

Study Protocol
CSP #556, "The Effectiveness of rTMS in Depressed VA Patients"
Department of Veterans Affairs Cooperative Studies Program
(VA CSP)

Principal Investigator:
Jerome A. Yesavage, MD
Director, VISN 21 MIRECC
Professor, Department of Psychiatry,
Stanford University School of Medicine
VA Palo Alto Health Care System 151Y
3801 Miranda Avenue
Palo Alto, California 94304
Telephone: 650-852-3287
Fax: 650-852-3297

Co-chairs:
J. Kaci Fairchild, Ph.D.
VA Palo Alto Health Care System 151Y
3801 Miranda Avenue
Palo Alto, CA 94304
Telephone: 650-493-5000 ext 63432
Fax: 650-852-3297

Mark S. George, MD
Ralph H. Johnson VA Medical Center
109 Bee Street
Charleston, SC
Telephone: (843) 789-7316 x5275
or 843-876-5142
Fax: 843-792-5702

IDE Sponsor:
Department of Veterans Affairs Cooperative Studies Program
Sponsor's Representative:
Anne H. Davis-Karim, PharmD
VA Cooperative Studies Program
Clinical Research Pharmacy Coordinating Center
2401 Centre Avenue SE
Albuquerque, NM 87106-4180
Phone: 505-248-3200
Fax: 505-248-3205

TABLE OF CONTENTS

VOLUME I

	Page
<u>List of Abbreviations</u>	1
<u>Executive Summary</u>	5
<u>Protocol</u>	8
I. <u>Introduction and Background</u>	8
A. <u>Importance of Treating Treatment-Resistant Major Depression (TRMD)</u>	8
B. <u>Overview of rTMS in TRMD</u>	8
C. <u>Special Considerations for Gender and Ethnic Disparities</u>	10
D. <u>Physics of rTMS</u>	11
E. <u>General Description of rTMS Procedure and Determination of Motor Threshold (MT)</u>	12
F. <u>rTMS Safety</u>	14
G. <u>Efficacy of rTMS and Meta-analyses</u>	15
H. <u>Overall Assessment of Effect Size and Assessment of Potential Clinical Impact</u>	16
I. <u>Justification of the Need within the VA</u>	17
1. <u>Assessing Effect on Suicidality</u>	18
2. <u>The Special VA Dual-Diagnoses Population</u>	18
3. <u>Economic Issues and Accessibility of Care</u>	19
J. <u>Summary Statement of Background and Rationale</u>	20
II. <u>Study Objectives</u>	21
A. <u>Primary Objective</u>	21
B. <u>Secondary Objectives</u>	21

III. <u>Outcome Measures</u>	22
A. <u>Primary</u>	22
B. <u>Secondary</u>	22
IV. <u>Study Design</u>	23
V. <u>Patient Population</u>	23
A. <u>Inclusion Criteria</u>	23
B. <u>Exclusion Criteria</u>	24
VI. <u>Methodology</u>	26
A. <u>Recruitment</u>	26
B. <u>Screening Assessments</u>	29
C. <u>Randomization to Treatment</u>	29
D. <u>Duration of the Study</u>	30
E. <u>Intervention Procedure</u>	31
F. <u>Treatment Regimen</u>	33
G. <u>Study Assessments</u>	37
H. <u>Adverse Events (AE) and Adverse Device Effects (ADE)</u>	48
I. <u>Dropouts and Follow-Up Procedures</u>	53
J. <u>Missed Visits and Study Termination</u>	54
K. <u>Follow-up Procedures for Non-Remitters and Non-Responders</u>	54
L. <u>Protocol Violations</u>	54
M. <u>Participant Compensation</u>	55
N. <u>Genetics [Section Removed]</u>	55
VII. <u>Data Management and Case Report Forms</u>	55
A. <u>Assessments, Case Report Forms & Frequencies of Collection</u>	55
B. <u>Data Collection and Data Entry</u>	55
C. <u>Study Documentation and Records Retention</u>	56
D. <u>Data Security Plan</u>	57

