Trial Outcomes for Massage: Care Ally-Assisted vs. Therapist-Treated (TOMCATT)

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1.0 Background

Data from the 2012 National Health Interview Survey indicate that during a 3-month period, 15% of adults reported neck pain. The 12-month prevalence of chronic neck pain is estimated to be between 30%-50%. Neck pain is especially common in adults older than 50 years and is the fourth leading cause of disability in the United States, after back pain, depression, and joint pain. In a 2008 VA study, Dobsha et al. found back and neck pain diagnoses were present in 67% of 401 Veterans. In another VA study, the two most common cervical spine diagnoses were stenosis (50%) and disk herniation (23%). In Veterans with these diagnoses, neck pain was reported by 96%. The impact of chronic neck pain is widespread, exerting negative effects on individuals' physical, psychological, and economic well-being. Chronic neck pain reduces functional status, quality of life, and is associated with deleterious psychological outcomes, including depression and anxiety. Chronic neck pain is a major reason for health care utilization, accounting for more than 10 million ambulatory medical visits per year. The economic impact of this utilization is significant.

Guidelines highlight a wide range of treatment options for chronic neck pain. In clinical practice, conventional treatments such as medications and physical therapy are most widely used. However, systematic reviews conclude there is still limited evidence for the effectiveness of these treatments for neck pain, relative to low back pain, and current therapies show only modest effect sizes. The mainstay of chronic neck pain treatment is non-steroidal anti-inflammatory drugs (NSAIDs), but NSAIDs often provide suboptimal pain relief, especially when used as mono-therapy, and their adverse effects, such as gastrointestinal, renal, and cardiovascular complications, are well known. Opioids for chronic neck pain are controversial for several reasons. First, their long-term efficacy is questionable. Second, opioids are associated with several problematic side effects. Third, opioids have potential for misuse, abuse, and addiction. Fourth, between 1999 and 2008, the rate of prescription opioid overdose deaths in the US raised four-fold. Thus, when medications and physical therapy fail to relieve pain, Veterans frequently live with chronic, often debilitating, pain. Clearly, effective and safer treatments to improve the management of neck pain are needed.

The National Center for Complementary and Integrative Health (NCCIH, formerly NCCAM) defines complementary health approaches as practices or products of non-mainstream origin. Patient demand for these approaches (previously termed complementary and alternative medicine, CAM) is high. More than 30% of US adults use complementary health care approaches outside of, or integrated within, conventional treatment. Fifty-eight percent of older adults surveyed used some type of alternative treatment. Pain is the primary reason individuals turn to complementary treatments. After low back pain, neck pain is the second most common pain condition for complementary health use. Massage is the second (after chiropractic) most commonly used complementary treatment for neck pain. Complementary health approaches are especially popular and in high demand by Veterans. In a VA study, 82% of Veterans reported use of at least one complementary therapy and nearly all (99%) were willing to try such approaches for pain. Of all complementary health approaches, massage was the most preferred by Veterans. Massage's popularity derives from its patient-centered and healing-oriented approach and emphasis on the therapeutic relationship.

Safer alternatives to conventional pain treatments such as NSAIDS and opioids are needed, especially in older adults. Dr. Josephine Briggs, Director of NCCIH stated: "The need for nondrug treatment options (for pain) is a significant and urgent public health imperative." Experts also argue that clinicians and patients need to reduce reliance on pharmacological treatment. It is in this context the VA implemented the high-priority, Opioid Safety Initiative (OSI). The OSI grew out of accumulating evidence that some opioid use is unsafe and may be

contributing to harm for Veterans. In addition to reducing use of high-dose (> 200mg a day) opioids and concomitant opioids and benzodiazepines, a major goal of the OSI is to provide safer alternatives for treating chronic pain. To accomplish this latter goal, VA facilities are being encouraged to implement programs that improve access to complementary health approaches, like massage therapy. Existing studies show massage is safe for all ages--it has few risks if it is used appropriately, and serious adverse effects are rare.

