appropriate follow-up. All contact in the control condition will take place on an individual basis. Upon completion of the study protocol, all Veterans in the individual education support program will be offered the VETPALS program.

Participants will complete follow-up assessments with study coordinators in-person or by telephone at 6 weeks and 6 months. Study coordinators will screen for any anticipated and unanticipated adverse events at scheduled follow-up visits and by telephone contact with participants at 3 weeks and 18 weeks. Coordinators will briefly call participants to check-in, do a few medical review questions, and give a reminder of the next study appointment. Coordinators who cannot reach participants by phone at 3 or 18 weeks for the medical review questions should alert another site researcher who can complete the assessment by medical record review in CPRS. At the end of the study, coordinators will conduct a final 1-year medical record review. Study coordinators do not access the medical record until all follow-ups are complete at the end of the study in order remain blind to intervention assignment.

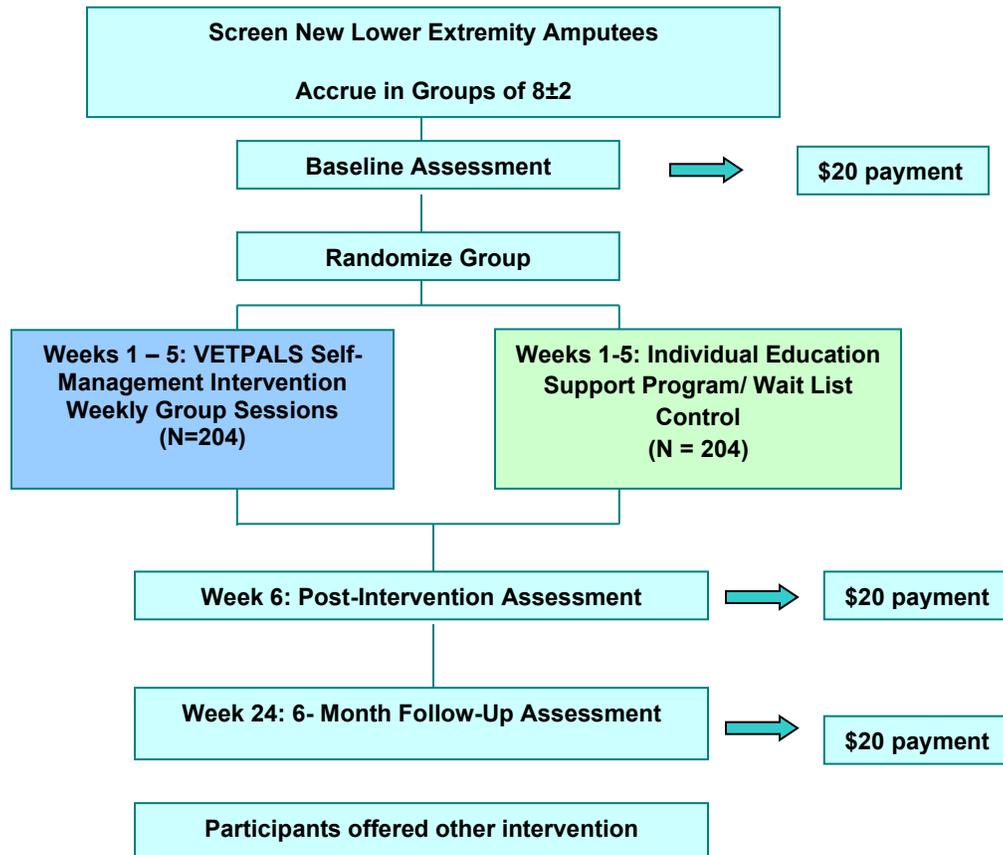
Additional details of the assessments and a study flow sheet can be found in the protocol document. Participants will receive reminders via telephone and mail for upcoming study visits from the study coordinator. The baseline assessment will take up to 60 minutes to complete and follow-up assessments will take up to 30 minutes to complete. Study coordinators remain blinded to treatment condition throughout the entire study and will be trained to ensure consistent and optimal administration of the assessments, as well as on strategies to remain blinded from treatment (e.g. strategies to remind patients not to reveal treatment).

Randomization

As described on page 21, this is a two-arm randomized controlled trial. The treatment allocation will automatically be matched to the study ID in the online randomization system. Clinical research staff at each location (site PIs and VETPALS facilitators) will receive the treatment allocation and proceed with study related activities for both conditions. Again, site study coordinators who conduct the baseline and follow-up assessments are blind to treatment.

This online randomization system (maintained by Spectrum Research) will have layers of security, including a requirement for a username and password to avoid intentional tampering with the treatment allocation, as well as the highest level of encryption of user information and storage into a secure SQL-based database. The system will maintain a log of all coordinators or study personnel (who have privileges) who have logged in with a time stamp. Data will be maintained in such a way that reports can be produced routinely that allow the investigators to review the treatment allocations per site. Each Site PI will also maintain a separate randomization log and patient selection log by study ID.

Participant Flow Chart



Potential Risk/Benefit Analysis

Risks to all participants: This project poses minimal risks to participants. Participants may find it inconvenient to schedule and attend appointments for the baseline, 6-week, and 6-month study interviews, which take up to one hour to complete. Participants may also feel uncomfortable about having the group assignment chosen randomly, but to minimize this risk of discomfort, all potential participants are informed that they have access to the other program once they complete the program that they are randomized to, including the follow-up assessments. The questionnaires also ask sensitive questions about physical and emotional health. Participants may be uncomfortable answering some questions. During the consent process and before each interview, participants are reminded that they can pass on any questions they do not comfortable answering. There is a risk of loss of confidentiality; although we make every effort to keep research information safe and secure, no system for protecting information can be completely secure. Finally, the study may have risks that are currently unforeseeable, but we will contact participants if new findings occur that pose a risk.

Additional risks to participants in the intervention condition: Participants may find it inconvenient to attend the VETPALS intervention sessions as the first session is 4 hours, and remaining sessions 2-5 are all 2 hours in length. Participants may also feel shy and/or

uncomfortable when participating in group discussion and other activities during the intervention sessions.

Risks to participants in the control condition: Participants in the control group may feel some discomfort or sadness about being randomized to the control/individual education support program. Participants may also feel some discomfort, sadness, or anxiety when reading post-amputation education materials, or when receiving a phone call from a researcher/clinician to confirm receipt of the materials and inquire about further questions. All Veterans in the control condition are offered the VETPALS intervention upon completion of the study protocol. This ethically ensures that study participation does not deprive Veterans of a potentially valuable service.

Anticipated benefits to society:

The VETPALS intervention is a potentially valuable health care service. This project is important to test the hypothesis that a group-based self-management intervention provides benefits above and beyond exposure to usual care and supplemental information alone in the five areas of: knowledge, problem solving, self-monitoring, behavioral goal setting, and skill acquisition. This study represents one of the only prospective randomized controlled trials of a behavioral intervention for individuals with limb loss. At the completion of the study, it is expected that the results will be used to inform the integration of self-management interventions into the VA Amputation System of Care.

Anticipated benefits to participants:

Previous research showed that the original PALS intervention improved physical and psychosocial functioning when delivered in existing community-based support groups for amputees. Other benefits of PALS include decreased isolation, greater optimism, improved knowledge of treatment and coping options, perceived coping ability, and functional social support. The PALS intervention was well tolerated in previous studies as indicated by a 90% or greater retention rate. VETPALS is an adaption of this empirically-supported self-management program.

Activities to minimize risk: Only the IRB-approved research staff will have access to research records. Patients screened for the study will be assigned a unique screening ID code, which will be linked to the last initial and full SSN (CPRS medical record). This log will be stored in a password-protected Excel file, on a secure VA network drive, in a restricted-access folder, behind the VA firewall that only the research staff has access to.

With respect to privacy and confidentiality, all enrolled participants will be assigned a unique study ID. All research data (which does not contain any PHI) will be stored entirely separate from research materials that contain PHI, such as a consent form, contact log, and consent enrollment log. The crosswalk document, which links the study ID to the patient's identity, will be maintained also in a password-protected Excel file, on a secure VA network drive, in a restricted-access folder, behind the VA firewall that only the research staff has access to.

The presence of study related adverse events will be regularly reviewed by the investigator team. The occurrence of 5 or more adverse events or 2 or more serious adverse events in either condition will trigger a review of the protocols at the time of occurrence. This process will serve several purposes. First, it will better accommodate the expected low-base rate of problems and allow for the early identification of issues than would a DSMB that met at an arbitrary regular interval.

