General Info

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Title: Automatic Self-transcending Meditation (ASTM) therapy versus Treatment As Usual (TAU) in late life depression: Implications for cardiovascular health and cross-fertilization across different levels of care.
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Project Members

Principal Investigator

Prefix: Dr.
Last Name: Vasudev
First Name: Akshya
Affiliation: Schulich School of Medicine and Dentistry\Psychiatry
Rank: Assistant Professor
Gender: Male
Email: akshya.vasudev@uwo.ca
Phone1: 519-667-6693
Phone2:
Fax: 519-667-6707
Mailing Address: LHSC Zone A, Door 4
Institution: London Health Sciences Centre
Country: Canada
Comments:

Others

Rank	Last Name	First Name	Affiliation	Role In Project
Assistant Professor	Burhan	Amer	Schulich School of Medicine and Dentistry\Psychiatry	Co-Investigator
Assistant Professor	Whetmore	Stephen		Co-Investigator
Resident	Maldeniya	Pramudith	Schulich School of Medicine and Dentistry\Psychiatry	Co-Investigator
	Patterson	Robert		Co-Investigator
Postdoctoral Fellow	Arena	Amanda		Co-Investigator
Postdoctoral	Amtul	Zareen		Co-

Fellow	Shoemaker	Kevin	Health Sciences\Kinesiology	investigator Other

Common Questions

1. 1. Registration Information

#	Question	Answer
1.1	Please confirm that you have reviewed the eligibility requirements for the Health Sciences Full Board application form.	Yes
1.2	Indicate the funding source for this study.	Granting Agency
1.3	Please specify the name of the funding source selected above.	AMOSO AHSC AFP INNOVATION FUND
1.4	Is this a student project?	No
1.5	Is this a multi-site study?	No
1.6	If YES has been selected in question 1.5 above, name the lead site and project leader for the study. If the study is administered by a Coordinating or Contract Research Organization (CRO) provide the name and contact information.	
1.7	Are the investigator(s) based at any of the sites below or will the study utilize any patient data, staff resources or facilities within any of these sites? (Please indicate all applicable sites and read the associated notes found in the blue information icon above)	LHSC - Victoria Hospital|LHSC - University Hospital|Regional Mental Health Care - London|Byron Family Medical Centre|Victoria Family Medical Centre|St. Joseph's Family Medical Centre
1.8	Lay Summary of the study (typically less than 5 lines).	Patients with an episode of late life depression will be randomized to Automatic self-transcending meditation (ASTM)plus Treatment as Usual (TAU) or TAU alone to assess changes in Heart Rate Variability (HRV, a measure of cardiovascular autonomic health, along with other secondary measures such as depression, anxiety and quality of life.

2. 2. Background, Methodology and Analysis

#	Question	Answer
2.1	Has the study undergone a formal scientific or peer review (i.e. CIHR, NSERC, NIH)? If yes, please attach the approval letter (or	No

	relevant correspondence).	
2.2	Outline the study rationale including relevant background information and justification. Cite references where appropriate.	LATE LIFE DEPRESSION AND CARDIOVASCULAR AUTONOMIC FUNCTION: Major depressive disorder in the elderly (in those >60 years of age), also known as late life depression (LLD), is common, disabling and associated with a high mortality rate caused by suicide as well as cardiovascular events1 compelling appropriate treatment. Research shows that in a naturalistic setting response rate to at least one antidepressant trial of adequate dose and duration alone is around 30-40%2 thereby necessitating usage of additional interventions3. Such therapies include psychological therapies, and, recently, various forms of treatments loosely defined as mind-body therapies such as biofeedback, energy healing, meditation, guided imagery, and yoga4. Mind-body therapies are being increasingly embraced by patients as they have negligible side effects, are easy to administer and display beneficial effects on the quality of life as well as comorbid anxiety. There is increasing research on the mechanisms and benefits of such therapies, however, good quality trial data is scant. It is well established that antidepressants work by mostly modifying neurotransmitter levels in the brain5. On the other hand, some mind-body therapies target multiple organ systems and hence could offer neurobiological advantages as depression is now recognised as a multi-system disorder. This is particularly relevant to the LLD population where there is increased prevalence of comorbid cardiovascular disorders 3. Hence, some mind body therapies when offered in combination with antidepressants might have a beneficial effect on both depression and the cardiovascular system. One of the ways of assessing the cardiovascular system is through measurement of various autonomic parameters i.e. heart rate, blood pressure and heart rate variability. The most commonly reported is heart rate variability (HRV) which is a manifestation of the interplay of the central nervous system and the autonomic nervous system on a beat-by-beat basis6. One of

		the ways of its estimation is by calculating the elapsed time between two consecutive waves, called R waves, on a person's electrocardiogram (ECG). A consistent finding has been that there is reduced HRV in people who have suffered a myocardial infarction (MI), and this phenomena is a predictor of subsequent cardiac arrhythmia and even death7. In addition, through previous work the PI has found that in LLD there are significant cardiovascular autonomic disturbances compared to age matched controls after controlling for various risk factors8. Other studies conducted in depression across the human life span have found similar results9,10. Hence, if there is a mind-body treatment that specifically targets autonomic dysfunction and has a positive benefit on depressive symptoms, it would be valuable to assess. The investigators would like to investigate such a therapy which has been selected based on previous reports of beneficial effects but has not been evaluated in a randomised controlled trial of LLD patients. AUTOMATIC SELF TRANSCENDING MEDITATION (ASTM): ASTM is a class of meditation that helps quiet the mind and induces physiological and mental relaxation whilst the eyes are shut. It utilizes a specific sound value (mantra) to draw attention inward and permit the mind to experience a restful but alert state of consciousness11-13. Research suggests that ASTM is easier to learn and to teach in comparison to other meditation techniques including mindfulness14. Studies of adult and elderly ASTM practitioners have documented reductions in depressive symptoms, as well as improvements in cardiovascular function among elderly with and without cardiovascular disease. A study of adults with CVD further demonstrated improvements in HRV 15-18. Research further suggests ASTM may be particularly well suited to elderly populations. In a randomized controlled trial of elderly retirement home residents which evaluated ASTM with two other meditative techniques and treatment as usual, ASTM produced significantly greater improvements in cognitive