In a review of complementary health approaches for neck pain, massage reduced pain and/or disability more than usual medical care (such as NSAIDs and exercise), physical therapy, or no treatment. Other systematic reviews have shown massage to be effective in the short-term for neck pain, but long-term benefits are unclear. Furthermore, massage is frequently perceived by patients as helpful. In a national survey, almost two-thirds (61%) of individuals with neck pain who used both complementary and conventional treatments perceived complementary therapies to be more helpful, whereas only 6% perceived conventional treatments to be better. A Cochrane review rated the overall quality of most massage trials for neck pain as poor, limited by small samples and lack of detail in published reports. However, recent studies by Sherman have set the standard for methodologically rigorous massage trials for chronic neck pain. In one trial, patients (N = 64) randomized to 10 weeks of massage were much more likely to achieve clinically meaningful improvements for neck pain disability compared to patients randomized to a pain self-care book. In a larger trial (N = 228), Sherman's group found that patients who received 60-minute massage sessions, 1 to 3 times weekly were more likely to reach clinically meaningful improvements on neck pain disability and pain intensity compared to patients in the control arm. In a follow up study, designed to evaluate a longer treatment period for massage, neck-related dysfunction and pain severity were assessed at 12 and 26 weeks. Patients who received booster doses of massage had improvements in both dysfunction and pain severity at 12 weeks but nonsignificant changes at 26 weeks.

Massage is theorized to work through a variety of mechanisms to relieve pain. These mechanisms include: 1) increased local blood circulation; 2) improved muscle tone; 3) increased joint flexibility; 4) heightened relaxation response; and 5) changed neuroendocrine and inflammatory status implicated in pain generation and sensitivity.

Despite its safety and potential benefits, the expense associated with massage therapy makes it inaccessible to most Veterans. The national average cost for a massage is approximately $60/hour, but varies significantly by region (urban areas are generally more expensive), setting (e.g., fitness clubs) and therapist training. Massage therapy is primarily an out-of-pocket expense that is rarely covered by health insurance and not affordable to most Veterans. While massage therapy is offered at some VA care settings it is not widely available to Veterans. While one study showed higher costs for massage compared to primary care for low back pain,[4] the cost-effectiveness of massage for neck pain has not been examined thoroughly.

Teaching informal care allies to provide massage (care ally -delivered massage) has been most commonly applied and found effective for patients with cancer. care ally -delivered massage has also been tested in the context of pediatric, obstetrical, and long-term care settings for dementia. Kozak et al demonstrated the feasibility of caregiver-given massage in 27 caregiver-Veteran dyads and found significant decreases in pain, stress/anxiety, and fatigue for Veterans with cancer (mean age 63.8 ± 10.2 years). In a larger study, Collinge recruited 97 patient/caregiver dyads (patient mean age 54.7 (SD 11.6), range 24-78 years; caregivers age range 18-82 years) to practice massage. The intervention, compared to attention control, led to decreases in patients' pain, depression, and other cancer-related symptoms. In addition, caregivers benefitted from doing active, hands-on massage. To our knowledge, care ally -

delivered massage has not been tested in Veterans with chronic non-cancer pain. We believe this is an important research gap that our study aims to fill. Caregiver-delivered massage is Veteran-centered and has promising preliminary data and implementation potential to be applied across VA since it can address system and Veteran-level barriers.

2.0 Rationale and Specific Aims

Study Aims:

1) **To compare the effect of a massage intervention (therapist-treated massage) vs. control on pain-related disability**
2) **To compare the effect of a massage intervention vs. control on secondary outcomes, including pain severity, health-related quality of life, depression, anxiety, and stress**
3) **To examine the implementation potential of the massage intervention, including facilitators and barriers, treatment and adherence, and intervention costs.**

3.0 Inclusion/Exclusion Criteria

Veterans will be eligible if they have:

1) chronic neck pain for 6 months or longer	3) access to a working telephone
	4) the ability and willingness to attend treatments
2) NDI score >=10	

Exclusion criteria will include:

1) neck pain secondary to vertebral fracture or metastatic cancer	10) moderate to severe cognitive impairment or dementia or TBI (as indicated in medical records)
2) complex neck pain (e.g., cervical radiculopathy or recent whiplash injury in the past 3 months)	11) pending neck surgery
3) potential contraindication for massage (e.g., hypersensitivity to touch)	12) involvement in ongoing pain trials or massage study
4) any professional massage therapy within the last 1 month or massage therapy specifically for neck pain within the past 3 months *excluding physical therapy, chiropractor, salon/hairdresser etc.	13) Hospitalized in the last 6 months for congestive heart failure
5) Hospitalized for psychiatric reasons in the last 3 months	14) Had a heart attack in the last 6 months
6) Had a stroke or TIA in the last 6 month	
7) Has been hospitalized for COPD or emphysema in the last 6 months	
8) Had a fracture or broken bone in neck during last 6 months	
9) active suicidal ideation (as indicated in medical records)	16) Active treatment for cancer other than skin cancer or palliative care for cancer

Access to a telephone is required because most of the outcome assessments will be conducted via phone. Exclusion criteria will be determined during the baseline eligibility survey conducted by our study team (not the patient's providers) and are designed to eliminate potential participants for whom the proposed interventions are inappropriate or for whom there may be disincentives for improvement.

As of the September 22, 2021 amendment, the TOMCATT study team is prioritizing patients for enrollment who have received a vaccine against COVID-19. The nature of the study treatment dictates that those enrolled in the TTM arm will need to have prolonged, in-person interaction with the massage therapists twice per week for 12 weeks. Therefore, we are prioritizing the enrollment of vaccinated participants to improve the safety of our research team and our study participants.

To determine if potential participants have received a vaccine against COVID-19, we will either confirm vaccination status in the medical record (if documented), or ask for this information on via recruitment letter and eligibility interview.

4.0 Enrollment/Randomization

Enrollment

Providers will be informed of TOMCATT study details and will be asked to provide signed approval so that our research team may contact their potentially eligible patients for participation in the study. The study will recruit providers at the Richard L. Roudebush VAMC and surrounding CBOC's. The research team, not the providers, will determine eligibility by applying the inclusion/exclusion criteria to potential participants during a comprehensive "eligibility interview." Potential participants will be identified by querying the VA's electronic medical record system, CPRS (Computerized Patient Record System), to create a master list of Veterans who meet the following criteria: 1) ICD 9/10 codes that identify neck pain, osteoarthritis, and musculoskeletal pain

A recruitment letter, signed by their provider, will be mailed to qualifying Veterans to describe the study. If a Veteran does not have a PCP, a separate letter signed by Matt Bair will be mailed instead. Potential participants will be contacted by phone within a week after receipt of the letter to assess eligibility and determine their interest in participating. If the Veteran is eligible, an appointment will be scheduled to obtain an IRB-approved, VA signed informed consent statement and HIPAA authorization from those who desire to participate. Consent may be collected in-person, or via Docusign accompanied by a virtual (Microsoft Teams or phone) conversation to explain consent and answer any questions about the study. The baseline interview and assessments will be conducted by a research assistant. A second method, if needed, will be in-clinic contact of potential participants by cross-referencing the CPRS list with the weekly appointment roster for each participating VA provider. A third method is self-referral by patients responding to a study advertisement displayed in hospital elevators and primary care and rehabilitation clinics. Brochures will also be placed throughout the community in places Veterans are likely to visit. This will include American Legion posts, DVA chapters, military recruiting stations, etc.

To increase recruitment pool, an email blast will be sent out to an official VA mass email list that the recipients have consented to being on. This email group is specifically targeted towards veterans enrolled in healthcare in Indiana. The address is a no-reply address and veterans will be given only phone numbers for staff to protect their privacy.

To further increase recruitment, a single-slide informative visual will be placed on televisions in the Roudebush VAMC. This visual will include a graphic, a brief description of who would be eligible, a brief description of the commitment the study entails for the veteran, a brief description of the protocol, and contact information for the study team.

In addition to these measures, the study team will place lockboxes in the primary care clinics with a small advertisement for the study, using the same slide from the television ad.

The interested participants will be able to fill out an NDI at and place it in the lockbox. Study staff will collect these at the end of the day.