5.2 Recruitment Methods

Up to 750 participants across all sites (including partner telehealth sites) will be recruited and enrolled in the project. The study has an overall final enrollment goal of 472. Table 1 below outlines expected enrollment by site and year.

	Year 1				Year 2				Year 3				Year 4					
Site	Q 1	Q 2	Q 3	Q 4	Q 1	Q 2	Q 3	Q 4	Q 1	Q 2	Q 3	Q 4	Q 1	Q 2	Q 3	Q 4	Enroll	Retention
Seattle			2 groups			4 groups				4 groups			2 groups				96	72
Cleveland			2 groups			4 groups				4 groups			2 groups				96	72
Houston			2 groups			5 groups				5 groups			3 groups				120	90
Tampa			2 groups			4 groups				4 groups			2 groups				96	72
Minneapolis			N/A			4 groups				4 groups			TBD				64	48
Total	E = 64		C = 48		E = 168		C = 126		E = 168		C = 126		E = 72		C = 54		472	354

Table 1: Projections assume group enrollment rate (E) of N=8±2 and completion rate (C) of N=6 per group. Based upon a 50% enrollment rate. Based upon a 75% follow-up retention rate.

The recruitment methods employed throughout the study ensure that the study sites can capture 100% of the patient population that meets inclusion and exclusion criteria. The recruitment plan ensures that we will be able to successfully identify patients in this specialized population, and that the only excluded patients are those that are clinically ineligible for this study.

Patient identification and Pre-screening

VA patients who recently had an amputation or are scheduled for an amputation are identified on an ongoing basis using computerized clinic lists from CPRS. Study coordinators may also receive alerts from ICD-9 codes and hospital admissions to identify VA patients. Alerts are created by CPRS programmers at each study site. The study coordinator screens the medical record to identify potentially eligible participants and determine if the patient has an upcoming clinic appointment for amputee-related post-operative care. The study coordinator attends clinic appointments and asks providers to determine if the patient might be eligible and interested. Providers approach patients who may be eligible and interested in the study, and ask if the patients would agree to be contacted by the study coordinator. If the patient agrees, the study coordinator initiates contact following the clinic appointment, either in person or by telephone.

As part of the initial approach conversation the coordinator may show a short recruitment video. The recruitment video is an adaptation of a PALS recruitment video and discusses the advantages of a self-management program. The video has been edited to best represent the self-management program as it is available to participants in the VetPals study. If the study coordinator is unable to attend the clinic appointment, providers can give the patient a brochure and a short recruitment video (e.g. CD, DVD, or link to video) with an overview of the study and a telephone number to call if interested or for questions. Additionally, the study coordinator may mail an approach letter, and when possible, a short recruitment video to potential participants who cannot be approached in clinic. Upon receipt of the approach letter, patients can call to opt-in or opt-out of the study. As stated in the approach letter, we will call patients who did not respond to the approach letter within approximately one week to determine interest and eligibility.

Study coordinators also screen surgery schedules from orthopaedics, vascular, and podiatry, and will screen medical records of anyone scheduled for an eligible surgical procedure. Study coordinators will then monitor the patient's progress and look for an upcoming clinic appointment to establish initial contact and determine if the patient is eligible and interested.

Providers from the multi-disciplinary PAVE Program (Prevention of Amputations in Veterans Everywhere) also identify potentially eligible patients through inpatient rounds and outpatient clinic appointments. The PAVE team includes providers from many service lines (orthopaedics, vascular, podiatry, skin/wound, physical therapy, rehabilitation medicine, prosthetics, rehabilitation psychology). Study coordinators screen medical records of patients referred by providers to determine eligibility and will attend a clinic appointment to establish initial contact, or will send an approach letter. Patients who previously agreed to be contacted may be contacted by telephone to determine interest and eligibility.

The study team also uses VA administrative data from the VHA Support Service Center (VSSC) to identify Veterans who recently had an amputation. VSSC data contains names and last 4 SSN. Study coordinators use this information to screen potentially eligible patients, and later contact the patient via an upcoming clinic appointment for amputee-related post-operative care.

Screening and Recruitment

Study coordinators initiate phone contact for any provider referrals for patients who do not have an upcoming clinic appointment but indicated an interest in the study and agreed to have a study coordinator initiate contact by phone. Also, study coordinators initiate phone contact for provider referrals from partner telehealth sites. Study coordinators use a phone script to introduce the study, verify basic criteria, and if eligible, proceed with the formal screening questions.

Study coordinators use a screening case report form (CRF) to verify inclusion and exclusion criteria, and obtain basic demographics. The screening CRF also contains the Short Portable Mental Status Questionnaire⁴² (SPMSQ), a brief test to determine inadequate cognitive or language function to consent or participate in the study. The screening CRF may originally be completed on a paper CRF, but later entered using an electronic CRF (eCRF), which is linked to

the study screening log and database. Study coordinators then initiate the informed consent process for interested and eligible patients.

Recruitment Materials

Study recruitment is heavily dependent on physician referrals and in-person initial contact between the patient and study coordinator. However, the study uses an approach letter, a study brochure, and video when in-person contact is not possible. The study brochure, and when possible a short recruitment video, are also used when participants may be interested, but not necessarily ready for screening and consent. See Appendix A.

Participant Payments

Enrolled participants are eligible to receive up to \$60 for study participation. Payments for the study are submitted by the study coordinator using VA Form 10-1078. Payment slips are routed through the fiscal office at each institution in order to issue payment by check/mail. Participants can request cash payment if an appointment is scheduled in advance for the coordinator to obtain necessary signatures on VA Form 10-1078. Cash payments require participants to take a payment slip and photo ID to the agent cashier at each VA Medical Center.

Participants are paid according to the payment schedule below. Payments are submitted (if by check/mail) or issued (if cash) following the completion of each study visit. If a participant withdraws or misses a study visit, they are compensated only for the visit completed.

Baseline: \$20

6 week follow-up: \$20

6 month follow-up: \$20

Participants are informed during the informed consent process that payments will take up to 8 weeks to receive a check by mail, and that cash payment on the day of the study is possible but may not always be available as it is reliant on advance scheduling and several signatures. Study staff will ensure that payments are submitted in a timely manner (within one week of participants completing a study visit).

Participants in the intervention group are eligible to receive travel pay for attending intervention sessions in accordance with the amount they receive for usual care clinic visits. Participants in the intervention group are scheduled to attend five in-person sessions, which are scheduled as usual clinical care visits. Participants are compensated travel pay for this usual clinical care visit even though the intervention is part of the research study. Participants in the control condition may also have usual care clinical visits during the time period when they are participating in this study. Any clinical visits associated with the control condition are eligible for travel pay in accordance with the Veteran participant's usual care travel pay amount. It is the responsibility of participants to claim travel pay for these visits, not the responsibility of the study staff.

5.3 Informed Consent Procedures

Waivers

We have a waiver of informed consent for screening and recruitment purposes so that participants can be screened without requiring completion of a full informed consent. The waiver

allows the site study coordinators to identify and approach only potentially eligible patients. Patients are identified through clinic lists in CPRS, CPRS alerts, physician referrals, surgery schedules, and VA administrative data on amputations obtained through the VHA Service Support Center. The CPRS medical record is screened to verify eligibility. The waiver will also allow staff to recruit potentially eligible patients. Providers who are part of a multi-disciplinary amputee team will approach patients who may be eligible and interested in the study, and ask if they can be contacted by study personnel. If the patient agrees, the patient can initiate contact with the study team by phone, the study coordinator can call the patient, or the study coordinator can speak to the patient after the clinic visit if the coordinator is able to attend the clinic appointment. Once the study coordinator confirms eligibility using the screening CRF, the informed consent will be obtained prior to any other research procedures. The screening CRF takes approximately 5 minutes or less to complete and is conducted in the form of an interview by the study coordinator.