		function, cardiovascular function and quality of life than all other treatment conditions19. A subsequent meta-analysis of all-cause mortality rates among hypertensive elderly who had participated in stress reduction interventions found that ASTM practitioners had a 30% lower cardiovascular mortality rate than four other meditative or relaxation interventions20. The investigators are currently conducting a pilot study to explore the feasibility of ASTM on HRV measurement and depressive symptoms in patients with LLD in a secondary care background (UWO HSREB #103966). Preliminary results suggest that patients can be recruited, find improvement in depressive symptoms and tolerate the therapy, confirming feasibility of a larger study through this grant. We predict that ASTM augmentation is an effective intervention that ameliorates the autonomic disturbance associated with LLD, and possibly has beneficial effects on depressive symptoms as compared to a control treatment as usual (TAU) group. REFERENCES: 1. Steffens DC, Skoog I, Norton MC, et al: Prevalence of depression and its treatment in an elderly population: the Cache County study. Archives of general psychiatry 2000; 57:601-607 2. Trivedi MH, Rush AJ, Wisniewski SR, Nierenberg AA, Warden D, Ritz L, Norquist G, Howland RH, Lebowitz B, McGrath PJ, Shores-Wilson K, Biggs MM, Balasubramani GK, Fava M; STAR*D Study Team. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. Am J Psychiatry. 2006 Jan;163(1):28-40. 3. Alexopoulos GS. Depression in the elderly. Lancet. 2005 Jun 4-10;365(9475):1961-70 4. Purohit MP, Wells RE, Zafonte R, Davis RB, Yeh GY, Phillips RS. Neuropsychiatric symptoms and the use of mind-body therapies. J Clin Psychiatry. 2013 Jun;74(6):e520-6. 5. Stahl SM, Grady MM. Differences in mechanism of action between current and future antidepressants. J Clin Psychiatry. 2003;64 Suppl 13:13-7 6. Heart rate variability for risk

		stratification of life-threatening arrhythmias. American College of Cardiology Cardiovascular Technology Assessment Committee. Journal of the American College of Cardiology 1993; 22:948-950 7. Barron HV,Viskin S: Autonomic markers and prediction of cardiac death after myocardial infarction. Lancet 1998; 351:461-462 8. Vasudev A, O'Brien JT, Tan MP, et al: A study of orthostatic hypotension, heart rate variability and baroreflex sensitivity in late-life depression. Journal of affective disorders 2011; 131:374-378 9. Gorman JM,Sloan RP: Heart rate variability in depressive and anxiety disorders. American heart journal 2000; 140:77-83 10. R R: Maharishi Mahesh Yogi's Transcendental Meditation. Primus 1994; Washington DC: 12. Toane EB: The Transcendental Meditation program. Canadian Medical Association journal 1976; 114:1095-1096 13. Travis F, Pearson C. Pure consciousness: distinct phenomenological and physiological correlates of "consciousness itself." Int J Neurosci. 2000;100(1– 4):77– 89 14. Lutz A, Slagter HA, Dunne JD, Davidson RJ. Attention regulation and monitoringin meditation. Trends Cogn Sci. 2008 Apr;12(4):163-9. 15. Eppley KR, Abrams AI, Shear J. Differential effects of relaxation techniques on trait anxiety: A meta-analysis. Journal of Clinical Psychology Volume 45, Issue 6, November 1989. 16. Paul-Labrador M, Polk M., Dwyer J, Ivan Velasquez I, Nidich, S, Rainforth M, Schneider R, et. al. Effects of a Randomized Controlled Trial of Transcendental Meditation on Components of the Metabolic Syndrome in Subjects With Coronary Heart Disease. Arch Intern Med/Vol 166, June 12, 2006. 17. Nidich, S, Mark T; Myers H; Rainforth M; Grandinetti, A, Salerno J, Gaylord-King C, Schneider, R. (2010) Change in Symptoms of Depression in Minority Subjects at Risk for CVD : Randomized Controlled Mind-Body Intervention Trials, In 31st Annual Meeting and Scientific Sessions of the Society of Behavioral Medicine, Seattle, WA. 18. Barnes VA,Orme-Johnson DW:

		Prevention and Treatment of Cardiovascular Disease in Adolescents and Adults through the Transcendental Meditation((R)) Program: A Research Review Update. Current hypertension reviews 2012; 8:227-242 19. Alexander, C. N., Langer, E. J., Newman, R. I., Chandler, H. M., and Davies, J. L. (1989). Transcendental Meditation, mindfulness, and longevity: an experimental study with the elderly. Journal of Personality and Social Psychology, 57 (6): 950–964 20. Schneider, R. H., Alexander, C. N., Staggers, F., Rainforth, M., Salerno, J. W., Hartz, A., et al. (2005). Long-term effects of stress reduction on mortality in persons =55 years of age with systemic hypertension. American Journal of Cardiology, 95 (9): 1060–1064 is a class of meditation that quiets the mind and induces physiological and mental relaxation whilst the eyes are shut. It utilizes a specific sound value (mantra) to draw attention inward and permit the mind to experience a restful but alert state of consciousness (9-11). There are many systems of meditative practices which vary widely in their cognitive procedures, goals and subsequently on their specific psycho-physiological outcomes. Based upon these differences, distinct classes of meditation have recently been identified (12, 13) MBCT belongs to the class of 'open monitoring' practices which are characterized by dispassionate, non-evaluative monitoring of ongoing thoughts, feelings, sensations and experiences. In contrast, the category of ASTM involves taking the attention to successively finer states of a thought until thought is transcended and the mind experiences 'pure awareness' itself', the screen of awareness without any object of awareness. [14].Open monitoring involves voluntary sustained attention, while ASTM involves automatic moving from attention to mental silence. According to several is recognized as ASTM easier to learn and instruct than Open Monitoring techniques (12). It also requires shorter daily practice. These factors may make ASTM particularly useful in clinically depressed populations where motivation and