VIII. <u>Biostatistical Consideration</u>	58
A. <u>Sample Size</u>	58
B. <u>Analysis Plan</u>	58
C. <u>Additional Analyses</u>	59
D. <u>Assessing Size of Treatment Effect</u>	61
E. <u>Supplemental Statistical Analyses</u>	62
F. <u>Economic Analysis</u>	62
IX. <u>Quality Assurance Procedures</u>	63
A. <u>Rater Training</u>	63
B. <u>Good Clinical Practices</u>	63
X. <u>Study Management, Monitoring and Training</u>	64
A. <u>Study Management</u>	64
B. <u>Monitoring</u>	67
C. <u>Training</u>	77
XI. <u>Research Results and Confidentiality</u>	78
A. <u>Confidentiality</u>	78
B. <u>Publication of Research Results</u>	78
C. <u>Planned Publications</u>	80
XII. <u>References</u>	80

APPENDICES

Appendix A Human Rights Issues and Informed Consent	A1
Appendix B Budget	B1
Appendix C Curricula Vitae	C1
Appendix D Biostatistical and Research Data Processing Procedure	D1

VOLUME II

Appendix E Research Data Forms	E1
Appendix F Device Handling Procedures	F1
Appendix G Investigator's Brochure (Device Information Report)	G1
Appendix H List of Exclusionary Drugs	H1
Appendix I Seizures	I1
Appendix J Removed	
Appendix K rTMS Treatment Regimen	K1
Appendix L Ethics, Belmont Report	L1
Appendix M Health Economics and Cost Analysis	M1
Appendix N Selected Sites	N1
Appendix O TMS Training and Certification	O1

LIST OF ABBREVIATIONS

ACLS	Advanced Cardiac Life Support
ACNP	American College of Neuropsychopharmacology
ADE	Adverse Device Effects
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT/SGPT	Alanine Aminotransferase
AST/SGOT	Aspartate Aminotransferase
ATHF	Antidepressant Treatment History Form
BCLS	Basic Cardiac Life Support
BDI	Beck Depression Inventory
BHS	Beck Hopelessness Scale
BOMC	Blessed Memory Orientation Concentration Test
BSS	Beck Scale for Suicidal Ideation
BUN	Blood Urea Nitrogen
CAPS	Clinician Administered PTSD Scale
CBC	Complete Blood Count
CBOC	Community Based Outpatient Clinic
CFR	Code of Federal Regulations
COWA	Controlled Oral Word Association
CPR	Cardio Pulmonary Resuscitation
CPRS	Computerized Patient Record System
CRADO	Chief Research and Development Officer
CRF	Case Report Form
CRP	Clinical Research Pharmacist
CSP	Cooperative Studies Program
CSPCC	Cooperative Studies Program Coordinating Center
CSPCRPCC	Cooperative Studies Program Clinical Research Pharmacy Coordinating Center
CSSEC	Cooperative Studies Scientific Evaluation Committee
C-SSRS	Columbia – Suicide Severity Rating Scale
CT	Computerized Tomography
<u>DAST</u>	<u>Drug Abuse Screening Test</u>

DMC	Data Monitoring Committee
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders
ECT	Electroconvulsive Therapy
EDC	Electronic Data Capture
EMG	Electromyogram
FDA	Food and Drug Administration
FWA	Federal Wide Assurance
GCP	Good Clinical Practice
GCPMG	Good Clinical Practice Monitoring Group
GCPSRG	Good Clinical Practice Standards and Resource Group
HIPAA	Health Insurance Portability and Accountability Act
HRC	Human Rights Committee
HRQL	Health-related Quality of Life
HRSD	Hamilton Rating Scale for Depression
HSS	Human Subjects Subcommittee
IRB	Institutional Review Board
ITTRS	Interactive Touch Tone Randomization System
JLO	Judgment of Line Orientation
LDH	Lifetime Drinking History
LDLPFC	Left Dorsolateral Prefrontal Cortex
LFT	Liver Function Test
LSC-R	Life Stressor Checklist - revised
MADRS	Montgomery-Asberg Depression Rating Scale
MAOIs	Monoamine Oxidase Inhibitors
MAST	Michigan Alcoholism Screening Test
MCS	Mental Component Summary
MDD	Major Depression Disorder
MIRECC	Mental Illness Research, Education and Clinical Center
MRI	Magnetic Resonance Imaging
MT	Motor Threshold
MUSC	Medical University of South Carolina
NAART	North American Adult Reading Test