Consent

Following screening, the study coordinator and patient will set-up a time to meet in person to go through the informed consent process and obtain the necessary signatures. The informed consent process will take place in a private clinic room, hospital room, room in the Clinical Research Unit, or in a quiet area of the hospital to protect the participant's privacy. The consent form clearly states that participation in this study is voluntary, and potential participants can decline participation at any time. Potential participants are also informed their participation is voluntary during the recruitment process. No attempt will be made to persuade patients who decline participation. Potential participants will also be asked if they need some time to consider their involvement before providing consent, and they will be given the opportunity to ask any and all questions related to the study before consenting. In the event the patient does not have an appointment at the VA, or cannot set up an appointment to come to the VA, the study coordinator will initiate the informed consent process by telephone/mail. Coordinators will mail a consent form using a USPS tracking number, establish telephone contact with the patient to answer questions during the informed consent process, and provide a postage-paid envelope for the patient to return the consent form. All study sites are Regional Amputation Centers and provide amputation-related care for participants from an expansive geographic area. The telephone/mail consent process will be used as appropriate to avoid unnecessary travel or inconvenience for patients for the consent process. The telephone/mail consent process will also be used in the event a participant is screened in person but requires additional time to consider study participation.

The study coordinators at each site will conduct the informed consent process, rather than the study PI/LSI, so that the participants do not feel obligated to participate. Alternatively, in the event the study coordinator is not available to obtain informed consent, another IRB-approved investigator designated by the PI/LSI may obtain consent. Finally, we will tell all potential participants that their decision about participation will not affect their clinical care in any way. See Appendix B.

The PI/SC and LSIs are responsible for training all applicable study staff at participating sites how to conduct the informed consent process. The PI/SC will hold pre-study training conference calls, which will cover the informed consent process. LSIs are also ensuring that site study coordinators receive additional training as necessary. Additionally, study staff will participate in ongoing monthly conference calls to discuss recruitment, enrollment, and retention and the consent process will be reviewed during these monthly meetings. Prior to the start of recruitment, Seattle will host a kick-off meeting for LSIs, VETPALS facilitators, and study coordinators. The consent process will be reviewed and practiced during this meeting.

Site coordinators will use the following guidelines for the consent process by telephone/mail. This guidance was provided by the Research Compliance Officer at the lead study site, VAPSHCS.

1. For studies that allow for consent to be obtained over the telephone, study staff will mail the Veteran, at the last known residential mailing address, a copy of the following documents:

Informed Consent Form
HIPAA Authorization Form
VA Form 10-3203

Note: Mail the above forms with a stamped, returned, addressed, VA envelope. It is helpful to add stickers or highlighting to indicate where to sign and date.

2. The study coordinator (SC) will call the Veteran to verify the receipt of the forms.
3. The SC will determine if there is sufficient time to explain and review the study details and forms received. If not, the SC will make a telephone call appointment to consent the Veteran.
4. The SC consents the Veteran to the study.
5. The SC will explain the study details to the Veteran and what it means for the Veteran to consent to participate in the study.
6. The SC will ensure the Veteran has plenty of time to consider study participation and a chance to talk it over with family and friends, if necessary.
7. The SC will direct the Veteran to sign and date all the forms where indicated.
8. The SC will advise the Veteran to mail the signed, dated and completed forms back to the study team in the VA envelope that was provided.
9. A member of the study team will call the Veteran to verify receipt of the forms.
10. The SC will sign and date all the forms.
11. The SC will mail a copy of all the forms to the Veteran or the Veteran will receive the signed copy if he/she has an upcoming appointment.

5.4 Inclusion/Exclusion Criteria

Inclusion criteria are intended to allow maximum inclusion of the majority of Veterans undergoing any new lower extremity amputation within 2 years prior to study enrollment. At the same time, it will allow for shared experience of managing the medical comorbidities that contributed to limb loss. Allowing multiple levels of amputation, as well as revisions, creates a study population that approximates the case mix of the VA Amputation System of Care and improves the generalizability of findings.

Inclusion criteria:

1. Ages 18 and older.

2. Transfemoral (above-knee), transtibial (below-knee), knee disarticulation (through-knee), Syme's/ankle disarticulation (through-ankle), and transmetatarsal amputation (through-foot, includes Chopart amputation and Lisfranc amputation) due to dysvascular disease/diabetes. Can include a revision of an amputation. Revision amputation is a soft tissue revision with bone shortening at the same or higher level.
3. Participant has a contact address and phone number so that s/he can be reached during the course of the study*.
4. Enrolled within 2 years of amputation.
5. Speak and comprehend English.

*We will ask a participant who do not meet eligibility criteria because of inclusion criteria item 3 if s/he will have one in the near future, and if yes, permission to contact them again that time. This allows the participant to be included, if interested and eligible, at a later date.

Exclusion criteria are intended to screen out a small number of individuals who would likely not benefit from participation in a group-based psychosocial intervention. Similar criteria are routinely used in the course of clinical care outside of the context of research study, and as a result are not thought to pose a significant threat to generalizability.

Exclusion criteria:

1. Inadequate cognitive or language function to consent or participate defined by ≥ 6 errors on the SPMSQ or diagnosis of dementia or Alzheimer's disease.
2. Active substance use disorder identified by chart review and initial screening. Note: No personnel involved in the study may identify, directly or indirectly, any individual patient or subject in any report of such research or otherwise disclose patient or subject identifies in any manner.
3. Major uncontrolled psychiatric illness (bipolar disorder, psychosis, severe suicidality) identified by chart review and confirmed as necessary by discussion with current providers.
4. Spinal cord injury

5.5 Study Evaluations

Screening

Study coordinators will collect screening information in the form of an interview. After discussing the study in person, or using the telephone script to introduce the study to patients recruited by telephone, interested patients will be asked to answer some screening questions. Patients will be asked to complete the SPMSQ, which is a brief test to determine inadequate cognitive or language function to consent or participate in the study. This is a 10 item questionnaire where a score of 5/10 or more is required to participate in the study. The screen also confirms eligibility by a series of inclusion/exclusion criteria, collects basic demographic information (age, gender, race, ethnicity, primary or telehealth site participant, and approximate driving distance from the study site), and documents informed consent for eligible patients who decide to participate in the study. Study coordinators may answer record screening answers initially on a paper CRF, but all screening CRF data will be transferred to the study database using the eCRF. Study

coordinators may also initially use the eCRF during the screening process if a computer is available or patients are being screened by phone. See Appendix C.

Baseline

All participants complete a baseline assessment that includes a medical record review, clinical interview, and administration of primary and secondary outcome measures and covariates. Site study coordinators conduct interviews with participants in person or by telephone, whichever is most convenient for the participant. In person interviews take place in a private hospital or clinic room, private room in the Clinical Research Unit, VA hospital library, or VA hospital computer lab. In person interviews may occur individually or in a small group of other study participants. To protect confidentiality and privacy, participants will be seated at separate computers and coordinators will conduct brief cognitive testing with participants individually in a separate room. If the interview is by phone, the study coordinator will ask the participant questions and answers will be marked using an eCRF that is linked to the study database. If the interview is in person, participants can sit at a private computer and respond to questions. The study coordinator is available to answer questions or conduct the interview if the patient does not wish to use the computer. All data are collected using EDC (no paper baseline CRFs) on VA approved and secure laptop and desktop computers. The baseline assessment takes up to one hour to complete.

During the clinical interview, the site study coordinator will collect medical information including amputation date (translated to time in days since original amputation), location, type (initial or revision), and level (e.g. transmetatarsal, transtibial, transfemoral). Although this information was verified and collected during screening, more detailed information, including time (in days) since original date of surgery, is recorded during the baseline assessment.

During the baseline medical record review we will use the Functional Comorbidity Index (FCI), amputation level, previous amputations, and contralateral limb assessment questions. Data will be recorded on eCRFs. A list of the measures used at baseline and follow-up are found in the *assessment measures* section and in Table 2.

Randomization

Participants will be randomized to a treatment group (group-based program/intervention vs. individual education program/control) following completion of the baseline assessment (see 5.1 Study Design). The site study coordinators will be naïve to treatment allocation throughout all of the assessments to minimize potential bias of the outcomes.

Group based self-management program (VETPALS Intervention)

Participants randomized to the intervention group will be asked to complete a checklist about their use of supplementary class resources, a checklist about their satisfaction with the classes, and selected participants will be invited to participate in a focus group to respond to and discuss implementation variables. The site PIs and VETPALS facilitator have primary responsibility in overseeing data collection on paper forms. Data will be entered into the central study database by the site PIs and/or VETPALS facilitator via eCRF. In the event a participant doesn't receive

any necessary materials during class sessions, a facilitator will mail materials to the participant and will include a return postage-paid addressed envelope if needed. Participants randomized to the intervention group are offered the other program at the end of their 6-month follow-up assessment. Study coordinators will record (yes/no) patients who elect to participate in the individual program and will refer patients to the facilitator who will discuss the other program and scheduling in more detail.

