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TITLE: A Randomized, Controlled Trial of Meditation Compared to Exposure Therapy and Education Control on PTSD in Veterans

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14. ABSTRACT This single-blinded, RCT will: 1) evaluate effects of Transcendental Meditation (TM) vs. Prolonged Exposure (PE) and PTSD health education control (EC), using the Clinician Administered PTSD Scale (CAPS) (primary outcome); 2) evaluate effects of TM vs. controls on PTSD symptoms (PCL-M), depressive symptoms and other psychological distress measures, quality of life, and physiological/biochemical stress markers; and 3) evaluate treatment compliance. The study will enroll 210 subjects (70 per group). The VA San Diego is the field site with testing conducted at 0 and 3 months The research will provide data on the feasibility and efficacy of TM as an alternative therapy for PTSD. Our collaborative group (Maharishi University of Management Research Institute, VA San Diego Healthcare System, University of California at San Diego) has made excellent progress in year one. Since securing IRB and DoD human subjects approvals the end of May 2012, we completed hiring all staff, finalized procedures for conducting the study, are currently on target for randomization, with 95 subjects randomized to date (target of 93) and have good treatment compliance, with over 70% treatment sessions attended. Post-testing compliance is greater than 80%.					
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INTRODUCTION

Posttraumatic stress disorder (PTSD) is a common and debilitating condition that affects up to 20% of all Veterans. PTSD is often a chronic problem for Veterans, affecting reintegration into society, family and marital relationships, sleep, employment stability, substance abuse rates, and risk for depression and suicide. Although standard treatments exist to treat PTSD, research shows that up to 50% of patients continue to have elevated symptoms. This suggests a need for developing and evaluating additional, alternative treatment options.

We are currently engaged in a collaborative research project that includes Maharishi University of Management Research Institute, VA San Diego Healthcare System, and the University of California at San Diego. This single-blinded, randomized controlled trial (RCT) will: 1) evaluate effects of Transcendental Meditation (TM) vs. Prolonged Exposure (PE) and a PTSD health education control (EC), using the Clinician Administered PTSD Scale (CAPS), as the primary outcome; 2) evaluate effects of TM vs. controls on PTSD symptoms (PCL-M), depressive symptoms and other psychological distress measures, quality of life, and physiological/ biochemical stress markers; and 3) evaluate treatment compliance. The study will enroll 210 subjects (70 per group) over four years. The intervention period for each arm is three months, with testing conducted at 0 and 3 months.

The research will provide important data on the feasibility and efficacy of the Transcendental Meditation program as an effective alternative therapy for PTSD. The results will serve to inform policy decisions on the study and application of this standardized and validated stress reduction program in Veteran populations.

BODY

The following tasks describe the actual Year 2 (Oct 1, 2013 thru Sept 30, 2014) achievements/milestones compared to the tasks originally outlined in the Statement of Work (SOW) (July, 2012, final-revised)

Task 1: Regulatory Review and Approval Processes (Completed)

Final DoD ORP approval was given for our staff to begin recruitment on May 31, 2013. This approval came after we made several human subjects-related adjustments based upon DoD ORP requests. The most significant of these requests involved receiving approval from the VASDHS IRB to do consenting over the phone prior to conducting initial phone screens. All subjects complete written informed consent, approved by the local IRB and DoD ORP, prior to baseline testing.

Task 2: Hiring and Training of Staff (Completed)

We completed the hiring and training of our three full-time staff coordinators during Year 1. After final approval from the DoD ORP, we were also able to officially hire the Prolonged Exposure study therapist – allowing us to have all of our study therapists in place.

Task 3: Development of Case Report Forms and Operation and Treatment Manuals (Completed)

We completed Case Report Forms and Operation and Treatment Manuals prior to beginning the study June 2013.

Task 4: Recruitment of Study Subjects (Consistent with Target Number)

After final DOD approval on May 31, 2013, we began recruitment of subjects. Since June 2013, we randomized (enrolled) 95 subjects, with a target goal of 93 (5.8 per month). To date, there have been approximately 250 phone screens with 155 potentially eligible, 122 consented (written consents) and completing baseline testing one, 95 completing baseline visit 2, and 95 randomized. Table 1 in the Supporting Data section shows the quarterly randomization of subjects.