Randomization

Stratified and blocked randomization will be performed. After providing written-informed consent and completing their baseline interview, participants will be randomized to one of 2 arms:

1) Therapist-treated massage (TT-M)
2) Waitlist control (WL-C)

The randomization process will be directed by Joanne Daggy, PhD (statistician) using statistical software with a random-number generator to create a list of group assignments before study recruitment begins. Randomization will be stratified by sex (men vs. women). Within strata, randomization with block sizes of 4 will be executed to ensure balance. Once an eligible participant has been screened, has signed informed consent, and has completed the baseline measures, the research assistant or project coordinator will pull the next sealed envelope. The randomization program locates the first unassigned record in the randomization list and assigns the participant to the group designated in that record. The participant identifier and date are written to the record. Dr. Daggy will remain blinded to group assignment.

5.0 Study Procedures

The intervention period will last 3 months. The baseline outcome assessment will be conducted in person or virtually (via Microsoft Teams or over the phone) and in a private space. All other outcomes will be completed in person, virtually, or mailed. If the interview is completed in person or on the phone it will occur in a private space. *Upon approval of the June 27, 2022 (A033) amendment, the study team will no longer complete 6-month interviews for participants who enroll after this date.* The length of follow-up and schedule of outcome assessments at 1, 3, and 6 months (6-months pre A033 only) (see table 2 below) are to detect three types of treatment effects: 1) "early response" (at 1 month); 2) immediate post-intervention benefits at 3 months; and 3) sustained effects at 6 months post-randomization (3 months post-intervention). Study subjects (Veterans) will be reimbursed $25 per completed outcome assessment (with 4 scheduled assessments each (baseline, 1, 3, and 6 months). Completion/payment of 6-month interviews will be for those enrolled prior to A033 approval only.

Table 2: Outcome Assessment Protocol: Measures and Schedule of Administration

Domain	**Measure**	**Items**	**Time (min)**	**Schedule**			
				BL	**1 mo**	**3 mo**	~~**6 mo**~~
Covariates	Demographics; disability compensation, comorbidity;	36	10	X			

	range of motion, treatments, BMI, medication list						
Neck pain disability	Neck Disability Index	10	3	X	X	X	~~X~~
Pain Severity	Brief Pain Inventory	10	3	X	X	X	~~X~~
Pain Interference	PROMIS—pain	4	1	X	X	X	~~X~~
Psychological	PHQ-9 Depression	9	2	X		X	~~X~~
	PROMIS-Depression	9	2	X		X	~~X~~
	GAD-7 Anxiety	7	2	X		X	~~X~~
	VA PTSD Screener	4	1	X		X	
	PTSD-PCL-17 (if screen positive)	17	5	X		X	
	Stress	10	3	X		X	
Generic HRQL	Medical Outcomes Study VR-36	36	10	X	X	X	~~X~~
Sleep	MOS Sleep Scale	12	3	X		X	
Somatic	Somatic Symptom Scale-8	8	3	X		X	~~X~~
	SSD-12	12	4	X		X	~~X~~
Pain beliefs	Pain Catastrophizing Scale	13	3	X		X	
Social support	Social Support Scale	12	2	X		X	
Treatment satisfaction	Pain-specific satisfaction	3	2		X	X	~~X~~
Intervention credibility	EXPECT Questionnaire	4	2	X		X	
Perceived Response	Global Impression of Change	1	1	X	X	X	~~X~~

<u>Therapist-treated massage</u>

Participants randomized to the therapist-treated massage (TT-M) arm will receive a standardized Swedish massage protocol tailored to chronic neck pain as used in Dr. Sherman's studies. We chose a Swedish massage protocol because they are the most widely taught and

practiced massage techniques, well defined procedurally, and safe when administered. Massage therapists will deliver the massage protocol to participants. To facilitate scheduling, improve convenience for therapists and patients, and standardize the TT-M treatment, all sessions will be delivered at approved sites at the VA or in Dr. Munk's Lab. The massage therapists will use the standard massage techniques applied to the neck region and associated trigger points. Massage sessions will involve a maximum of 60 minutes of hands-on, table time and occur up to twice a week (a frequency which balances practicality and efficacy) for 3 months. During the first massage session, the massage therapist will provide an introduction and overview of massage. A medical history with relevant diagnoses will be pulled from the patient's medical record so the massage therapist will be aware of any issues they might have to work with or around. Thereafter, therapist-treated massage will involve a standardized sequence: 1) hands-on assessment; 2) Swedish massage techniques (e.g. effleurage, pétrissage, compression) applied directly to the neck and associated trigger points; and 3) identification and treatment of compensatory patterns. While massage therapists will be permitted to use the range of Swedish massage techniques in the protocol, we will discourage them from providing self-care recommendations about postures, behavioral changes, and sleep.