We will use a digital voice recorder to audio-record the VETPALS sessions. The purpose of audio-recording the VETPALS sessions is to monitor treatment fidelity, assess feedback, and ensure protocol adherence. Each participating site will consult with the local R&D office to ensure that the digital audio-recorder meets local VA guidelines, and all recorders will use FIPS 140-2 validated encryption. Sites will use the device(s) listed in the local site Central IRB applications.

Individual education support program (Control)

Participants randomized to the control group will not have any additional assessments or evaluations to complete. In the event a participant doesn't receive any necessary materials during the individual education support program, a facilitator will mail materials to the participant and will include a return postage-paid addressed envelope if needed. Participants in the control group are offered the VETPALS intervention classes at the end of their 6-month follow-up assessment. Study coordinators will record (yes/no) patients who elect to participate in the intervention classes and will refer patients to the facilitator who will discuss the other program and scheduling in more detail.

Patients who are randomized but unable to begin VETPALS or the Individual Education Support Program

In the event a participant is randomized but cannot begin participating in the assigned intervention, the participant will be given several options. There may be unexpected circumstances (e.g. personal or family illness, change in job status, personal situation) that may prevent a participant from starting the assigned intervention with their cohort as originally planned. VETPALS facilitators will discuss options with the participant.

1. The participant can be included in the same randomized intervention at a later date. The facilitator will wait for the next cohort that is assigned the same intervention and will contact participants to determine if they can participate with the next cohort.
2. If the participant agrees to be included in the next cohort, the facilitator will notify the study coordinator of this change so the study coordinator can include the participant in all subsequent follow-up assessments. The facilitator will only share the participant's study ID number so the coordinator remains blinded to treatment.
3. Participants may be asked to complete a second baseline assessment with the study coordinator. This will be assessed on an individual participant basis and site investigators and the PI will use their discretion when deciding if a second baseline should be completed. Collecting the baseline data again prior to starting the intervention

ensures that the research data reflects the most current responses. Participants who complete a second baseline will receive \$20 for their time and participation.

Periodic medical record review

Site study coordinators will conduct a brief medical review at scheduled assessments (baseline, 6 weeks, and 6 months) and at 3 weeks, 18 weeks, and 1 year. Site study coordinators will call participants by telephone at these intervals to do a brief medical screening to capture all anticipated and unanticipated adverse events. Site study coordinators will alert another site researcher to complete the assessment via medical record review for participants who cannot be contacted by phone. This ensures the study coordinator will remain blind to treatment assignment. At the end of the study, coordinators will conduct a final 1-year medical record review. Site study coordinators will record any anticipated adverse events, including complications such as stump non-healing, revision amputation, contralateral amputation, and mortality. For individuals who undergo a revision or new amputation, we will calculate the time in days since the qualifying event (original amputation). See 6.0 Reporting for a list of all anticipated AEs. Periodic medical record review allows study coordinators to also check for any UAE or SAEs. All data are collected on an eCRF using the EDC system.

Complications and anticipated AEs include stump non-healing, revision to same or higher level, contralateral amputation, and mortality. These will be monitored and collected during the subjects' hospital stay and after discharge by systematically reviewing the subject's medical record at designated intervals and during formal follow-up interviews at 6 weeks and 6 months.

Follow-up

All participants will complete follow-up assessments at approximately 6 weeks after randomization (coinciding with the end of the intervention sessions) and at 6 months. Similar to the baseline assessment, site study coordinators conduct follow-up interviews in-person or by phone, whichever is most convenient for the participant. All follow-up data are collected using EDC on VA approved and secure laptop and desktop computers and assessments take up to 30 minutes to complete. A list of the measures used at baseline and follow-up are found in the *assessment measures* section and in Table 2.

Temporary changes: Baseline, periodic medical record review, and follow-up

In the event a site study coordinator is unavailable (e.g. planned absence) the site study coordinator and/or project coordinator from the lead site (VA Puget Sound Health Care System, Seattle, WA) may conduct baseline, medical record review, and follow-up assessments by telephone. Site study staff will inform participants of this temporary change by mailing or hand delivering a letter that explains the site study coordinator's absence. Participant study ID number, name, and phone number will be shared with the Seattle site study coordinator and/or project coordinator. Local site staff will contact Seattle staff by telephone or PKI-encrypted email to share this information. All information from other sites will be stored in accordance with this study protocol. See section 7.0 Privacy and Confidentiality for more details.

Participant Assessment Measures

All data are collected using EDC. Measures are displayed on a computer screen and site study coordinators and/or participants respond using VA approved and secure computers and responses are automatically placed in the study database. There are no paper CRFs for baseline and follow-up assessments as all questionnaires are displayed on eCRFs. In the event of a technical problem, data will be recorded on paper CRFs and transferred to an eCRF. The coordinator will use a secure shredding bin to discard the paper CRF the eCRF is complete. A description of each measure used is below, followed by Table 2, which displays a summary of the baseline and follow-up assessments.

Primary Outcomes

Physical functioning will be measured using the Musculoskeletal Function Assessment Short Form (MFA-SF). The MFA-SF is a 46-item questionnaire designed to measure functional status across a broad range of musculoskeletal disorders. Participants are asked to rate difficulties associated with daily activities ranging from "not at all difficult" to "unable to do," as well as the frequency of problems, ranging from "none of the time" to "all of the time." Responses are combined into a single physical functioning score. Twelve of the items constitute a separate subscale examining how much individuals are bothered by their limitations. This scale will also be computed, but is not the primary outcome. The MFA-SF has been utilized extensively in research,⁴³ and has established validity, reliability.⁴⁴

Psychosocial functioning will be evaluated by examining depression using the Patient Health Questionnaire Depression Module (PHQ-9). The PHQ-9 is a brief self-report screening instrument designed to identify depressive symptoms consistent with criteria of the Diagnostic and Statistical Manual for Mental Disorders, 4th Edition.^{45,46} The module instructs participants to rate the degree to which they experienced each of 9 symptoms of depression over the last 2 weeks, ranging from 0 = "not at all" to 3 = "nearly every day". The PHQ-9 has shown utility in estimating the level of depressive severity in medical patients using the sum of scores on each of the 9 items.⁴⁷ The PHQ-9 has been utilized extensively in research and has established validity and reliability.⁴⁵

The last item on the PHQ asks "Over the last 2 weeks, how often have you been bothered by any of the following problems?...Thoughts that you would be better off dead, or of hurting yourself in some way?". Responses range from 0-3 where 0 (not at all), 1 (several days), 2 (more than half the days), 3 (nearly every day). For participants who respond >0, the study coordinator will refer to the Suicide Risk Reduction Protocol (Appendix D). This plan reflects the importance of activating hospital procedures for suicide assessment and prevention.

Secondary Outcomes

Quality of Life will be measured using the brief form of the World Health Organization Quality of Life Scale (WHOQOL-BREF). The WHOQOL-BREF is composed of 26 items examining the domains of physical health, psychological health, social relationships, and environment. WHOQOL-BREF has demonstrated discriminant validity, content validity, internal consistency

and test-retest reliability.⁴⁸ and has been utilized extensively in medical, rehabilitation and general population settings.⁴⁹ In this study, we will focus on the two global items, "How would you rate your quality of life?" with response items ranging from "very poor" to "very good" and "How satisfied are you with your health?" with responses ranging from "very dissatisfied" to "very satisfied."

Positive Affect will be measured using the Positive and Negative Affect Schedule (PANAS).⁵⁰ The PANAS consists of adjectives rated from 1 (very slightly/not at all) to 5 (extremely) that measure positive feelings such as joy, pleasure and negative feelings such as anxiety or sadness. For the current study, only the 10-item positive affect scale will be utilized. The PANAS has good internal consistency, reliability, and construct validity established in large normative samples.⁵¹

Intermediate Outcomes

Self-Efficacy for managing limb loss will be measured using the modified Self-Efficacy scale (MSES). The MSES is a 22-item questionnaire designed to measure patients' perceived self-efficacy to cope with the consequences of chronic disease with 3 subscales: self-efficacy for pain management, self-efficacy for coping with symptoms, and self-efficacy for physical function.⁵² Each item is presented as a question (e.g. How certain are you that you can keep your amputation from interfering with the things you want to do?). Respondents rate each belief on a 10 point Likert-type scale. Items are summed to produce a total score. Psychometric properties have been established.