NIH	National Institute of Health
NIMH	National Institute of Mental Health
NP	Nurse Practitioner
ORO	Office of Research Oversight
PCC	Pharmacy Coordinating Center
PCL	PTSD Checklist
PCS	Physical Component Summary
PDR	Physician's Desk Reference
PTSD	Post-Traumatic Stress Disorder
PV	Protocol Violation
QIDS-C	Quick Inventory of Depressive Symptomatology
QOL	Quality of Life
RAVLT	Rey Auditory Verbal Learning Test
RCT	Randomized Controlled Trial
R&D	Research & Development
rTMS	Repetitive Transcranial Magnetic Stimulation
SA	Substance Abuse
SACL	Substance Abuse Checklist
SAE	Serious Adverse Event
SC	Study Coordinator
SCID-I	Structured Clinical Interview for DSM-IV Axis I Disorders
SDMT	Symbol Digits Modalities Test
SI	Site Investigator
SMART	Site Monitoring, Auditing and Resource Team
SSRI	Selective Serotonin Reuptake Inhibitors
STAXI-2	State-Trait Anger Expression Inventory -2
TBI	Traumatic Brain Injury
THQ	Trauma History Questionnaire
TLFB	Alcohol / Drug of Choice Timeline Followback
TMT	Trail Making Test
TRMD	Treatment-Resistant Major Depression
TSH	Thyroid-Stimulating Hormone

UADE	Unanticipated Adverse Device Effects
ULN	Upper Limits of Normal
VA	Veterans Affairs
VR-36	Veterans RAND 36 Item Health Survey
VISN	Veterans Integrated Service Network

VA Cooperative Study #556

THE EFFECTIVENESS OF rTMS IN DEPRESSED VA PATIENTS

EXECUTIVE SUMMARY

PURPOSE:

This study will evaluate the efficacy, safety, durability of benefits and cost-effectiveness of repetitive Transcranial Magnetic Stimulation (rTMS) in the resolution of Treatment-Resistant Major Depression (TRMD) with emphasis on the unique VA population of depressed patients that are commonly comorbid for substance abuse and/or Post-Traumatic Stress Disorder (PTSD).

HYPOTHESES:

Primary Hypothesis:

Initial Remission Rate. In VA patients with TRMD, rTMS will result in a greater remission rate (Hamilton Rating Scale for Depression (HRSD24) of ≤ 10) than sham rTMS at the end of acute treatment.

Primary Objective:

To assess the efficacy of rTMS in veterans with TRMD to bring about remission of TRMD. This reflects the new American College of Neuropsychopharmacology (ACNP) recommendation (Rush et al., 2006) that “remission” rather than “recovery” be considered the primary outcome measure in such trials since “recovery” is “highly” dependent on baseline severity measures.

Secondary Hypotheses:

1. Sustained Remission (“Recovery”) Rate. At the end of the 24 week post treatment follow-up, patients who received rTMS who remitted will be more likely to continue in remission, i.e. show “recovery,” than patients who received sham rTMS who remitted.

2. Response Rate. Active rTMS will result in a greater response rate ($\geq 50\%$ decrease in HRSD24) than sham rTMS after treatment.
3. Secondary consequences of TRMD will improve with rTMS treatment, i.e. quality of life, symptoms of PTSD and substance abuse will improve with rTMS treatment.
4. Moderators of Response. Age, severity of symptoms at baseline, type of comorbidity (PTSD, substance abuse, or both), duration of illness and prior treatment resistance may affect or “moderate” treatment response.
5. Cost Offset. TRMD patients who received active rTMS will have lower average VA costs of care following treatment than will TRMD patients who did not receive rTMS.