Therapist-treated massage intervention: adherence

To track adherence to TT-M, we will record attendance at massage sessions. Veterans will be encouraged to call study staff if any problems arise. As above, we will define adequate adherence as completion of at least 75% (18) of massage therapy visits. Adherence will be considered as a potential moderator of treatment effect.

We acknowledge the tension between individualizing treatment which is patient-centered and aims to best help patients and standardizing to facilitate reproduction. First, massage sessions will be delivered by therapists with experience in treating neck pain and will enable therapists to develop and provide individualized treatments within a standardized protocol framework. Second, all therapists who participate will receive a training workshop from Dr. Munk to emphasize standardization of techniques used within specified timeframes of treatment intent. Third, the therapists will document treatment delivery details (techniques, time) with online, REDCap forms which will also assist with fidelity measures. Finally, in an effort to address fidelity concerns with multiple therapists adhering to the therapist delivered massage protocol framework, each study massage therapist trained and scheduled participants will have delivered sessions randomly observed and assessed by a massage assistant with the developed fidelity checklist (attached). We will randomly observe each therapist's delivered sessions.

Co-interventions

The massage intervention will complement usual care and standard medical treatments for chronic neck pain. We will assess whether TT-M participants continue massage beyond the active intervention period (e.g., 3 months) for those who enroll prior to approval of A033. Participants in all study arms will continue to be followed by their treating physicians/providers for all medical care unrelated to the trial. This includes continuation of other medications as prescribed, clinic visits, and other care as usual. Specifically, use of medications, and specialist consultations (rehabilitation, pain clinic, and orthopedics) for neck pain will be permitted (and assessed), both to adjust for co-intervention differences between arms in the analyses.

Waitlist Control Arm

Participants in the control arm will undergo outcome assessments on the same schedule (baseline, 1, 3, and 6 months) as the treatment group. Six month interviews will only be completed for participants who enroll prior to approval of A033. Participants in the waitlist

control will be instructed to continue their medical care as normal and to not begin any massage treatment during the 3-6 months of the study (dependent on enrollment date). At the completion of the final 6-month outcome (pre A033 approval) or 3-month outcome (post A033 approval) participants in the control arm will be eligible to attend a massage self-care training session with Dr. Munk. Those enrolled prior to the approval of A033 will also be offered an incentive massage to be completed by a study massage therapist.

Emailing Participants

The TOMCATT Team will utilize Azure RMS – an encryption system approved for email communication with Veterans by the VA nationally – to communicate with study participants. The TOMCATT team will use Azure RMS for consent/enrollment purposes and will use Azure RMS to email participants about their massage schedule and follow-up interviews, when needed.

Remove Care-Ally Arm

Those enrolled in the CAM arm who the study team enrolled without an ally with the intent of pairing them with a Veteran volunteer will receive four incentive massages in lieu of the CAM arm. They will be reconsented on a new form prior to this. They will also be invited to the single MT self-care session with Dr. Munk after reconsenting, which will consist of the self-care components of the CAM class.

Current CAM participants who have not yet attended a class will have three months to attend the class before it is discontinued. Serious effort will be made to reach these participants and notify them.

Current CAM participants who have already continued the class will continue as normal.

Incentive CAM Class: TTM and WLC Participants consented on the new form will be welcome to attend the new incentive class that replaces the CAM arm. It will consist of all the self-care portions of the CAM class. Participants consented on the pre-modification form will have access to the incentive CAM class, to maintain the protocol they were consented with initially. The last incentive CAM class will be held 9 months after the amendment is approved (giving participants a three month buffer to attend).