Patient Activation will be measured by the Patient Activation Measure (PAM). The PAM is a 13-item survey tool designed to assess a person's engagement in care, confidence in the ability to understand and act upon health challenges, commitment to making needed lifestyle changes, and efforts to sustain those changes over time.⁵³ Response options for the 13 PAM questions use a Likert-type agreement scale with 4 response options. The options are *strongly disagree* (1), *disagree*, *agree* (3), *strongly agree* (4), and N/A. The raw score is calculated by adding all the responses to the 13 questions. The measure has shown good internal consistency and validity in both convenience and large national probability samples.⁵⁴

Problem Solving will be measured using the 10-item version of the Social Problem-Solving Inventory-Revised (SPSI-R).⁵⁵ This scale assesses two adaptive problem-solving dimensions (positive problem orientation and rational problem-solving) and three dysfunctional dimensions (negative problem orientation, impulsive/careless style, and avoidance style).⁵⁵ Items on the SPSI-R are rated on a five-point Likert-type scale (0, not at all true of me, to 4, extremely true of me) and summed to produce a single total score from 0-40. The SPSI-R has good internal consistency, construct validity, and has been used to assess problem solving in a broad range of populations.⁵⁶

Potential Covariates

The following variables have been established in the literature as correlates of one or both of our primary outcomes. They will be collected primarily to demonstrate the comparability at

baseline of the intervention and control conditions. In instances where randomization does not achieve comparability, outcome analyses will include them as covariates.

Comorbidity will be assessed primarily using the Functional Comorbidity Index (FCI).⁵⁷ The FCI is an 18-item list of diagnoses, each of which is given 1 point if present. The final score of the FCI is the sum of the items. The FCI was designed with physical function as the outcome of interest.⁵⁷ It has been found to have both content and criterion validity. We will also collect a limited number of pre-operative co-morbidity factors and concomitant diseases particularly relevant to amputation outcome (e.g., currently on dialysis - yes/no) from patient interview.

Pain will be measured using questions from the Chronic Pain Grade (CPG) questionnaire.⁵⁸ Participants will be asked to report the intensity and the interference of overall pain as well as pain in each of four different body regions. Response options range from 0 to 10. This assessment of pain location, intensity and impact conforms to established guidelines.⁵⁹ The CPG itself was designed for interview-based studies due to its relatively simple and brief format. The instrument has good internal consistency and reliability.⁵⁸

Complications include stump non-healing, revision to same or higher level, contralateral amputation, and mortality. These will be monitored and collected during the subjects' hospital stay and after discharge by systematically reviewing the subject's medical record every three months as well as during formal follow-up interview at 6 months.

Social support will be assessed using the Multidimensional Scale of Perceived Social Support (MSPSS),⁶⁰ a 12-item self-report measure of perceived social support from three specific sources: family, friends, and significant other. For each item, participants are asked to rate their degree of agreement on a 7-point Likert scale. Possible total scores range from 12 to 84, with higher scores indicating greater perceived social support. Items primarily reflect perceived availability of emotional, informational, companionship and affection support. Internal consistencies of the subscales and total scale are all excellent, and the scales have demonstrated strong test-retest stability over two- to three-month intervals.⁶⁰

Cognitive functioning will be evaluated using three brief tests from several well established neuropsychological instruments including: (1) The List Learning and List Recall Subscales of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS); (2) the Controlled Oral Word Association Test (COWAT); and (3) the Digit Span subtest of the Wechsler Adult Intelligence Scale – 3rd Edition (WAIS-III). All of the selected instruments have sound psychometric properties and extensive data are available on their reliability, validity, and population norms.⁶¹ The RBANS is a brief cognitive screening tool designed to balance the need for an instrument that is sufficiently sensitive to detect mild to moderate cognitive deficits, but also able to differentiate lower levels of cognitive performance without pronounced floor effects. It was specifically designed for use with older adults and for individuals in medical settings. The WAIS-III is the industry “gold standard” intelligence test. We propose to use only a single subtest, Digit Span, which includes two parts: Digits Forward and Digits Backwards. Both are tests of attention and working memory. Finally, the COWAT is a test of phonemic verbal fluency. It reflects abilities in a number of areas, including executive functioning. The norms for these neuropsychological tests are based on protocols that are designed to ensure

standardized administration. Site coordinators will be provided with written instruction scripts and trained by an experienced psychologist with extensive experience in neuropsychological testing to ensure optimal administration.

Alcohol use will be measured with the Alcohol Use Disorders Identification Test (AUDIT-C). This three-item measure queries individuals about the quantity and frequency of use as well as binge drinking episodes and has been extensively validated as a screening tool for identifying use disorders in medical populations.⁶²

Smoking status will be assessed by three standard questions addressing quantity, frequency, and recency of smoking established by the Center for Health Quality, Outcomes, and Economic Research (CHQOER) for the VA administered as part of a large health survey of Veteran health behaviors.

Internal Study Evaluations/Process Measures

Treatment engagement and adherence will be assessed using the Psychosocial Treatment Compliance Scale (PTCS).⁴¹ The PTCS is a 17-item, therapist-rated scale of compliance and perceived treatment engagement with psychosocial interventions. Although initially designed for individuals with serious mental illness, the items have broader applicability to other populations. The scale is comprised of two subscales (participation and attendance). Sample items (paraphrased) include “was able to remember the contents/skills taught in previous sessions”, “was attentive in treatment”. The scale has excellent internal consistency and construct validity.⁴¹

Actual versus planned intervention participation in the VA context will be assessed by the screening log and screening data of all potentially eligible participants. VETPALS facilitators will maintain a weekly log documenting attendance and modality of participation (in-person or telehealth), tardiness or early departures from each session, and completion of homework assignments. These two methods, along with the PTCS, will allow investigators to examine differences in participation by delivery modality, understand retention, and quantify treatment exposure.

Use of supplementary resources will be assessed for both the intervention and control conditions by administering a brief survey coinciding with the end of the intervention sessions. The survey measures the use of supplementary project resources, including the recommended websites and participation in concurrent therapeutic/clinical activities (e.g. therapies, locally available programs such as peer visits, Amputee Support Group, and Amputee Coalition resources). This brief survey also will assess several potential factors in engagement, including perceived credibility of the treatment and perceived self-reported engagement in the treatment.

We will formally assess treatment satisfaction using a pencil and paper satisfaction measure used in the original PALS program. The VETPALS facilitator will not directly administer or collect the satisfaction measure. The Veteran peer amputee or another designee will collect all paper copies and place them in a sealed envelope. The facilitator will deliver these to the PI or Co-PI at the Seattle site either by hand delivery, secure and traceable mail (e.g. UPS), or scanning

PDF copies and uploading to a secure SharePoint. The PI and Co-PI are responsible for reviewing these questionnaires and entering data into the database.

To describe and understand barriers and facilitators to implementation of VETPALS in the VA, Investigator study staff (Drs. Turner, Williams, Norvell) will conduct structured interviews with the site study coordinators, VETPALS facilitators, and peer facilitators at the study conclusion. These interviews will assess the time commitment required to lead each group, the administrative procedures used, and any local clinical or organizational factors that facilitated or hindered recruitment, scheduling, retention, or delivery of the intervention.

Focus Groups

To better understand any barriers and facilitators to implementation from the Veteran's perspective, we will conduct 2-4 focus groups in the final year of the study (additional details in *3.0 Objectives*). Focus groups will be facilitated by Investigator-level study staff using guided questions to ascertain treatment, psychological, and organizational and logistical factors that may have affected participation.

Staff Research Interviews

To better understand any barriers and facilitators to implementation from the research staff perspective, we will conduct individual interviews with site study coordinators and VETPALS facilitators. Investigator-level study staff (Drs. Turner, Williams, and Norvell) will conduct structured interviews with these staff to assess time commitment required to lead each group, administrative procedures used, and any local clinical or organizational factors that facilitated or hindered recruitment, scheduling, retention, or delivery of the educational programs.

Table 2: Assessment Timeline

See Appendix E for a copy of all measures and interview questions.