		compliance with treatment are of concern. ASTM has been found to reduce stress and improve cardiovascular function in healthy adults (12), and to improve cardiovascular function, cognitive function and quality of life in elderly retirement home residents (13). However, its feasibility and effects on HRV in people with LLD has not been investigated in a randomised trial. Personal experiences of two self-paying LLD patients from the PI's clinical case load who recently completed ASTM training, as well as a study of retirement home residents (13) suggest that ASTM could be feasible, appropriately suited to their age, as well as effective in reducing their depression symptoms. STUDY JUSTIFICATION: We suspect that both ASTM would be a feasible intervention that can later be tested for its potential to ameliorate the autonomic disturbance, and possibly have beneficial effects on depressive symptoms, in LLD. If so, this technique could be offered as treatment choices in the future for patients with LLD. REFERENCES 1. Steffens DC, Skoog I, Norton MC, et al: Prevalence of depression and its treatment in an elderly population: the Cache County study. Archives of general psychiatry 2000; 57:601-607 2. Vasudev A, O'Brien JT, Tan MP, et al: A study of orthostatic hypotension, heart rate variability and baroreflex sensitivity in late-life depression. Journal of affective disorders 2011; 131:374-378 3. Gorman JM,Sloan RP: Heart rate variability in depressive and anxiety disorders. American heart journal 2000; 140:77-83 4. Kemp AH, Quintana DS, Felmingham KL, et al: Depression, comorbid anxiety disorders, and heart rate variability in physically healthy, unmedicated patients: implications for cardiovascular risk. PloS one 2012; 7:e30777 5. Kemp AH, Quintana DS, Gray MA, et al: Impact of depression and antidepressant treatment on heart rate variability: a review and meta-analysis. Biological psychiatry 2010; 67:1067-1074 6. Servant D, Logier R, Mouster Y, et al: [Heart rate variability. Applications in

		psychiatry]. L'Encephale 2009; 35:423-428 7. Heart rate variability for risk stratification of life-threatening arrhythmias. American College of Cardiology Cardiovascular Technology Assessment Committee. Journal of the American College of Cardiology 1993; 22:948-950 8. Barron HV,Viskin S: Autonomic markers and prediction of cardiac death after myocardial infarction. Lancet 1998; 351:461-462 9. http://www.artofliving.org/ca-en/meditation: 10. R R: Maharishi Mahesh Yogi's Transcendental Meditation. Primus 1994; Washington DC: 11. Toane EB: The Transcendental Meditation program. Canadian Medical Association journal 1976; 114:1095-1096 12. Lutz, A., Slagter, H. A., Dunne, J. D., & Davidson, R. J. (2008). Attention regulation and monitoring in meditation. Trends in cognitive sciences, 12(4), 163-169. 13. Luders, E., Toga, A. W., Lepore, N., & Gaser, C. (2009). The underlying anatomical correlates of long-term meditation: larger hippocampal and frontal volumes of gray matter. Neuroimage, 45(3), 672-678. Travis, F., & Pearson, C. (2000). Pure consciousness: distinct phenomenological and physiological correlates of "consciousness itself". International Journal of Neuroscience, 100(1-4), 77-89.
2.3	Study Objectives.	PRIMARY HYPOTHESIS: We hypothesise that in patients with LLD, ASTM+TAU will lead to a significant increase in HRV from baseline to end of study period as compared to TAU alone. SECONDARY HYPOTHESES: We hypothesise that ASTM+TAU will cause a) significant fall in depression scores b) significant improvement in other autonomic parameters including resting heart rate and blood pressure c) significant improvement in depression related symptom pathologies including impaired quality of life and anxiety; compared to TAU alone.
2.4	Describe the study design and methodology. Please be specific (e.g. Randomized, cohort, double blind).	STUDY DESIGN: We plan to conduct a single-centre, single blind longitudinal randomized controlled naturalistic trial. Research participants will be 96 men and women (48 in each group), 60-85 years of age, who have

		treatment resistant mild to moderate major depressive disorder (MDD). Diagnosis of MDD will be confirmed through a structured clinical interview (Structured Clinical Interview for DSM Disorder (SCID)). Participants will be recruited from primary, secondary and tertiary care centres in London, Ontario. SCREENING AND INITIAL ASSESSMENTS: Potential participants will be screened as per inclusion and exclusion criteria by the PI at the Geriatric Mental Health Program (as written in another part of the protocol). Upon selection, the following scales will be administered: interview for comorbid medical conditions (Cumulative illness rating scale- Geriatrics, CIRS-G), a screening cognitive examination (Mini Mental State Examination (MMSE)), depression severity assessment (Hamilton Depression score (HAM-D 21 items), Clinical Global Impression (CGI), self rated Geriatric Depression Scale (GDS)), anxiety (Geriatric Anxiety Inventory (GAI)), side effects (Toronto Side Effects Scale, (TSES)), Quality of Life (QOL profile seniors version (QOLPS), physical activity assessment (Physical activity scale of the elderly, PASE questionnaire) RANDOMIZATION: Participants will be randomized to either ASTM+TAU or TAU equally (1:1) using computer generated randomisation numbers available at random.org. Concealment of randomisation will be ensured by independent staff performing randomisation using a third party web based provider (http://www.sealedenvelope.com/). Computerised randomization will occur from the Geriatric Mental Health Program outpatient unit in London Health Sciences, London, Ontario. A telephone number will be available for study concerns/queries. Pre-randomized information will be stored using unique de-identifiers and downloaded on a secure database. It will not be possible to blind participants to intervention status. Outcome assessors and investigators will be blinded to treatment. It will not be possible to blind participants or staff providing treatment to the

		intervention status. TRIAL INTERVENTIONS/TREATMENT ARMS: 1. Automatic Self-Transcending meditation (ASTM): Following the initial clinical and lab measurements (common to both ASTM and control group), participants in the ASTM group will undergo ASTM training in groups of four by certified teachers under the supervision of one of the study co-investigators (RN) at a room in Victoria Hospital, LHSC or at the Lawson Building on 750 Baseline Road East. This involves participating in four, 90-120 minutes sessions each of four consecutive days. This will be followed by once weekly 45-60 minute follow up sessions for 12 weeks. In addition participants will be asked to practice ASTM at home for 20 minutes twice daily over the study period (12 weeks). Participants will be asked to log practice frequency and any other noteworthy observations in the log sheet provided to them. 2. Control Intervention: Participants randomized to control arm (Treatment as Usual, TAU) will continue to receive their treatment as usual including antidepressant medications and/or non-structured supportive psychotherapy. They will follow assessment and study procedures as listed below. Following a duration of week 12 into the study participants in TAU arm will also be offered the opportunity to learn ASTM and attend follow up meditation sessions. No study procedures will be applied or any other information collected during this period. MEDICATION ADHERENCE FOLLOW UP THROUGH 24 WEEK STUDY PERIOD: All medication types will be permitted in this study. Any dosage modifications will be recorded. Medication adherence will be monitored by pill count and history at follow up appointments. STUDY RECRUITMENT: It is expected that the study will recruit from primary secondary and tertiary care practices in London identified by the investigators at a rate of at least 2 patients per week over a period of 76 weeks allowing attainment of sample size of n=96. Advertisements about the study will be placed at key areas around the city including various