6.0 Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others

We follow local IRB guidelines for reporting adverse events. These include:

- Upon becoming aware of a death of an enrolled TOMCATT participant, which was both unanticipated and related to the research, the study team will immediately notify the IRB via verbal notification. If required, a written notice to the IRB will be submitted within 5 business days following the event

For additional oversight of massage application safety and to pre-emptively address potential concerns, Dr. Munk and massage assistants will review all treatment related notes (TT-M arm) daily

7.0 Study Withdrawal/Discontinuation

Subjects will be allowed to withdraw from the trial at any time. If a patient withdraws, we will determine the reason for withdrawal. Possible reasons will include: 1) death, 2) worsening of comorbid medical conditions making follow-up impossible, 3) treatment side

effects, and 4) other. If subjects withdraw, we will attempt to obtain their permission to complete the remaining outcome assessments. Data will be analyzed on an intent-to-treat basis.

Subjects will be removed from the TT-M intervention but allowed to continue in the study (data collection and incentives) if they a) fail to show-up or notify study personnel for the need to reschedule three times during the three month intervention period or b) demonstrate inappropriate conduct (i.e., sexual advancement, expectation, or harassment).

8.0 Statistical Considerations

Sample size and power

The TOMCATT RCT was 'paused' on enrollment, study assessments, and massages in the TTM arm (massage arm) during an almost one year time period due to underlying safety concerns of trying to provide the intervention during the COVID-19 pandemic, although the control group was only 'paused' on enrollment. This impacted 16 patients enrolled in the TTM arm, of which 8/16 had completed their 1 Month assessment. The study will now be 'unpaused' for all, in which case new patients will be randomized and enrolled to the two study arms.

The primary intention-to-treat analysis will include all participants randomized and all assessments collected prior to pause for the TTM and all assessments for the waitlist control arm. Data will be analyzed as in the original analysis plan assuming data collection points were collected at TRT END and FOLLOW-UP on same time schedule (baseline, 1M, 3M, and 6M). Since 16 subjects were paused on their treatments and it has been over a year since they received a massage, for the primary analysis these patients will be considered lost-to-follow-up. Thus, we will recruit additional subjects to account for the increased LTF rate over what was originally expected due to COVID-19.

Original modification sample size: The modified study will focus on comparison of the TT-M and the waitlist control group (WL-C). We need 100 patients per group (N = 200) by 3 months to have 80% power to detect a 0.4 SD difference in change in NDI from baseline between TT-M and control with Type I error = 0.05 for the comparison of interest: TT-M vs WL-C. All analysis will be conducted under the intention-to-treat principle. Sample size was derived based on an independent two-sample t-test which is conservative compared to the contrast from our proposed linear mixed model.

Assuming total attrition for the TTM and WL-C arm is (27+20)/(98+99) = 47/197 = 24%, we will seek to enroll a Total N = 264 (200/.76) or 132 per group in the TT-M and WL-C study groups. As we already have approximately 100 per group, with our current recruitment rate of 12 per month, we should be able to enroll an additional 64 subjects over 6 months.

New modification sample size: For the comparison of the TT-M and the waitlist control group (WL-C) we need 100 patients per group (N = 200) by 3 months to have 80% power to detect a 0.4 SD difference in change in NDI from baseline between TT-M and control with Type I error = 0.05 for the comparison of interest: TT-M vs WL-C. All analysis will be conducted under the intention-to-treat principle. Sample size was derived based on an independent two-sample t-test which is conservative compared to the contrast from our proposed linear mixed model.

Previously we assumed a total attrition for the TTM and WL-C arm of (27+20)/(98+99) = 47/197 = 24%, thus we sought to enroll a Total N = 264 (200/.76) or 132 per group in the TT-M and WL-C study groups. We will now enroll Total N = 296 (264 + 16 x 2) so that we will

have an additional 16 in the TTM arm to account for the 16 that were paused due to COVID but will also maintain the current randomization allocation. For IRB purposes, we will continue to recruit to reach at most N = 308 this would increase the 16 COVID paused to also account for potential 24% attrition (16/.76 = 22 per group). However, this is not necessarily required as the COVID paused will still be included in the linear mixed model up until their one month assessment. This should allow us to reach our sample size of 100 per group to complete the 3 month assessment.