	Measure	Screening	Baseline	Treatment Completion	Month 6 Follow-Up
Screening					
Mental Status	SPMSQ	X			
Primary Outcomes					
Physical Functioning	MFA-SF		X	X	X
Psychosocial Functioning	PHQ-9		X	X	X
Secondary Outcomes					
Quality of Life	WHQOL-BREF		X	X	X
Positive Affect	PANAS		X	X	X
Intermediate Outcomes					
Self-Efficacy	MSES		X	X	X
Patient Activation	PAMS		X	X	X
Problem Solving	SPSI-R		X	X	X
SM Stages of Change	SOC		X	X	X
Prosthesis Use	Prosthesis Use		X	X	X
Potential Covariates					
Memory	RBANS		X		
Fluency/Executive Function	COWAT		X		
Attention	Digit Span		X		
Comorbidity	FCI		X		
Pain	CPG		X	X	X
Complications	Chart Review		X	X	X
Social Support	MSPSS		X	X	X
Alcohol Use	AUDIT-C		X	X	X
Smoking Status	CHQOER Ques.		X	X	X
Implementation Variables					
Treatment Engagement*	PTCS			X	
Treatment Fidelity*	Audio Recording Review		Ongoing		
Use of Supplementary Resources	Checklist			X	
Satisfaction	Checklist			X	
Implementation Barriers (Facilitator)*	Focus Group				Project Completion
Implementation Barriers (Participant)	Focus Group			Subsample	

* Completed by Study Staff

5.6 Data Analysis

Data analysis will be performed by the study biostatistician (Dr. David Yanez) and consultant (Dr. Daniel Norvell) with input from investigator-level study staff (Drs. Turner, Czerniecki, Williams, site PIs). Data analysis will occur at Spectrum Research, Inc. (Tacoma, WA), the University of Washington (Seattle, WA), and Oregon Health & Science University (Portland, OR). Data that is off-site at Spectrum Research, University of Washington, and OHSU for analysis will be coded and will not contain any HIPAA identifiers. See 7.0 *Privacy and Confidentiality* for additional details on data analysis and storage at these locations.

Descriptive Statistics

We will produce descriptive statistics for the recruitment and retention of participants, as well as the frequency of session participation in the intervention group. We will also produce descriptive statistics of patient demographic characteristics, covariates, and outcome measures. For categorical variables, proportions and frequency counts will be calculated. For continuous variables, means, standard deviations, medians, minimum and maximum will be computed. Missing, extreme, and variable distributions will be explored. Missing values patterns will be analyzed.

Statistical analysis of the primary aims

For hypotheses 1a and 1b, we will use Generalized Estimating Equations (GEE) linear regression to investigate mean change over time in MFA-SF. We will model the mean MFA-SF change over time as the outcome, using contrasts $D = MFA-SF[Post\ Intervention] - MFA-SF[baseline]$ and $D = MFA-SF[6\ months] - MFA-SF[baseline]$, versus a treatment indicator, T. The treatment indicator assigns patients T=1 if they receive the VETPALS intervention and T=0 if they receive enhanced usual care. The GEE model will account for intra-cohort level correlation among patients' measurements. The GEE model will provide valid statistical inference if the correlation or variance structure is mis-specified. It does not require normality of model errors. Since the focus of the investigation is to estimate within-patient changes (over time) and the outcome are intra-patient level differences, repeated measures correlation is appropriately accounted for in the model variance estimates. Similarly, we will model the mean PHQ-9 change over time as the outcome, using contrasts $D = PHQ-9[Post\ Intervention] - PHQ-9[baseline]$ and $D = PHQ-9[6\ months] - PHQ-9[baseline]$, versus a treatment indicator, T. The primary analysis will be an as-randomized efficacy assessment comparing the self-management intervention and individual education groups for improvements in depression and physical functioning. The follow-up assessments of participants who do not complete all self-management sessions in the intervention condition will still be included with those who complete the expected course of treatment. This type of analysis provides a more conservative and ecologically valid estimation of treatment effect because it retains all participants and does not screen out individuals who do not tolerate the intervention. Effect size estimates will be obtained. We will assess the randomization assignment by comparing patient-level characteristics (e.g., age, gender, and amputation level) by the treatment indicator and adjust our models with appropriate covariates as necessary.

For hypotheses 2a-e, similar to above, we will fit a GEE model to investigate differences in mean changes in each outcome variable (VAR). We will model the mean change over time as the outcome, using contrasts $\Delta = VAR[Post\ Intervention] - VAR[baseline]$ and $\Delta = VAR[6\ months] - VAR[baseline]$, versus a treatment indicator, T. The treatment indicator assigns patients T=1 if

they receive VETPALS and T=0 if they receive individual education support. The primary analysis will again be a randomized efficacy assessment comparing the self-management intervention and control groups for improvements in self-efficacy, patient activation, and problem solving. The follow-up assessments of participants who do not complete all self-management sessions in the intervention condition will still be included with those who complete the expected course of treatment. This type of analysis provides a more conservative and ecologically valid estimation of treatment effect because it retains all participants and does not screen out individuals who do not tolerate the intervention. Primary analyses will examine changes between baseline and 6-month follow-up scores on outcome measures by treatment group, but we will also examine changes in outcome immediately following the intervention. Effect size estimates will be obtained. Models will be adjusted for covariates as necessary.

For hypothesis 2f, we will produce mean change scores, $\Delta = VAR[6\ months] - VAR[baseline]$, for each outcome measure. We will utilize Pearson product moment correlations to establish associations between changes in our intermediate outcomes and changes in our primary outcomes. This series of analyses is both secondary and exploratory, and is intended to produce preliminary data for a future explanatory model hypothesizing that improvements in self-efficacy, patient activation, and problem solving represent causal mechanisms of self-management intervention that in turn produce improvements in physical and psychosocial outcomes.

Sample Size Justification

Enrollment: Between our 5 sites, we anticipate enrolling approximately 157 subjects per year of recruitment based on previous numbers from the National VA Registry and our already established record of enrollment and follow-up in previous amputation studies conducted by the same core group of investigators. This is a conservative estimate as the inclusion/exclusion criteria for this proposal are more lenient than in our previous studies examining individuals with their first, unilateral amputation. Nonetheless we cautiously project enrollment at 55% of 286, or 157 participants per year. Over the course of 3 years, we expect to accrue 472 enrollees.

Retention: The original PALS self-management study maintained a greater than 90% retention rate. Even assuming a more conservative 75% retention rate for the proposed study, 118 participants per year would be expected to participate and successfully reach their final follow-up. Over the course of 3 years, we expect to retain 354 enrollees. In sum, our sample size estimates are grounded in the specific experience of our team enrolling actual Veterans with limb loss at VA facilities and reflect conservative estimates of recruitment and retention. This is done out of an abundance of caution and we expect that actual rates of recruitment and retention are likely to be higher.

Each primary site intends to recruit one additional secondary site to partner with each primary site (e.g. Seattle partners with Tucson VA). Enrollment, retention, and power analysis sections do not reflect these anticipated partners and do not require them. The purpose of including additional sites is to extend the recruitment and generalizability of the project aims to integrate VETPALS into the VA Amputation System of Care.

Statistical Power

Power estimates are based upon the sample size projections provided in Table 1 below (also in 5.2 Recruitment Methods). Effect size estimates were obtained using the estimates provided in the original PALS study. We anticipated an enrollment of N=51 cohorts in total for the study and

between 6-10 patients per cohort. The treatments, VETPALS and individual education, will be evenly and randomly assigned by cohort. We project between 300 to 500 total patients participating in this study. We investigated changes in each outcome by first computing intra-patient change and accounting for possible intra-cohort level correlation. We assume the baseline and six-month values for the outcomes are highly correlated, with Pearson correlation between 0.6 and 0.8, and the correlation among the change values within a cohort to be modestly correlated, with an intra-class correlation between 0.01 and 0.10. To estimate statistical power to detect the anticipated effect sizes at these proposed sample sizes and correlations, we conducted a series of Monte Carlo simulations based on the analytic framework outlined above. Each of the power calculations were based on 1,000 simulated datasets. Power was computed empirically as the proportion of Wald tests (from correlated data regression estimates from the simulated datasets) that correctly rejected the null hypothesis of no effect, at a five percent alpha level (Type I error rate).