		community centres and libraries.
2.5	Indicate the inclusion criteria.	Participants will be considered eligible for inclusion in the study if they are: 1. Of either gender, between the age range of 60-85 years. 2. Have an Axis 1 diagnosis of mild to moderate major depressive disorder or bipolar disorder with HAMD-21 score of 8 to 22. 3. Consuming single agent or combination antidepressant therapy at therapeutic doses for a minimum of four weeks. 4. Of good general physical health with no severe cardiovascular disease in the past 12 months, no past history of neurological disease or seizures or history of diabetic neuropathy. 5. Sufficient hearing to be able to follow verbal instructions and able to sit without physical discomfort for 45 minutes. 6. Willing and able to attend 4 initial ASTM training sessions and 75% of weekly follow up sessions.
2.6	Indicate the exclusion criteria.	Participants will be considered ineligible for participating in the study if they are: 1. Participating in other similar studies. 2. Other significant mental health diagnosis (including Dementia, Substance dependence, Post traumatic stress disorder, panic disorder, Obsessive compulsive disorder, dissociative disorder, neurocognitive disorder and Personality disorder) 3. High risk of suicide as elicited by clinical interview. 4. Psychotic episodes within the past 12 months. 5. Recent (within the past 6 months) head trauma that required emergency care 6. Currently practicing any type of formal meditation, mindfulness or breathing techniques. 7. patients with severe cardiovascular disease in the past 12 months (myocardial infarction, stroke or TIA) as well as history of neurological disease (including Parkinson's Disease) or seizures NOTE: We are aware that patients with depression in this age group (60-85 yrs of age) have usually a number of comorbidities including hypertension, diabetes mellitus and a history of cardiovascular as well as cerebrovascular events for which they receive appropriate medications including, but not limited to, beta blockers, calcium channel blockers and antiarrhythmics. Hence, realistically speaking it would be impossible to

		exclude patients who have a history of a cardiovascular disease and are on treatment with various cardiovascular drugs that could influence the autonomic variables that we are interested in. However, the investigators are confident that by the process of randomization to the two treatment arms (ASTM+TAU and TAU alone) we shall be able to control for these variables equally to both the study arms.
2.7	Document the usual standard of care at the trial site(s) for this population (including diagnostic testing, frequency of follow up visits).	The standard of care for patients with late life depression involves starting them on an appropriate antidepressant from various classes such as SSRIs, (fluoxetine, fluoxamine, paroxetine, citalopram, escitalopram, sertraline, paroxetine), or NaSSA (mirtazapine) or Bupropion. Patients are also prescribed additional anxiolytic medications like benzodiazepines and trazodone if deemed necessary. Participants will be initiated and maintained on appropriate dosages of such medications as part of standard of care. The psychiatrist and/or his multidisciplinary team members might offer supportive therapy as part of standard of care.
2.8	Document the study procedures and any study specific testing that will be done.	Automatic self-transcending meditation treatment sessions will be conducted, details have been provided above. This is a minimally invasive treatments not routinely performed as part of standard and is done for research purposes only. Furthermore, three extra visits to the neurovascular research lab will be required as a part of this study. These involve HRV testing through ECG measurements, along with BP measurements.
2.9	Will any participant(s) be withdrawn from or denied usual therapy, or be subjected to other restrictions for any condition in order to participate in the study?	No
2.10	If YES has been selected in question 2.9 above, please explain.	
2.11	Describe the primary and secondary outcomes of this study and how they will be measured.	PRIMARY (HEART RATE VARIABILITY) OUTCOME MEASURES AT WEEK 0, 12 AND 24: Participants from both arms will be asked to report to room 402, Neurovascular Research Laboratory or the Laboratory for Brain

		and Heart Health, Labatt Health Sciences Building, Western University Campus (Only participants in the ASTM arm will be asked to attend follow up assessments at 24 weeks). 1. Heart rate will be monitored using an electrocardiogram (ECG) with three adhesive leads situated on the chest. 2. Blood pressure will be measured using a small cuff placed on a finger (Finometer) or using a wrist cuff device (Colin Pilot). These continuous measures of blood pressure will be confirmed against values obtained periodically by an automated sphygmomanometer (Dinamap). 3. Electrocardiogram: A standard electrocardiogram will be collected via small surface electrodes on the chest to determine heart rate. 4. A bellows placed around the chest will provide information on respiratory excursions. The main outcome of interest, HRV, will be calculated by standard deviation of all R-R intervals (SDNN) on ECG, root-mean square of successive differences (RMSSD), and number of R-R intervals differing by >50 m sec from adjacent intervals (NN50) in time domain analysis. All of these tasks are validated and performed in this laboratory. A number of approved HSREB protocols are in place for the same. SECONDARY OUTCOME MEASURES (WEEKS 0, 4, 8, 12, and 24): Depression and comorbid anxiety symptoms will be assessed by a blinded rater on various scales at study visit days (week 0, 4, 8, 12 and 24 weeks) (Again, only participants in the ASTM arm will be asked to attend follow up assessments at 24 weeks). These scales are (Hamilton Depression score (HAM-D 21 items), Clinical Global Impression (CGI), self rated Geriatric Depression Scale (GDS)), anxiety (Geriatric Anxiety Inventory (GAI)), Antidepressant medication adherence threshold will be set at 80% of pills consumed; other consumed medications will also be recorded. In addition other outcome measures including scales Physical activity (PASE), adverse events (TSES) and quality of life (QOLPS) will be assessed at all study visits (week 0, 4, 8, 12 and