Data analysis: Baseline characteristics of TOMCATT sample

As an RCT, we expect characteristics of study participants to be balanced across the two study arms. We will compare all baseline demographic and clinical characteristics between the treatment groups using the appropriate test (ie, ANOVA, Kruskal-Wallis test, or Chi-square test). Variables found to significantly differ will be included in subsequent regression models.

Main analysis (Aim 1) of the primary outcome (NDI total score)

All outcomes will be collected at baseline, 1, 3, and 6 months. Six-month outcomes will only be collected for those who consent prior to approval of A033. For the primary outcome of Neck Disability Index (NDI) total score, we will use a linear mixed effect model with an appropriate covariance structure to compare the treatment arm to the control arm on rate of change as well as difference in outcome at the 3-month time point. Fixed effects will include treatment, time (as categorical), and treatment by time interaction. Difference in amount of change in outcome between groups at the other time points (1 and 6 months (pre A033 only)) will also be estimated and reported. We will examine the associations among the repeated measures within subjects and use a data driven approach in determining the appropriate variance-covariance structure.[71] We will use the Šídák method to adjust for multiple comparisons. All analyses will include checking of assumptions and model fit. We plan intent-to-treat with the primary endpoint at 3 months and evaluation of "early" response at 1 month and "sustained" response at 6 months post-randomization (pre A033 only).

Analysis of secondary outcomes (Aim 2)

Since this study is not specifically powered for secondary outcomes, these results should be interpreted cautiously. Pain intensity, pain interference, health-related quality of life (HRQL), depression, anxiety, and pain cognitions are all continuous measures. These subscales will be analyzed with the same approach as the primary outcome. For the pain intensity score, we will also report a clinically relevant descriptive statistic in which we define patients with > 30% reduction from baseline as "responders." For the NDI, a "responder" will be defined as a decrease of more than 5 points from baseline. This binary outcome will be observed at 1, 3, and 6 months (pre A033 only) for each participant. A generalized linear mixed model with predictors of group, time, and their interaction will be used that also includes a random subject effect to accommodate the potential correlation among observations from the same participant. The primary contrasts of interest will be the difference in proportions at 3 months between each treatment and the control group. We will use the Šídák method to adjust for multiple comparisons. Differences in proportions between treatment groups at the other time points will also be reported. For exploratory measures regression models will be used based on data type and will include pain coping, sleep problems, satisfaction, and social support.

Moderator analyses

As a secondary analysis for the primary outcome (NDI) as well as secondary outcomes, we will test baseline anxiety (GAD-7 and PTSD) and depression (PHQ-9) as moderators. This will be done separately for each potential moderator by re-running each mixed model for primary and secondary outcomes while additionally including the moderator, the moderator by treatment group interaction, and the moderator by treatment by time interaction. The treatment by time by moderator interaction represents the moderation effect on the treatment difference. If the treatment term is significant then moderation is occurring. Testing these measures as moderators will provide insight into generalizability of the interventions. For example, if the intervention loses effect in patients with high anxiety or depression, these patients may not be suited to the intervention.

Missing data

We expect missing data in two different forms: missing by attrition and intermittent missing of observation. Attrition of < 15% is expected at the 3-month follow-up. We do not expect differential attrition between study arms. We will examine effects of missing observations due to attrition by examining patient characteristics associated with dropout. Factors associated with intermittent missing can similarly be identified. If missing data appears to be unrelated to any observed patient characteristics, and there are no obvious reasons to believe they are related to any unobserved characteristics, we will analyze the data under the assumption of missing completely at random (MCAR). If examination reveals observed factors are related to data missing, we will analyze data under the assumption of data missing at random (MAR). Multiple imputation techniques will be used to alleviate the impact of missing data. Importantly, the proposed mixed model methods for longitudinal data are appropriate if data are MCAR or MAR. However, if the pattern of missing data is nonignorable, more complex modeling approaches that model the missing data mechanism based on the EM algorithm or pattern-mixture models that include variables defined by the subject's pattern of missing data may be used. Finally, we will conduct sensitivity analyses to ensure the validity of study findings.

Data Collection for Aim 3

Aim 3 will examine the intervention implementation potential, including facilitators and barriers, and adherence, and intervention costs. Findings from this aim will help to maximize implementation potential and shorten the timeline to implementation in VA clinical settings.