The results indicate that for the modest effect sizes provided, low levels of intra-cohort correlation (ICC) and modest Pearson correlation levels between baseline and six-month measurements (ρ), we will have adequate power to detect differences between the study conditions. To provide two examples, given these conditions we will have power of greater than .8 to detect differences in the primary outcome physical functioning (MFA-SF) (and the additional outcome self-efficacy (MSES).

Anticipated Enrollment

Table 1 (page 25) indicates anticipated enrollment across all 5 sites throughout the 4-year study period. Projections assume a group enrollment rate of 8 ± 2 participants and completion rate of 6 participants per group. We estimate a 50% enrollment rate and expect a 75% retention rate.

5.7 Withdrawal of Subjects

Participants are systematically notified that they are free to withdraw from the study at any time. No special provisions for withdrawal are necessary. Participants are free to retain other usual amputation-related care without interruption. As this study examines the feasibility of a self-management intervention in the VA Amputation System of Care, it is highly unusual that a participant would be withdrawn from the research without consent. The study is interested in tracking withdraws and citing reasons for withdrawal. Investigator-initiated withdrawals will be evaluated and discussed by site PIs and the lead PI/SC and/or Co-PI. The PI/SC and/or site PI may also suspend enrollment of an individual participant if it is determined it was not in his/her best interest to continue, or it was not in the best interest of the intervention group (e.g. participant was consistently combative and argumentative in group). All reasons for investigator initiated withdrawals will be documented in the notes section of the eCRF.

7.0 Reporting

6.1 Adverse Events

Definitions

An **Adverse Event (AE)** is defined as any unfavorable and unintended diagnosis, sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the study intervention, which may or may not be related to the intervention. AEs include any new events not present during the pre-intervention period or events that were present during the pre-intervention period but have increased in severity.

Anticipated AEs are those that might reasonably be expected to occur in this population with significant medical comorbidity and can include, but are not necessarily limited to, re-hospitalization, revision amputation, conversion to higher-level amputation, contralateral limb amputation, pain, stroke, myocardial infarction, deep venous thrombosis, dialysis, superficial or deep infection, and death. Each site will maintain a log of all anticipated AEs, including those captured on eCRFs through medical record review.

An **unanticipated adverse event (UAE)** is an adverse event that is not expected to occur in this population with significant medical comorbidity.

Unanticipated problems (UAP), also the phrase “unanticipated problems involving risks to subjects or others”, in general, include any incident, experience, or outcome that meets all of the following:

1. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
2. Related or possibly related to participation in the research (*possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

A **Serious Adverse Event (SAE)** is defined as any untoward medical occurrence that results in death, is life-threatening, requires or prolongs hospitalization, causes persistent or significant disability/incapacity, results in congenital anomalies/birth defects, or, in the opinion of the investigators, represents other significant hazards or potentially serious harm to research participants or others.

Reporting Requirements

Study coordinators conduct medical record reviews at the regular study intervals coinciding with assessments (baseline, 6 week, and 6 month). Coordinators also review the medical record periodically (at 3 weeks, 18 weeks, 1 year) following the baseline assessment to determine if any anticipated AEs, SAEs, or UAEs occurred. Study staff are also informed to contact the site PI upon learning of a participant AE. The site PI reviews the AE to determine how to record and report the event, if applicable. Directing AE information to the site PI that is discovered separately from medical record review helps ensure that the study coordinator remains naïve to the treatment group (intervention or control). All AE reports are reviewed by the site PI before final documentation and submitting a report.

Notably, although the expected occurrence of non-study related anticipated AEs is high, the expected occurrence of study-related AEs associated with the intervention (participation in a group based self-management program), control (individual education support program), or study assessments (self-report questionnaires and cognitive testing) is low.

The VAPSHCS will evaluate the implications of AE information according to an identified protocol, specifically, the occurrence of 5 or more AEs or 2 or more SAEs will prompt a review of the study procedures for safety.

All anticipated AEs will be tracked and recorded on eCRFs used at regular study assessments, as well as at intervals of scheduled chart reviews. Study staff are trained to follow VA Central IRB reporting requirements for unanticipated SAEs and UAPs involving risks to participants or others. Reports must be submitted on the template (See Appendix F) to the VA Central IRB within 5 business days after the study staff becomes aware of the event. Additionally, site study staff (coordinators and PIs) should receive a copy of the SAE/UAP report.

All AEs (includes anticipated AEs, UAEs, UAPs, and SAEs) must be followed until resolution or a stable endpoint is reached, such as:

- AE is resolved and has returned to normal/baseline values or has stabilized.
- Subject is lost to follow-up or has withdrawn consent.
- AE is judged by the site PI, lead PI/SC, and/or Co-PI to be no longer clinically significant.
- Participant has completed study required follow-ups (6 month visit).

Additionally, the investigators will monitor all AEs and study activity. Although it is unlikely, the following conditions would trigger an immediate suspension of the research project:

- There was reason to believe the study procedures (assessments, intervention, control) were adversely affecting a participant's overall health, including mental health, as demonstrated by inpatient hospitalizations for mental health or suicide.
- The occurrence of 5 or more study-related AEs or 2 or more study-related SAEs in either condition will trigger a review of the protocols at the time of occurrence. It will better accommodate the expected low-base rate of problems and allow for the early identification issues than would a DSMB that met at an arbitrary regular interval.

6.2 Protocol Deviations

Definitions

A **protocol deviation** is any unplanned excursion from the protocol that is not implemented or intended as a systematic change. A protocol deviation could be a limited prospective exception to the protocol. Deviations initiated by the PI must be reviewed and approved by the IRB and sponsor prior to implementation, unless the change is necessary to eliminate apparent immediate hazards to human subjects (21 CFR 312.66), or to protect the life or physical well-being of the participant (21 CFR 812.35(a)(2)). A **protocol deviation** is also any other, unplanned, instance(s) of protocol non-compliance.

Reporting Requirements

Study sites, under the direction of the site PI, are responsible for reporting any protocol deviations, violations, or non-compliance to the VA Central IRB within 5 business days after being made aware of the deviation (see Appendix F). Study sites must report any protocol deviations that are likely to substantially adversely affect:

- The rights, safety, or welfare of the research participant;
- The participant's willingness to continue participation; or
- The integrity of the research data, including VA information security requirements.

Additionally, the PI/SC should be informed by the site coordinator and/or site PI of the protocol deviation at the earliest opportunity and should receive a copy of the report of protocol deviations, violations, and/or non-compliance.

8.0 Privacy and Confidentiality

The study has a HIPAA Authorization Form (Appendix B) that participants review and sign following the informed consent process. This study uses Protected Health Information (PHI) related to amputation surgery and post-operative care.

We will protect participant's privacy interests by the doing the following:

- Screening and consent will take place in a private clinic room, hospital room, room in the Clinical Research Unit, another quiet area of the hospital, or by telephone/mail following initial contact and study introduction by a provider.
- The EDC system used for data collection stores the information collected in a PostgreSQL database secured by the webhost for this application (Heroku, <https://heroku.com/policy/security>). A username and password will be required for each person accessing the database and will only be supplied after credentials are verified with Spectrum Research, Inc. Data collected and stored in the database are coded and do not contain protected health information.
- Site study coordinators maintain an electronic screening and enrollment log. All participants who complete the screening process receive a screening ID (e.g. S1001, S1002, etc.) where the first digit runs 1-5 based on the number of VA sites. A

screening log is maintained locally by each site in a password protected file, in a restricted access folder, on the VA network behind the VA firewall. A master web-based electronic screening log will be maintained by Spectrum Research. This file will not contain individual identifying information such as last names or first initials of the participants, but will contain the screening ID, date of screening, eligibility status, and reason for screen failure/refusal, and if enrolled, the enrollment study ID. Access to the master screening log is regulated by a secure login ID and password for each user.