		24 weeks). ADDITIONAL PROTOCOL CONDITIONS: Individual patients will be withdrawn from the study interventions if it appears that to continue would be deleterious for their mental health or safety. This can be determined by the patient, the treating clinician and/or the research team and will be supported by the use of the HAM-D 21 particularly if there is an increase in the score for question 18 "suicide", or an increase in total HAM-D score.
2.12	What is the local sample size?	96
2.13	What is the total sample size?	96
2.14	Is the sample size justified in the sponsor or other study protocol?	No
2.15	If YES in question 2.14 above, indicate the protocol page number. If NO, provide sample size justification.	The design for this investigation is a split-plot partial hierarchical factorial design analysis of variance with 2 primary treatment conditions (ASTM+TAU vs TAU) tested at fixed time intervals. Because the ASTM treatment is to be conducted with groups of 4 participants, sampling will be done to form random groups of four participants each which will be randomly assigned to the ASTM or Control condition. That is, participants are nested in groups that are nested in Treatment condition. The primary focus is the interaction effect of treatment on heart rate variability at Weeks 0 and 12, with the long term benefits assessed at 24 weeks. On the assumption that this effect size is medium (Cohen's f = .25), calculations (using G*Power)23 indicate that a sample size of 80 (4 in each of 20 groups) yield power estimates of .99 for both the interaction and the main effect of time. The power estimate for relevant simple main effects of time for the ASTM treatment condition is .93 (.83 Bonferroni adjusted). Simple main effects of treatment at each level of time are not expected for early time periods, but could be at 24 weeks with a significant linear by linear interaction of time and treatment. This contrast is estimated to have a power of .72 assuming a medium effect, but the effect might well be stronger with the cumulative effects of time. All secondary variables measured at the five time points will be analyzed with a similar design (i.e., a 2x5 split plot factorial design

		analysis of variance with groups crossed with time but nested in Treatment condition). With the total sample size of 80 this yields power estimates of .999 for both Time, and the Treatment x Time interaction. It is intended to test a total of 96 participants to cover a conservative estimate of 20% loss to follow up.
2.16	Describe the method(s) for data analysis.	Please see section 2.15
2.17	Is an interim analysis planned?	No
2.18	If YES to question 2.17 above, please describe.	
2.19	How will the results of this study be made public?	Peer reviewed publication|Presentation
2.20	If report to participants or other is selected above, please explain.	
2.21	Does this study include any use of deliberate deception or withholding of key information that may influence a participant's performance or response?	No
2.22	If YES in question 2.21 above, describe this process and provide justification for the planned deception or partial disclosure. Also describe how and when the participants will be debriefed. Please include the debriefing letter of information and consent.	
2.23	Are biological specimens to be taken or analyzed for the purposes of this research protocol?	No
2.24	Are any biological specimens being taken for future genetic testing or other unspecified testing or studies?	No
2.25	The subsequent use of tissue or biomaterials (except blood) originally collected for diagnostic purposes must be approved by the Department of Pathology Tissue Use Committee prior to submission to the HSREB and a copy of their approval appended to this form. If the Tissue Committee approval is not available at the time of submission to the HSREB, ethics approval will be withheld until a copy of Tissue Committee approval is received.	Not applicable

3. 3. Drugs and Natural Products

#	Question	Answer
3.1	Does the study involve drugs or natural products? If NO, please proceed to the Clinic Trials tab.	No
3.2	Is Drug 1 an investigational drug?	
3.3	Drug 1 - Generic Name	
3.4	Drug 1 - Brand Name	
3.5	Drug 1 - Dose	
3.6	Drug 1 - Frequency	
3.7	Drug 1 - Route	
3.8	Drug 1 - Duration	
3.9	Is Drug 2 an investigational drug?	
3.10	Drug 2 - Generic Name	
3.11	Drug 2 - Brand Name	
3.12	Drug 2 - Dose	
3.13	Drug 2 - Frequency	
3.14	Dose 2 - Route	
3.15	Drug 2 - Duration	
3.16	Is Drug 3 an investigational drug?	
3.17	Drug 3 - Generic Name	
3.18	Drug 3 - Brand Name	
3.19	Drug 3 - Dose	
3.20	Drug 3 - Frequency	
3.21	Drug 3 - Route	
3.22	Drug 3 - Duration	
3.23	Is Drug 4 an investigational drug?	
3.24	Drug 4 - Generic Name	
3.25	Drug 4 - Brand Name	
3.26	Drug 4 - Dose	
3.27	Drug 4 - Frequency	
3.28	Drug 4 - Route	
3.29	Drug 4 - Duration	
3.30	Is Drug 5 an investigational drug?	
3.31	Drug 5 - Generic Name	
3.32	Drug 5 - Brand Name	
3.33	Drug 5 - Dose	
3.34	Drug 5 - Frequency	
3.35	Drug 5 - Route	
3.36	Drug 5 - Duration	
3.37	Is Drug 6 an investigational drug?	

3.38	Drug 6 - Generic Name	
3.39	Drug 6 - Brand Name	
3.40	Drug 6 - Dose	
3.41	Drug 6 - Frequency	
3.42	Drug 6 - Route	
3.43	Drug 6 - Duration	
3.44	Is Drug 7 an investigational drug?	
3.45	Drug 7 - Generic Name	
3.46	Drug 7 - Brand Name	
3.47	Drug 7 - Dose	
3.48	Drug 7 - Frequency	
3.49	Drug 7 - Route	
3.50	Drug 7 - Duration	
3.51	Is Drug 8 an investigational drug?	
3.52	Drug 8 - Generic Name	
3.53	Drug 8 - Brand Name	
3.54	Drug 8 - Dose	
3.55	Drug 8 - Frequency	
3.56	Drug 8 - Route	
3.57	Drug 8 - Duration	
3.58	Is Drug 9 an investigational drug?	
3.59	Drug 9 - Generic Name	
3.60	Drug 9 - Brand Name	
3.61	Drug 9 - Dose	
3.62	Drug 9 - Frequency	
3.63	Drug 9 - Frequency	
3.64	Drug 9 - Route	
3.65	Drug 9 - Duration	
3.66	Is Drug 10 an investigational drug?	
3.67	Drug 10 - Generic Name	
3.68	Drug 10 - Brand Name	
3.69	Drug 10 - Dose	
3.70	Drug 10 - Frequency	
3.71	Drug 10 - Route	
3.72	Drug 10 - Duration	