Participants for Qualitative Interviews

For Veterans, the Aim 3 interviews will be conducted after the 3-month outcome assessment. We will purposefully sample Veterans with wide variations in change in pain disability (NDI total) from baseline to the 3-month assessment, and intervention adherence (e.g., number of massage sessions during the intervention period). Analysis will occur in parallel with data collection to allow sampling to theoretical saturation (i.e., no new properties, dimensions, or other qualities are seen in the data). Based on our experience and recommendations for qualitative sampling of subgroups, we expect to conduct up to 36 interviews.

Qualitative Interviews

The staff members will conduct the interviews. Interviews will last approximately 45-60 minutes and will be tailored to each respondent's role. Development of the interview guide is informed from our previous qualitative work questions will be further developed, revised, and piloted prior to beginning interviews. Interview questions will focus on perceptions of barriers and facilitators to using massage therapy and whether the massage interventions were helpful/valuable or not and why. Interviews will be audio-recorded and transcribed. Interview responses will help guide the next study as we plan for implementation while simultaneously evaluating, and working to maximize, effectiveness. We have found qualitative work like this to be highly informative in elucidating trial results.

Qualitative Data Analysis for Aim 3 Interviews

Dr. Matthias will lead the qualitative analysis, which will occur in two broad phases: open coding and focused coding. Open coding facilitates development of a code list for further analysis. In this phase, two experienced qualitative data analysts (Drs. Matthias and Bair) will independently read through selected transcripts to gain a general understanding of the data and variation across participants. Then, analysts will independently label each line of data with initial codes, or categories that reflect meanings or themes emerging from the text, and meet to discuss these interpretations. This will occur iteratively until analysts agree on emergent thematic categories (codes). In phase 2, focused coding, all transcripts will be divided evenly among analysts, who will apply the codes derived in the first analytic phase to assigned transcripts. A subset of transcripts will be coded by all analysts and discussed to ensure consistency in coding, with discrepancies resolved by consensus. NVivo 10 will facilitate data management and analysis.

Intervention costs

We will use both micro- and gross costing methods to estimate intervention costs. Applying VA Health Economics Resource Center (HERC) guidelines, we will measure intervention-related activities and their associated costs. These intervention costs will include: 1) massage therapist average salaries plus fringe; 2) study materials (DVDs, manual) provided to intervention patients; 3) parking; 4) facility overhead; and 5) professional time required for care ally - assisted massage training and supervision. These costs will allow us to calculate the cost of professional time per Veteran patient across the treatment arms. Costs will be reported in current year's dollars. Sensitivity analyses will be used to account for assumptions, including changes in intervention costs. If the treatments are found to be differentially more effective, we will perform a cost-outcome analysis (i.e., incremental cost-effectiveness). We will estimate the effect of the massage on the primary outcome (NDI). The incremental cost to achieve a clinically meaningful decrease in NDI due to massage, i.e., the cost-effectiveness ratio, is calculated as the difference in intervention costs between the two treatment arms, divided by the difference in effectiveness between groups. This data will provide useful information to VA administrators and managers about the short-term budget implications of implementing each of the interventions.

9.0 Privacy/Confidentiality Issues

Computerized files will be protected by the electronic firewall at the Indianapolis VAMC, will be kept in locked areas accessible only by authorized persons (i.e. locked offices), and will be

password protected. All data will only be accessible to the PI and research staff. We have put procedures in place which successfully minimize this risk:

- All stored electronic data will be de-identified and placed behind the VA firewall.
- All paper forms with provider participant's demographic information will be locked and secured in file cabinets only accessible by authorized study personnel in locked offices.
- All study assessments will be conducted in private locations.
- All audio recordings will saved on a secure VA computer and the original file stored on the audio recording device will be deleted immediately.
- Provider participants' names will not appear on any of the data collected, including audio recordings. All provider participants' responses will be matched with a code number only. The key to this code number will be stored in a password protected computer file, separate from other data, locked behind closed office doors accessed by the research team for this study only.

10.0 Follow-up and Record Retention

This study will last for 4 years. Records will be retained according to all applicable laws and regulations. VA research records will be archived and stored in accordance with the VHA Records Control Schedule, currently indefinitely.