- Once the participant signs a consent form, the site study coordinator assigns an enrollment study ID number (e.g. 1001, 1002, etc.) where 1-5 designates the VA site. The sites maintain a consent enrollment log that links the study ID to the participant's name, last 4 SSN, and date of consent. The sites also maintain a contact information log that includes necessary contact information for telephone and mail contact, or sites can access this information in the CPRS medical record. All identifiable information, including the crosswalk document (consent enrollment log) is stored locally in a password protected file, on a restricted access folder, on the VA network and behind the VA firewall. Only IRB-approved researchers have access to this document. These documents will never leave the VA sites, and Spectrum Research and The University of Washington never receive information that could identify patients.
- In the event a site study coordinator is unavailable to perform baseline and follow-up assessments, the Seattle study coordinator or project coordinator may conduct these assessments by phone. Site study staff will share participant ID number, name, and phone number with Seattle staff. This exchange will take place by PKI-encrypted email or telephone. Seattle staff will maintain a crosswalk document that is stored locally at the VAPSHCS in a password protected file, on a restricted access folder, on the VA network and behind the VA firewall. This log will also include dates the assessments occurred by telephone and any other relevant notes. This information will only be stored temporarily at VAPSHCS. Once the site study coordinator is available, this information will be returned to the site by PKI-encrypted email or telephone and will be removed from the temporary crosswalk file.
- Once a group of 8 participants (± 2 when necessary) complete the baseline assessment, the coordinator alerts the site PI and VETPALS facilitator. Because the coordinator is blind to treatment group, the site PI or VETPALS facilitator enter a secure web-based randomization scheme also maintained by Spectrum Research. The user access the website with a secure login ID and password and selects participant IDs from the electronic master screening log to obtain the treatment group. The group treatment allocation will be automatically matched to the study IDs in the system. The randomization technique will allow for a random distribution without providing any discernible pattern. Each site PI will also maintain a separate randomization log containing study IDs, name, and randomization group. This log will be in a password protected file, in a restricted access folder, on the VA network behind the VA firewall. Only the site PI and VETPALS facilitator have access to this file.
- Data from each eCRF is stored into a secure database electronically using the web-application provided by Spectrum Research. Study coordinators will have the ability to log into this web-application with their designated log-in credentials. Once the coordinator has logged in, the ability to enter participant data into a variety of web-forms becomes available. The coordinator will not have the ability to edit or view data

that has been entered from another VA site, and user-privileges will be assigned to limit or advance the abilities of the coordinator. Without a proper username and password there is no ability to view/edit any of the study data.

- Coded research data obtained from the eCRFs will be stored through SSL database encryption, behind local and master firewalls hosted by Heroku, and encrypted if necessary. Again, data will only be accessible with a valid and confirmed user ID and password. Each user ID will be assigned viewing/editing privileges based on the needs of that user, allowing or disallowing the viewing/editing of select data.

The data, after it has been entered by a verified user, will be transmitted from one of the web-application's data collection forms via SSL (Secure Socket Layer) encryption and stored in a PostgreSQL database using the encrypted database connection. HTTPS will also be enabled for this website. Ultimately this means that the data will be securely transferred from over the Internet via HTTPS, and then stored in the database using a SSL encrypted database connection.

Heroku's physical infrastructure is hosted and managed within Amazon's secure data centers and utilizes Amazon Web Service (AWS) technology. Amazon continually manages risk and undergoes recurring assessments to ensure compliance with industry standards. Heroku utilizes ISO 27001 and IFSMA certified data centers that are managed by Amazon. The AWS technology is currently in compliance with a variety of regulations, standards, and best-practices. Please review these sources for a more complete understanding: <https://www.heroku.com/policy/security/> <https://aws.amazon.com/compliance/>

Data files, which are coded and do not contain any identifiable information or HIPAA identifiers, will be periodically downloaded from database to a physical computer for the purpose of analysis and will be password protected and encrypted on these devices. These files will only be accessible by the data manager and IRB approved study personnel who will be handling the data for analysis purposes.

- Research records, including eCRFs, will be identified with a unique study ID. The crosswalk documents (enrollment log and randomization log) will be stored separately from all other study data at each VA site. Again, all of the study files will be stored on a VA secure network behind VA firewall with required password protections, at each VA site. Only IRB-approved study personnel have access to the study records.
- All paper records for the study (telephone scripts, paper screening CRFs, consent forms, and other study-related documents) will be secured in locked filing cabinets in locked VA offices that only the IRB-approved research personnel have access to.
- VA-issued laptop computers (with FIPS 140-2 encryption) and VA-issued desktop computers are used to enter all electronic data (screening log, eCRFs) and access all study-related files on the VA network. When not in use, the laptops will be stored in locked cabinets inside of locked offices at each site.
- VA-issued and approved digital voice recorders (with FIPS 140-2 encryption) are used to audio-record the VETPALS and focus group sessions. Voice files from each

site will be stored on VA computers on the VA network in restricted-access folders that only the site PI, Co-I, and VETPALS facilitator have access to. Sites will transfer voice files to the main study site, VAPSHCS. Files may be transferred by one of the following methods: (1) PKI-encrypted email, (2) burned to encrypted CD and mailed using a secure, traceable mail service (e.g. UPS, FedEx), (3) uploaded to a secure SharePoint that is only accessible by IRB-approved research staff. At the main study site, the PI/SC, Co-PI/SC, Co-I, and VETPALS facilitator will also store these files on the VA network in a restricted-access folder. Voice files will also be reviewed by Dr. Dawn Ehde, PhD from the University of Washington who is a Co-I on this project. Files will be reviewed at the VAPSHCS, via secure VPN connection to the VA. When not in use, the digital voice recorders will be stored in locked cabinets inside of locked offices at each site.

- Following the completion of all study-related procedures, the master subject-ID and identifier crosswalk from each site will be securely shipped (e.g., via UPS with shipment tracking or transferred electronically using a VA-approved encryption method and will be consolidated and retained in Seattle. Individual, redundant, site cross walks will be destroyed. Coded datasets (that do not contain any HIPAA identifiers or other identifiable information) will remain at Spectrum Research, University of Washington, and OHSU for analysis purposes. These datasets will be password protected and encrypted on computers located at Spectrum Research, Inc., 705 S. 9th Street, Tacoma, WA 98405, Room 203. Additionally, datasets will be password protected and encrypted on computers located at University of Washington, and at OHSU in the office of the biostatistician, Dr. David Yanez (Gaines Hall, Room 155). Spectrum Research, University of Washington, and OHSU do not receive or have access to the key to the code. Data will be returned to VA Puget Sound no later than two years following the completion of the last period of data analysis.

9.0 Communication Plan

General Communications

The PI/SC and LSIs are responsible for training all applicable staff at participating sites. The PI/SC will hold a series of pre-study training conference calls to establish regular communication among the site study coordinators and site PIs. Prior to the start of recruitment, VAPSHCS in Seattle will host a kick-off meeting for LSIs, VETPALS facilitators, and study coordinators. The protocol will be reviewed during this meeting, including a plan for keeping in regular communication.

The site PIs and coordinators will also participate in regular monthly conference calls. The purpose of the monthly meetings is to discuss study progress, issues with recruitment, enrollment, and retention, and to share strategies to ensure the success of the study at each site. The meeting frequency may adjust throughout the course of the study (e.g. meetings occur bi-weekly at the start of the project), but staff will meet monthly at a minimum.

Additionally, the site PIs, VETPALS facilitators, and other investigator-level staff (e.g. Drs. Turner, Czerniecki, Williams, Ehde, Norvell, Wegener, Yanez) will meet monthly to discuss any issues related to randomization, intervention delivery or fidelity, AEs, SAEs and UAPs, and other necessary topics.

Site Communications

In order to ensure adherence to the protocol and Central IRB reporting requirements, the PI/SC and VAPSHCS study personnel will do the following:

- Collect and track site* IRB approval letters prior to study initiation.
- Collect and track site* R&D approval letters, including ACOS letters, prior to study initiation.
- Collect and track all site protocol modifications and continuing review approvals for IRB and R&D.
- Distribute amendments and the most current version of the protocol, consent form, and HIPAA authorization form to all sites. Staff will also track the receipt of these documents by all sites, including the approval of any required protocol modifications.
- The PI/SC will contact the director of the telehealth partner sites via written Memorandum by email to notify the site contact and hospital director that the research study was approved by Central IRB and assistance in participant identification and referrals can begin.
- VAPSHCS will track all written and verbal communication with all sites, including telehealth partner sites, using a communications log.
- Discuss any AEs and SAEs during monthly teleconference meetings and review reporting requirements as necessary.

*Site IRB approval letters will be issued by VA Central IRB. VA Central IRB is the IRB of record for all participating study sites. Sites will submit the study to their local R&D Committee for review and approval.

Additional details on site communications for this VA multi-site study can be found in the *Protocol-Supplement for Multi-Site Studies Overseen by the VA Central IRB* (Appendix G).

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