Recruitment methods have included the use of posters, flyers, presentations to Veterans groups and community centers, placing information in VA and Veterans newsletters and presenting the study to VA healthcare providers for referrals. In August, we also purchased advertising space in local San Diego newspapers that contain sections targeting military populations. Weekly teleconference meetings are held on an ongoing basis with all staff and investigators, led by the initiating and partnering PIs.

Task 5: Testing of Subjects – baseline and 3-month post-testing (on target)

Baseline testing began June 2013. Through September 2014, 95 subjects, meeting eligibility criteria and completing baseline testing, were randomized (22% female; mean age= 45.5). Three-month posttesting compliance is 82.1%

Task 6: Delivery of Treatments (on target)

Through the end of September, 2014, 95 subjects have been randomized which meets our target goal. Of these, over 90% of the randomized subjects have gotten into treatment or were scheduled for their first treatment session to begin the first week of October. Treatment sessions are held at the VASDHS for all treatment arms and last approximately 60-75 minutes. Sessions are provided by trained instructors in each of the treatment arms: Transcendental Meditation, Prolonged Exposure, and PTSD Health Education, and are supervised by the research team for quality control.

No study-related adverse events have been reported to date.

Task 7: Treatment Compliance (on target)

Overall approximately 71.4% of the treatment sessions held through September 30, 2014, have been attended. Treatment sessions are held at the VASDHS for all treatment arms and last approximately 60-75 minutes. Sessions are provided by trained instructors in each of the treatment arms: Transcendental Meditation, Prolonged Exposure, and PTSD Health Education, and are supervised by the research team for quality control. For home practice, over 70% of subjects have indicated compliance with their home practice program (at least once per day). These figures satisfy the 70% milestones for treatment compliance.

Task 8: Data Entry and Management (on target)

The Access database for data entry at VASDHS was developed and completed by study statistician, Maxwell Rainforth, and pilot tested by the VA data manager in Spring 2013. Data entered and stored is under strict quality control procedures. 100% of the data received thus far has been entered. This meets our milestone established of collected data being entered.

Task 9: Data Analysis (on target)

Baseline data is presented in the Supporting Data section of this document. The data is presented by treatment arm in a blinded manner. Posttest data is not being analyzed or presented in any form per the instructions of our Data Safety and Monitoring Board. Data analysis procedures are on target.

Task 10: Overall Project Management (on target)

The initiating PI, Dr. Nidich at MUMRI, and partnering PI, Dr Rutledge at VASDHS, and their teams along with Dr. Mills at UC San Diego have been engaged in weekly or bi-monthly teleconference calls since the first month of the award, October 2012. In addition, Dr. Nidich and Dr. Rutledge frequently communicate each week on study management issues by phone and email. Other group members and staff have also frequently communicated by email and phone on a regular basis on study implementation issues, supervised by Drs. Nidich and Rutledge. Group conference calls with PIs, investigators, and staff will be ongoing throughout the trial.

Dr. Nidich from MUMRI made a site visit in July 2013 to VASDHS and had several important meetings with Dr. Rutledge, Dr. Mills, study staff, and treatment providers.

Drs. Nidich, Rutledge, Mills, and Rainforth attended both Data Safety and Monitoring Board (DSMB) meetings (2013 and 2014), chaired by the study's medical monitor, Dr. Charles Elder, M.D. Other members of the DSMB include Dr. Kerri Boutelle, psychologist, Dr. Arpi Minassian, psychologist, and Dr. Loki Natarajan, biostatistician.

Task 11: Quarterly and Annual Reports

This document represents the study's second Annual report. All previous quarterly and annual reports to the DoD were written, submitted and received in a timely manner.

KEY ACCOMPLISHMENTS

- Study recruitment began in June 2013 immediately following DOD ORP human subjects approval.
- All study staff and treatment therapists have been hired and trained as of the end of May 2013, with recruitment beginning June, 2013.
- We assembled a four-member Data Safety and Monitoring Board (DSMB) to oversee our study, with the panel meeting on July 18, 2013 in San Diego to review our study protocol. A second DSMB meeting was held on February 6, 2014. The DSMB membership is chaired by Dr. Charles Elder, M.D., the study's medical monitor, and includes two clinical psychologists, who are active

researchers and faculty at the UC San Diego Dept of Psychiatry and a biostatistician with the Dept. of Family and Preventive Medicine at UC San Diego

- Dr. Sanford Nidich, initiating PI, presented the study progress at an In-Person Meeting at Ft. Detrick, MD, on September 10, 2014.
- As of Sept 30, 2014, 95 subjects have been recruited (93 target).