4. 4. Clinical Trials

#	Question	Answer
4.1	Is this a clinical trial? If this is NOT a	Yes

	clinical trial, please select NO and proceed to the Risks and Benefits section.	
4.2	Proposed type of clinical trial:	Phase 3
4.3	Does this trial involve a drug, device or natural health product used for an indication outside the Health Canada Notice of Compliance (NOC) or Drug Identification Number (DIN) application or Medical Device License?	No
4.4	If YES to question 4.3 above, have you received a No Objection Letter (NOL) or comparable document from Health Canada?	
4.5	Is this a US Food and Drug Administration monitored study?	No
4.6	Has this study been or will this study be registered on a publicly accessible clinical trial registry?	Yes
4.7	If YES is specified in question 4.6 above, please indicate the registry name and registration number.	Will be registered on clinicaltrials.gov
4.8	Is there a data safety monitoring board (DSMB)? If YES, please note that you must submit the Data Safety Monitoring Committee report(s) to the Office of Research Ethics using Form 2-F-014.	No
4.9	If there is a DSMB, is it independent of the sponsor?	No
4.10	If NO in question 4.9 above, please provide justification.	
4.11	Has the drug or other therapy been evaluated in previous human trials?	Not applicable
4.12	If NO in question 4.11 above, please describe any animal studies that have led to this study. (Cite references where applicable)	
4.13	Will this trial use a placebo or active comparator?	No
4.14	If YES in question 4.13 above, please describe the placebo or active comparator and justify its inclusion. Also, please describe how the risks to participants will be minimized.	

5. 5. Risks and Benefits

#	Question	Answer
5.1	Describe any direct benefits to the study participants.	Automatic self transcending meditation participants may benefit from participating in this treatment. The technique is known to draw attention inward and permit the mind to experience a restful but alert state of consciousness. (1, 2, 3) There has been some evidence for ASTM to reduce stress and improve cardiovascular function in healthy adults(5). Also, there is documented improvement in cardiovascular function, cognitive function and quality of life in elderly retirement home residents (4). We are uncertain whether these benefits would translate to elderly depressed subjects and this is one of the purpose of our study. 1) R R: Maharishi Mahesh Yogi's Transcendental Meditation. Primus 1994; Washington DC: 2) Toane EB: The Transcendental Meditation program. Canadian Medical Association journal 1976; 114:1095-1096 3) Travis F, Pearson C. Pure consciousness: distinct phenomenological and physiological correlates of "consciousness itself." Int J Neurosci. 2000;100(1– 4):77– 89 4) Barnes VA,Orme-Johnson DW: Prevention and Treatment of Cardiovascular Disease in Adolescents and Adults through the Transcendental Meditation((R)) Program: A Research Review Update. Current hypertension reviews 2012; 8:227-242 5) Alexander, C. N., Langer, E. J., Newman, R. I., Chandler, H. M., and Davies, J. L. (1989). Transcendental Meditation, mindfulness, and longevity: an experimental study with the elderly. Journal of Personality and Social Psychology, 57 (6): 950–964 6) Karavidas MK, Lehrer PM, Vaschillo E, et al: Preliminary results of an open label study of heart rate variability biofeedback for the treatment of major depression. Applied psychophysiology and biofeedback 2007; 32:19-30 7) Siepmann M, Aykac V, Unterdorfer J, et al: A pilot study on the effects of heart rate variability biofeedback in patients with depression and in healthy subjects. Applied

		psychophysiology and biofeedback 2008; 33:195-201
5.2	Describe the potential benefits to society.	At present it is difficult to determine direct potential benefits to society.
5.3	List and describe the potential risks/harms/inconveniences of the study, including risks from radiation exposure. This information must be included in the informed consent documentation.	During study period: Automatic Self-transcending meditation, will be applied to subjects over a 12-week period. Even though there are no known direct risks of ASTM, some reported adverse effects include relaxation-induced anxiety; boredom; feeling addicted to the technique; and mild dissociation with all meditative techniques. However, such effects have been found mostly in individuals who practice meditative techniques for several years; no other short-term adverse events have been reported. At week 0 and week 12: we shall measure height, weight, ECG, pulse monitor, blood pressure measurement (with finger cuff and arm cuff), respiratory belt around ribcage (to assess breathing rate and depth) These are minimally invasive tests with no known direct risks. With the use of finger and arm cuffs possibly, with prolonged use there may be numbness and discolouration but this resolves upon removal of the cuff. ECG testing may cause some discomfort when electrodes are removed and the adhesive may cause some redness to the skin.
5.4	For the study risks listed above, describe the monitoring to be undertaken during and following the study conclusion.	All scientific instruments and the therapy modality has been previously seen to have minimal to no discomfort. All sites have access to first aid and CPR in the event of an emergency. Participants will also be asked to indicate any discomfort, at which time the appropriate adjustments will be made, including discontinuation of the experiment for that participant if necessary. Whilst participants are practicing ASTM techniques at their own homes, there is no additional perceived risks to their physical or mental health. To minimize risk of acute suicidality and acute distress, based on inclusion criteria we shall recruit patients who are considered at low risk of suicide as elicited by clinical interview. At both the initial interview and during frequent follow up interviews (4 weeks, 8 weeks and 12 weeks into

		the study period), any concerns of acute distress and active suicidality/self harm will be first of all assessed by the PI and/or his clinical team and if there is considered an imminent risk such patients will be referred to the Psychiatry Emergency (CEPS) at Victoria Hospital.
5.5	If a research participant is/or becomes pregnant, breastfeeds a child or fathers a child while in the study, does their participation in the study pose a possible risk to the fetus or child?	No
5.6	If YES is selected in question 5.5 above, please discuss these risks and indicate what monitoring will be undertaken during the study and following the study conclusion?	
5.7	If a research participant fathers a child while in the study, will access to the health records of the "pregnant" partner and/or her child be required and/or will the woman or child be monitored by this study during and/or after the pregnancy?	No

6. 6. Recruitment and Informed Consent

#	Question	Answer
6.1	Describe the method(s) for recruiting participants.	Investigators will approach their own patients/students|Investigators will receive referrals from other Healthcare providers|Advertising (i.e. poster or email or web-based). Please submit a copy of all advertisements.|Database of people who consented to future contact (please provide REB number or database name below)
6.2	If OTHER or DATABASE OF PEOPLE is selected in question 6.1 above, please specify here.	REB protocols #102574, #100749,
6.3	Will personal health information (PHI) be used to identify potential participants?	No
6.4	If PHI will be used, please describe the screening and consent process regarding PHI.	
6.5	How will potential participants be contacted? Please provide a copy of all telephone scripts and correspondence documents in the attachments tab.	In Person|Other