Secondary Objectives:

1. To evaluate the durability of benefit of rTMS in treatment of TRMD (patients receiving rTMS are more likely to remain in remission at 24 weeks post treatment than those receiving sham). This reflects the ACNP criteria for “recovery” (Rush et al., 2006) that requires “recovery” to be defined by at least 3 months of “remission”.
2. To evaluate the efficacy of rTMS in bringing about a significant decrease in depressive symptoms ($\geq 50\%$ decrease in the Hamilton Rating Scale for Depression). This is consistent with the ACNP criteria for “response” (Rush et al., 2006).
3. To determine whether depressive symptoms, suicidality, PTSD symptoms, substance abuse, cognitive function and quality of life improve with rTMS treatment.
4. To determine whether age, severity of symptoms at baseline, type of comorbidity, duration of illness, and prior treatment resistance, affect or “moderate” response to rTMS.
5. To evaluate the cost offset of rTMS in the treatment of depression in the VA Healthcare System.

Design and Methods:

Three hundred and sixty veterans diagnosed with TRMD will be enrolled at 9 VA Medical Centers over a three year period. Participants will be randomized into a double blind clinical trial to left prefrontal rTMS treatment or to sham (control) rTMS treatment (180 participants each group) for up to 30 treatment sessions. All participants will be evaluated on a wide variety of measures including cognitive, neurological and functional parameters. All will meet DSM-IV criteria for Major Depression and all will have failed at least two prior pharmacological interventions as defined by the Antidepressant Treatment History Form (ATHF) (Sackeim et al. 1990), i.e., they are TRMD patients. Veterans with PTSD or history of substance abuse will not be excluded but detailed history regarding these disorders will be obtained. Participants will also not be required to stop using anti-depressant medication. The primary dependent measure will be remission rate ($HRSD24 \leq 10$), and secondary analyses will be conducted on other indices. Comparisons between the rTMS and the sham groups will be made at the end of the acute treatment phase to test the primary hypothesis.

Protocol

I. INTRODUCTION AND BACKGROUND

A. Importance of Treating Treatment-Resistant Major Depression (TRMD)

Major Depression (MD) is prevalent in about 10% of American medical outpatients in any given year (Kaplan and Sadock 1996). Among these patients, as many as 20% respond incompletely or not at all to successive trials of multiple classes of antidepressant and mood stabilization medications, and of psychotherapy (Keller et al. 1992; Thase 2004). Thus, within the VA population, there are roughly 100,000 patients with Treatment-Resistant Major Depression (TRMD). In such cases, the general treatment strategy is usually to advance treatment delivery in a way that increases response rates, albeit at the expense of increased risks and increased side effects. One example would be the use of monoamine oxidase inhibitors (MAOIs). Another preferred treatment modality for TRMD is electroconvulsive therapy (ECT) (Anonymous 2002; Kaplan and Sadock 1996; Olfson et al. 1998). However, despite being the most effective antidepressant in the acute setting, ECT usage is limited by post-treatment amnesia and confusion, the medical risks of general anesthesia, the high costs associated with inpatient hospitalization, general apprehension about the procedure among candidate patients, and some administrative impediments (Martin et al. 2003). Such approaches may be reasonable for those depressed patients who are suicidal or who have the most severe symptoms. However, for the majority of patients with TRMD whose symptoms are more moderate, the decision to escalate treatment decisions is more difficult. Thus, new TRMD treatments are needed, preferably without major safety concerns or side effects as seen with aggressive polypharmacy or ECT.

B. Overview of rTMS in TRMD

rTMS is a method of delivering brain stimulation without the seizures or risks associated with ECT, nor the potential side effects and risks of MAOI therapy. It may offer a viable alternative to ECT. Several studies have reported response of TRMD to rTMS (Avery et al. 1999; George et al. 1997; Loo et al. 1999). Systematic review and meta-analysis of the studies to date, which are typically of a small scale, appear to show a positive effect in TRMD (Martin et al. 2003). With a minimal side effect profile, and the rarity of untoward events and side-effects

(Pascual-Leone et al. 1993; Wassermann 1997), safety concerns regarding the use of rTMS are considerably less than with ECT. Importantly, rTMS is much less expensive to administer than ECT (largely due to not requiring anesthesia) (Kozel et al. 2004), and rTMS produces no detrimental cognitive side effects (Little et al. 2000; Triggs et al. 1999). Thus, there is the potential for a significant advance in care, with associated cost savings, if rTMS were to be shown effective in treating TRMD in VA patients.