REPORTABLE OUTCOMES

Due to the study being blinded, there are no reportable outcomes.

There was one journal publication on the study rationale and design and one conference presentation in Year 2.

1) Rutledge, Nidich, et al. Design and rationale of a comparative effectiveness trial evaluating Transcendental Meditation against established therapies for PTSD.

Contemporary **Clinical Trials**, 2014. <http://dx.doi.org/10.1016/j.cct.2014.07.00>

2) Gomez, M., Heppner, P., Rutledge, T., Nidich, S. et al. Suicide ideation in a sample of treatment-seeking veterans with PTSD. Military Health System Research Symposium (MHSRS), August 2014, FL.

CONCLUSION

This report summarized the study progress through Year 2. We are meeting all of our Statement of Work targets for the study. Study recruitment began on June 2013 immediately following DoD ORP human subjects approval. As of the end of September 2014, 95 subjects have been randomized, which meets our target goal for the study. A Data Safety and Monitoring Board (DSMB) meeting was held on February 6, 2014. There have been no “substantive” amendments to the study protocol. There were no study-related adverse events to date.

SUPPORTING DATA

Table 1 Overall Enrollment
Cumulative Enrollment

Quarterly Period		# Randomized	Cumulative No.	Cum. Target
From	To			
6/1/13	9/30/13	24	24	23.2
10/1/13	12/31/13	17	41	40.6
1/1/14	3/31/14	19	60	58.0
4/1/13	6/30/14	18	78	75.4
7/1/14	9/30/14	17	95	92.8

APPENDICES

1) DSMB February 6, 2014 Minutes

- Updates/ study progress
 - Study was recently awarded a UCSD Academic Senate grant for telomerase testing. Any testing outside of study protocol with outside funding does not require DoD approval
 - Recent IRB amendment approval to increase blood draw amount to conduct telomerase testing.
 - Additional funding has been allocated to provide participants initially allocated to exposure therapy or education control the option to receive free Transcendental Meditation instruction after completing the study. Subjects will also have the option to be referred to other VA treatments after completion of the 3-month study.
 - Following DSMB approval in July, 2014, the VA IRB has approved the amendment to expand the inclusion criteria to allow veterans with both military and non-military related trauma. The amendment will not be acted upon until approval by the DoD; it has not been sent to DoD due to recruitment continuing to be on target. The PIs will submit this amendment to the DoD for approval only if warranted by a change in recruitment.
- Recruitment, enrollment, retention
 - The study is currently meeting target enrollment. 48 total randomized to date (exceeding expect target of 46 for this time frame)
 - 12 week follow up data completeness:
 - 19 participants have completed post-tests; 4 participants currently in post-testing; 9 participants did not return for post-testing = 71.8% retention
 - The DSMB emphasized the importance of retaining the maximum possible number of participants for the intent to treat analysis
 - The DSMB requested that future reports describe and tabulate where possible reasons for participants' discontinuing treatment
- Adherence, compliance
 - Discussions w/ those providing intervention suggest there may be a difference in clinical response between those with more recent as opposed to remote military discharge
 - Some of the older veterans may be concerned with having service-connected benefits taken away. This may have an effect on compliance with treatment as well as interview and self-reported outcomes.
 - Some Veteran subjects may be motivated to participate in studies for personal benefit i.e. increases their opportunity to become service connected.
 - A statistical imbalance among treatment groups on time since service (discharge) is observed in the sample to date
 - The DSMB agreed with the expressed concern that this scenario has potential to confound the analysis
 - The DSMB agreed that adding a stratification variable related to years from service might be prudent and suggested that the PIs use their discretion in adding a second stratification variable (that matter was encouraged to be resolved in no later than 6 months)
 - Note: The PIs subsequent to the DSMB meeting met with the study biostatistician and decided to officially add a second stratification variable, i.e., time since service (≥ 15 years/ < 15 years). (Prior to this meeting, all investigators on the prior Monday investigator conference call had decided to add a second stratification variable and recommended that the PIs and study

statistician work out the details.) The study will now stratify on two variables at randomization: gender (female/male) and time since service (≥ 15 years/ < 15 years).