6.6	If OTHER is selected in question 6.5 above, please specify in this box.	A poster in various primary care offices will be used to recruit participants to our study. Posters shall be placed in various community centres and libraries as well. Please see attached poster.
6.7	Describe the process for obtaining informed consent. Please attach a copy of the Information Letter/Consent Form, Audio/Video Recording Consent Form, and the content of any telephone script and/or any other material that will be used in the informed consent process.	Please see attached Letter of information.
6.8	Indicate if the research will involve any of the following:	Patients
6.9	Will minors or persons not able to consent for themselves be included in the study?	No
6.10	If YES is selected in question 6.9 above, describe the consent process and indicate who will be asked to consent on their behalf and discuss what safeguards will be employed to ensure the rights of the research participant are protected.	
6.11	When the inability to provide an informed consent is expected to be temporary, describe what procedures will be used to regularly assess capacity and to obtain consent if the individual later becomes capable of providing consent. Alternatively, if diminished capacity is anticipated for the study population, describe the procedure used to assess capacity and obtain ongoing consent.	
6.12	List any anticipated communication difficulties:	None
6.13	Describe the procedures to address any communication difficulties (if applicable):	
6.14	Indicate what compensation, if any, will be provided to participants and include a justification for compensation.	Each participant will be reimbursed for travel costs by receiving $ 150 in total for the assessment visits.

7. 7. Confidentiality and Data Security

#	Question	Answer
7.1	Are you collecting personal identifiers for this study?	Yes

7.2	Identify any personal identifiers collected for this study. Select all that apply.	Full name|Telephone number|Email|Date of birth
7.3	Explain and justify the use of this identifier - Full name:	The name, phone number and email address of the participants will be collected so that we can contact them regarding the scheduling of the tests.
7.4	Explain and justify the use of this identifier - Initials:	
7.5	Explain and justify the use of this identifier - Health card number:	
7.6	Explain and justify the use of this identifier - Address:	
7.7	Explain and justify the use of this identifier - Full postal code:	
7.8	Explain and justify the use of this identifier - Partial postal code:	
7.9	Explain and justify the use of this identifier - Telephone number:	The name, phone number and email address of the participants will be collected so that we can contact them regarding the scheduling of the tests.
7.10	Explain and justify the use of this identifier - Email:	The name, phone number and email address of the participants will be collected so that we can contact them regarding the scheduling of the tests.
7.11	Explain and justify the use of this identifier - Family Physician:	
7.12	Explain and justify the use of this identifier - Date of birth:	
7.13	Explain and justify the use of this identifier - Partial date of birth:	For the study purposes year and month only be collected. Some participants might have the same year of birth hence additional month as an identifier will be collected.
7.14	Explain and justify the use of this identifier - Hospital number:	
7.15	Explain and justify the use of this identifier - Other:	
7.16	Where will information collected as part of this study be stored? (select all that apply)	University or Hospital network drive (specify below)|Memory stick
7.17	If required, please specify further information below.	All participant data will be kept on password protected and encrypted, secure portable media drives or on LHSC secure network servers.
7.18	If identifiable participant information is stored on a hard drive or portable device, the device must be encrypted. Describe the	Data will be encrypted and password protected through freely available software, 7-zip. www.7-zip.org/. The data contained on portable

	encryption being used.	media would be stripped of all participant identifiers.
7.19	How will you record study data?	Data will be recorded first using a case report form that is attached to this proposal. These will be kept in a locked facility in the PI's office in London. Patient identifiers will not be included in the case report file. Only participant ID included and data will remain anonymous when statistically analyzed.
7.20	Describe the coding system to protect identifiable information or explain why the data must remain identifiable.	Datasets will only have information pertaining to the participant unique code as the identifier e.g. PNS001.
7.21	How will you store and protect the master list, signed original letters of information and consent documents or other data with identifiers?	Paper file (Required Protection: Locked cabinet in locked institutional office)
7.22	If any options are selected above, please provide the specific details here.	The master list, signed letters of information and case report forms containing the personal identifiers will be kept in a locked facility in the PI's office in London, Ontario.
7.23	How will you store and protect data without identifiers?	Data will be encrypted and password protected through freely available software, 7-zip. www.7-zip.org/. The data may also be stored in flash drives that would be encrypted and password protected as well as secure LHSC servers.
7.24	If you plan to de-identify the study data, please describe the method of de-identification.	Datasets will only have information pertaining to the participant unique code as the identifier e.g. PNS001.
7.25	How long will you keep the study data?	Participant data will be kept up to a maximum of 10 years.
7.26	How will you destroy the study data after this period? (If applicable)	Study data on flash drives and other media will be wiped and formatted afterwards to ensure proper destruction. Similarly, folders on network drives will be formatted as well.
7.27	Does this study require you to send data outside of the institution where it is collected? This includes data taken off-site for analysis. Please note that Western/Robarts are considered off-site locations for hospital/Lawson based studies, and vice-versa.	Yes
7.28	Where will the data be sent?	Deidentified data will be transferred between Dr. Vasudev and his coinvestigators, Mrs. Newman, Dr. Shoemaker. Dr. Shoemaker is

		located at Western University. Mrs. Newman belongs to the Art of Living Foundation, Canada.
7.29	Does the data to be transferred include personal identifiers? If yes, a data transfer agreement may be necessary.	No
7.30	List the personal identifiers that will be included with the data sent off-site.	
7.31	How will the data be transmitted?	Secure file transfer
7.32	Please specify any additional details on data transmission below.	Data may be sent electronically to co investigators in a secure and safe format through the internet using e-mail systems of Western University or LHSC. Prior to transmittal, de-identified data will be encrypted and password protected through freely available software, 7-zip. www.7-zip.org/.
7.33	Will you link the locally collected data with any other data sets?	No
7.34	If YES is selected in question 7.33 above, identify the dataset	
7.35	If YES is selected in question 7.33 above, explain how the linkage will occur.	
7.36	If YES is selected in question 7.33 above, provide a list of data items contained in the dataset.	
7.37	Will the study data be entered into a database for future use?	No
7.38	If YES is selected in question 7.37 above, please specify where it will be stored, who the custodian will be, who will have access to the database and what security measures will be in place.	
7.39	Please list agencies/groups/persons outside of your local research team who will have access to the identifiable data and indicate why access is required.	NONE

8. 8. Conflict of Interest

#	Question	Answer
8.1	Will any investigators, members of the research teams, and/or their partners or immediate family members function as advisors, employees, officers, directors or	No

	consultants for a study-related sponsor or funding source?	
8.2	Will any investigators, members of the research team, and/or their partners or immediate family members have a direct or indirect financial interest (including patents or stocks) in the drug, device or technology employed in this research study?	No
8.3	Will any investigators, members of the research team, and/or their partners or immediate family members receive any personal benefit (apart from fees for service) as a result of, or connects to this study?	No
8.4	If YES is selected in any of the above, please describe the nature of the conflict of interest and how all conflict(s) of interest will be managed.	