A major industry trial of rTMS in TRMD has just been completed. This randomized controlled trial involved 301 medication-free patients with TRMD and excluded patients dual-diagnosed with comorbid substance abuse (past year) or PTSD. Response and remission rates were significantly better in rTMS than in controls at the end of 6 weeks treatment, but results were smaller and not significantly better after 4 weeks treatment. Because the 4 week outcome was the a priori defined primary end point, the FDA Advisory panel reviewing this study did not accept this result as adequate support of this new indication for rTMS. Nonetheless, this trial performed the most vigorous rTMS treatment to date of any trial with a maximum of 90,000 stimuli delivered per patient with no significant adverse reactions and good evidence for efficacy after the full 6 weeks of treatment. The device used in this trial was subsequently approved (October, 2008) by the FDA.

A multi-site NIH trial (OPT-TMS) was recently completed but results are not yet available. There was, however, a new single-site NIH study completed by Avery and associates (2006). This randomized controlled trial of 68 patients with TRMD excluded patients with substance abuse in the past two years as well as patients with PTSD. Response and remission rates were significantly better in rTMS patients than in controls. Results were obtained at the end of 15 sessions after a total of only 24,000 stimuli delivered. These patients showed a substantial clinical response with a 20% remission rate compared to 3% in sham controls.

In summary, there is an increasing literature demonstrating that rTMS may be a safe and effective treatment for TRMD. Although one device has been approved by the FDA, clearly there is a need for more data, and given the unmet needs of VA patients with TRMD at risk for suicide, the VA cannot await industry efforts to fund further study since treatment of such patients is a major VA priority. Questions also remain about its applicability in VA populations that differ substantially from the population used in the industry and NIH trials.

TRMD patients typical to the VA have been excluded from both large industry and NIH studies and thus their relevance to VA patients may be limited. Data analysis by health economists at VA Perry Point found that more than 80% of VA depressives have a dual psychiatric diagnosis. Thus, there is a substantial knowledge gap relevant to the VA Mental Health mission insofar as a large proportion of VA depressives would have been excluded from both industry and NIH studies.

The proposed study is an advance and necessary for the VA because:

It will include dual-diagnosis patients.

It will include patients with some suicidal ideation.

It will include patients on antidepressant medications.

It will address some of the limitations in the industry trial by collecting main outcome measures after a minimum of 20 and a maximum of 30 sessions, as described in Section VI.E., rather than collecting all crucial data after only 4 weeks (maximum of 20 sessions) of treatment.

Furthermore, the proposed study will use a sham rTMS procedure that will be more difficult to distinguish from the actual rTMS than the approach used in the industry trial.

C. Special Considerations for Gender and Ethnic Disparities

A recent study examining the 12-month prevalence rates of Major Depression Disorder (MDD) in multiple ethnicities reported significantly different prevalence rates based on gender and ethnicity. Females (Caucasian: 12.7%; Black: 7.6%; Latino: 9.9%; Asian: 5.0%) had consistently higher rates than men (Caucasian: 7.9%; Black: 4.0%; Latino: 5.8%; Asian: 4.1%) (Gavin et al., 2010). Recent trials of rTMS using community based samples have been reflective of these prevalence rates. For example, the proportions of women participating in two recent trials of rTMS were 53% (O'Reardon, 2007) and 57% (OPT-TMS trial) respectively, which is in line with the consistent findings that MDD is more prevalent in women (Marcus et al., 2005). Additionally, these trials also reported significantly higher amounts of Caucasians (both 92%) than other ethnicities (8% "other" vs. 2% African American, 3% Asian American). Historically, ethnic minorities have presented for treatment of depression at significantly lower rates than non-Latino whites. Specifically, recent research has found that of those

experiencing a depressive disorder in the previous year, 63.7% of Latinos, 68.7% of Asians, and 58.8% of African Americans did not access mental health treatment compared to 40.2% of non-Latino whites ($p < .001$) (Alegria et al., 2009). The lower numbers of ethnic minorities represented in these rTMS trials may be reflective of the fact that fewer minorities present for mental health treatment. Major depressive disorder may also have a different symptom presentation depending on a patient's ethnic background. For example, research has shown that Hispanic cultures may present with more anxious and somatic complaints when describing depressive symptoms than other ethnic groups (U.S. Department of Health and Human Services, 2001).