- Safety data and adverse events
 - To date, no study related unexpected serious adverse events have been reported
 - All reported adverse events are due to physical ailments and injuries and have been deemed not study related
- Summary of DSMB recommendations
 - The DSMB requested that future reports describe and tabulate where possible reasons for participants' discontinuing treatment (i.e. subject preference to one treatment arm)
 - The issue of potential confounding related to "number of years since service (discharge)" requires follow up no later than 6 months. For participants yet to be randomized, adding a stratification variable related to years from service might be prudent. The PIs, Drs. Nidich and Rutledge, subsequent to the DSMB meeting, met with the study biostatistician, Dr. Rainforth, and decided to officially add a second stratification variable, i.e., time since service (≥ 15 years/ < 15 years).
- Next meeting
 - The study investigators will submit a follow up report in 6 months. If any topics are in need for discussion, the board will reconvene via conference call @ that time.
 - Otherwise, the next DSMB meeting is anticipated for 1 year from now.
- Meeting adjourned

Respectfully submitted,

A handwritten signature in black ink, appearing to read "Charles R Elder". The signature is fluid and cursive, with the first name "Charles" being the most prominent.

Charles Elder MD MPH

DSMB Chair

2) Study Amendment for Additional Genetic Testing Approved by IRB, December, 2013

The VASDHS IRB and the study DSMB in December, 2013 approved adding a biomarker for telomerase to the study. The approved IRB amendment increases the amount of blood drawn from participants from the currently approved 10 ml to 28 ml. Blood draws occur once at baseline and once at post-treatment ~ 3 months later. The 28 ml total is a substantial relative increase but remains a small absolute total (about 1/15th of a standard pint collected at a Red Cross blood donation, for example).

Karen Eaton from the DoD (email on 12/19/13) stated that since the additional funding to conduct the genetic testing comes from a non-DoD source (University of California at San Diego) no further approval is needed from the DoD human subjects committee. "As the DoD is not funding the changes you are making to the research study, there is no requirement that the MRMC ORP HRPO review and approve the revisions. As you have your local IRB approval, you are free to move forward to implement the new procedures."

The approved IRB amendment is attached below.

DEPARTMENT OF VETERANS AFFAIRS
VA San Diego Healthcare System
3350 La Jolla Village Dr. San Diego, CA 92161
Human Research Protection Program
Institutional Review Board
(858) 642---6320

December 05, 2013

To: Thomas R Rutledge

Re: IRB Protocol # H120042 A RANDOMIZED, CONTROLLED TRIAL OF MEDITATION COMPARED TO EXPOSURE THERAPY AND EDUCATION CONTROL ON PTSD IN VETERANS

Dear Dr. Rutledge:

Your 12/02/2013 request to amend IRB protocol H120042 was reviewed and approved on 12/05/2013. This amendment included the following reported revision:

This is a follow-up to the 9/12/13 amendment concerning the addition of genetic markers to the biomarker collection. The PI has not acted on this amendment to date, first wanting to specify that the collection of the additional biomarkers will require an increase in the amount of the blood drawn from each participant (participants complete blood draws once prior to and once following treatment over a three month period). This will require an increase from the original 10 ml of blood collected to 28 ml at each of the two assessment visits.

The Informed Consent document has been revised to reflect this. Protocol application Section 9.6 now contains this updated blood draw quantity.

This amendment was reviewed and approved by the expedited review process as authorized by

38 CFR 16.110(b)(2) and VHA Handbook 1200.05 Paragraph 18a(2) following VASDHS SOPP 37 Chapter 15 Section 1.4. In the judgment of the IRB the changes do not affect the assessment of the risks and benefits of the study by substantially altering any of the following: research aims or methodology, nature of subject participation, level of risk, proposed benefits, participant population, qualifications of the research team, or the facilities available to support the safe conduct of the research.

Please note that the amendment approval date does not alter the study expiration date. A modification is given approval only to the expiration date that was received at the most recent initial or continuing review. Also, please check your most recent initial or continuing review approval letter and sure that continuing review materials are submitted approximately 45 days prior to that expirations. If this amendment modified the Informed Consent or HIPAA Authorization, the newly approved versions will be those stamped with the current approval date noted above.

Thank you for keeping us informed.

On behalf of the Institutional Review Board

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William Penny, M.D. Chair, VASDHS IRB
cc: R&D Committee