9. 9. Industry Sponsored Protocols

#	Question	Answer
9.1	Is this an industry sponsored protocol?	No
9.2	Billing Information - Company Institution:	
9.3	Contact Person:	
9.4	Email of Contact Person:	
9.5	Street Address:	
9.6	City:	
9.7	Country:	
9.8	Province/State:	
9.9	Phone Number:	
9.10	Fax:	
9.11	Contract and/or protocol reference number required:	
9.12	Additional Sponsor Reference or contact information:	
9.13	Do you wish to apply for a REB Administration Fee Adjustment/Waiver?	
9.14	Do you agree to the Conditions for Industry Funded Research Investigators?	
9.15	Do you agree to provide supporting documents? (These can be added in the attachments section)	

10. 10. Confirmation of Responsibility

#	Question	Answer
10.1	I assume full responsibility for the scientific and ethical conduct of the study as described in this REB application and submitted protocol.	Yes
10.2	I agree to conduct this study in compliance with the Tri-Council Policy Statement (TCPS2), Ethical Conduct in Research Involving Humans and any other relevant regulations and guidelines.	Yes
10.3	I certify that all researchers and other personnel involved in this project at this institution are appropriately qualified and experienced or will undergo appropriate training to fulfill their role in this project.	Yes
10.4	I certify that any and all conflicts of interest have been declared.	Yes
10.5	I have obtained all necessary resource utilization signatures, and all costs associated with the use of these resources have been declared.	Yes
10.6	On behalf of my research team, I recognize the importance of maintaining the confidentiality of all personal information, including personal health information, and the privacy of individuals with respect to that information. I will ensure that the personal information is used only as necessary, to fulfill the specific research objectives and related research questions described in this application and approved by the REB. This includes all conditions and restrictions imposed by the REB govern	Yes
10.7	I will adhere to the Protocol and Informed Consent document as approved by the Health Sciences REB.	Yes
10.8	Have you exported a copy of this submission to Word using the "Export to Word" button? Note that you will be unable to submit future revisions if this is not done.	Yes

Attachments

Description	File Name	Version Date
CGI - I -Received Jan 29, 2014	ClinicalGlobalImpressionCGI-I(1).doc	08/01/2014
CIRS G-Received Jan 29, 2014	Appendix_5_CIRS_G[1].pdf	
Medication Adherence Form-Received Jan 29, 2014	Medication Adherence Record(1).docx	
HAMD21-Received Jan 29, 2014	HAMD(1).pdf	
Physical Assessment Scale for Elderly, PASE (Standardized Clinical Questionnaire)-Received Jan 29, 2014	CSM_PASE.pdf	
Geriatric Depression Scale (standardized questionnaire)-Received Jan 29, 2014	GDS(1).pdf	
original	ASTM versus TAU AMOSO protocol, January 12th 2014 final.docx	18/01/2014
Quality of Life Profile Seniors Version-Received Jan 29, 2014	QOLPS scale.pdf	
Letter of information	2 arm RN comments_ LOI ASTM vs TAU January 06 2014 final.docx	06/01/2014
Case Report File	Case Report form- ASTM versus TAU Dec 13 2013 final.docx	08/12/2013
Advertisement	ASTMvs TAU ad final.docx	18/01/2014
Geriatric Anxiety Inventory-Received Jan 29, 2014	GAI new English-USA.pdf	
Toronto Side Effects Scale-Received Jan 29, 2014	Toronto Side Effects Scale.docx	18/01/2014
original	104936 Vasudev Protocol.docx	
	104936 Vasudev.docx	
	28th Feb ASTM vs TAU ad final.docx	28/02/2014
v2, TRACKED	28th Feb 2014 REB protocol ASTM versus TAU with changes.docx	28/02/2014
	28th feb 2014 LOI ASTM vs TAU .pdf	28/02/2014
Tracked	28th feb 2014 LOI ASTM vs TAU .docx	28/02/2014
Recommendation #2	104936 Vasudev (recomm..pdf	28/03/2014
V2 Case Report form- ASTM versus TAU -TRACKED	28th Fec V2 Case Report form- ASTM versus TAU .docx	27/02/2014
V2 Case Report form- ASTM versus TAU	28th Fec V2 Case Report form- ASTM versus TAU .pdf	27/02/2014
	28th Feb Appendix ASTM Vs TAU.pdf	28/02/2014
	28th Feb Appendix ASTM Vs TAU.docx	28/02/2014

v2, including Appendix ASTM Vs TAU	28th Feb 2014 REB protocol ASTM versus TAU with changes.pdf	28/02/2014
v2	28th Feb ASTM vs TAU ad final.pdf	28/02/2014
2nd recommendation letter	104936 Vasudev (recomm..pdf	28/02/2014
	104936 Vasudev.pdf	14/02/2014
Response to board recommendation	Response to Health Science Research Ethics Board recommendations april 3rd .pdf	02/04/2014
Version 3	V3 ASTM vs TAU ad final March 31ST 2014.docx	31/03/2014
Version 3	V3 MARCH 31ST 2014 LOI ASTM vs TAU .pdf	10/03/2014
Word tracked document of version 3 advertisement	V3 ASTM vs TAU ad final March 31ST 2014.docx	31/03/2014
Word tracked document of version 3 of letter of information	V3 MARCH 31ST 2014 LOI ASTM vs TAU .docx	31/03/2014
V3 Case Report form- ASTM versus TAU	1st April V3 Case Report form- ASTM versus TAU .pdf	01/04/2014
CGI –I, version 2	v2 Clinical Global Impression Scale April 10th 2014.pdf	10/04/2014
V3 Case Report form- ASTM versus TAU-TRACKED	1st April V3 Case Report form- ASTM versus TAU .docx	01/04/2014
initial approval notice	DOC042414-04242014151641-0004.pdf	