D. Physics of rTMS

rTMS stimulates and induces firing in cortical neurons by producing brief pulses of an intense magnetic field, which ultimately lead to neuronal summation and depolarization (Bohning 2000). An rTMS device stores electricity in large capacitors, which when discharged, transiently creates about 3,000 amps of current. High-intensity, but extremely brief (2mS) electric power of approximately 5 million watts (5MW) is quickly switched on and off by thyristors, regulating the electromagnetic coil through the discharge of large capacitors. (Barker 1989; Barker et al. 1987; Barker et al. 1985; Bohning et al. 1997; Davey et al. 1991; Roth et al. 1991; Roth et al. 2002). It is these large but transient electric currents that create a powerful magnetic field, up to 2 Tesla, in accordance with the principles described in Maxwell's equations and Faraday's law. Thus, the magnetic field is significantly greater than that associated with common permanent magnets. The rapidly pulsing magnetic field ($\sim 30\text{KT/s}$) then travels across the scalp and skull and induces an electric field within the aqueous extracellular matrix of the brain ($\sim 30\text{V/m}$). The resultant transmembrane potential leads to summation and, at sufficient doses, action potential (Bohning 2000). Hence, with rTMS, there is no direct passage of electrical currents through the brain, as occurs in ECT.

An rTMS magnetic field consists of pulses of only 2 ms. in length, which is of significant strength only directly under the rTMS coil. For these reasons, it is accepted by most rTMS researchers that rTMS produces its effects solely through the production of electrical currents in the cortex of the brain, and secondary neuronal network augmentation. Because magnetic fields induced by rTMS decline rapidly with distance from the coil, current rTMS coils are only able to directly electrically stimulate the superficial cortex, and are not able to produce direct

electrical stimulation deep in the brain (Bohning 2000; Roth et al. 1994; Roth et al. 2002). Deep brain structures are influenced secondarily through the activation of cortical-subcortical tracts.

E. General Description of rTMS Procedure and Determination of Motor Threshold (MT)

An rTMS procedure is non-invasive and no anesthesia is required. Participants are awake and alert as an electromagnetic coil is placed over the head (See Figure 1). Participants typically notice only a loud clicking noise, and tingling sensation on the scalp. This scalp sensation results from the sound wave emitted as electricity passes through the coil, and from the rhythmic tensing of superficial nerves and scalp muscles. Routine rTMS is usually mildly uncomfortable, but in some cases, when applied over certain peripheral or cranial nerves, can be painful. The TMS treatment produces a sensation on the head that most patients tolerate without problems. The painfulness is linked to the intensity of stimulation, which varies from subject to subject because doses are based on their motor threshold. Thus some patients with very high motor thresholds receive higher dose TMS than do other patients, and there is a rough correlation of painfulness with intensity. The rate of self reported discomfort is generally low. For example, in the recent NIH OPT-TMS trial, site discomfort was reported by 18% of the patients receiving active, and 10% sham, for an average of 14% reporting this. This pain only rarely causes patients to drop out, and the NIH trial had an 88% retention rate to completion of the initial phase, with only 2-3 patients listing the painfulness as the reason for stopping.

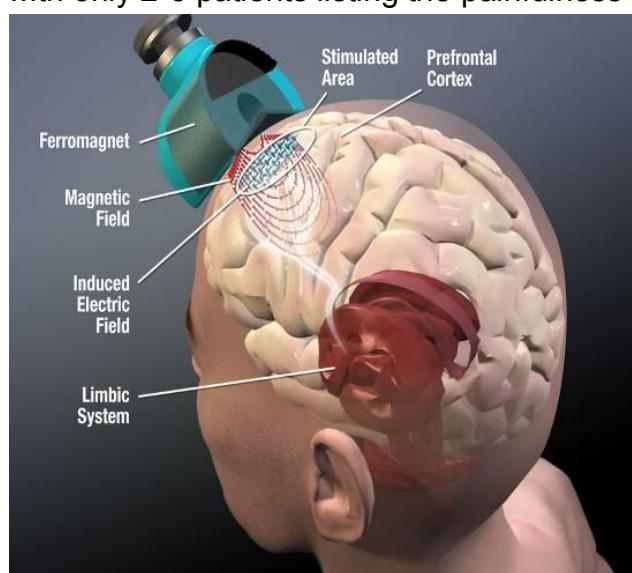


Figure 1. Diagram of simulated rTMS delivery.
(Device not necessarily that to be used in protocol.)

Another interesting comment about the painfulness is that this improves over time or goes away. In fact, often patients fall asleep in the second week while receiving the same treatment that on the first day was reported as very painful. It is not clear why this occurs. (Anderson et al. 2009).

The amount of electricity passed through the coil (and hence the power of the magnetic field generated) necessary to induce cortical firing varies from person to person, and also from one brain region to the next (Stewart et al. 2001).

To determine the necessary level of power that must be used, the establishment of a “motor threshold” (MT) is the most commonly employed technique (Kiers et al. 1993; Pridmore et al. 1998). The MT is usually defined as the minimum amount of electricity needed to produce movement in the contralateral thumb, when the coil is placed in the appropriate spot over the primary motor cortex (Pascual-Leone et al. 1993). The MT determining method has been improved with the use of an electromyograph (EMG) that is easier to teach, train, and operationalize than the visual method. In the recently completed NIH TMS trial, 3 of 4 sites used the EMG method, while one site used visual movement. The TMS vendor has incorporated a sophisticated EMG system within the TMS device and will provide the necessary software. A procedure called Maximum-Likelihood Strategy using Parameter Estimation by Sequential Testing MLS-PEST is a mathematical algorithm that is a promising alternative to traditional, time-consuming methods for determining MT. Because the EMG-PEST method is totally automated, it may prove useful in studies using MT as a quickly changing variable, as well as in large-scale clinical trials (Mishory et al. 2004). Dr. George’s Brain Stimulation Lab has developed simple algorithms to use with the EMG system that can make MT determination rather rapid (8 pulses) and highly reproducible, essentially reducing and eliminating operator error, and almost like an automatic blood pressure cuff.

rTMS patients sit upright or slightly reclined, wear ear plugs and headphones, and may close their eyes and rest during a procedure. The patient’s head and neck is fixed in place by a positioning pillow, while the rTMS coil is initially positioned by the administrator, and held in place against the scalp using a coil-holder. Because rTMS treatment produces no significant cognitive or physical side effects, patients are typically treated on an outpatient basis, driving themselves to and from their rTMS treatment appointment, and attending to their usual daily activities.

F. rTMS Safety

rTMS is generally regarded as safe and without lasting side effects. There have been no significant cognitive (Triggs, McCoy et al. 1999; Little, Kimbrell et al. 2000), neurological (Nahas, DeBrux et al. 2000) or cardiovascular sequelae reported as a result of rTMS. Patients treated with rTMS may experience discomfort at the site of stimulation due to depolarization of sensory and motor neurons in the scalp under the point of stimulation. A muscle tension headache may result in some patients (generally estimated at less than 10% of sessions), and can persist for 1-2 hours post stimulation. These headaches are never disabling and always respond to acetaminophen or ibuprofen. The primary safety concern with rTMS has been the risk of seizure induction. Eight seizures have been reported secondary to rTMS (Wassermann 1997). These have occurred in a sample size estimated to be over several thousand rTMS treatment sessions. The rTMS community has adopted and widely used the guidelines prescribing a safe interval between pulse trains (Chen, Gerloff et al. 1997) and the safety guidelines from a National Institute of Neurological Disorders and Stroke (NINDS) workshop on rTMS. These guidelines were revised in 2008 and our treatment parameters will comply with the 2008 guidelines (Rossi et al. 2009). To our knowledge there have been two publications since 1997 describing events during rTMS that might be considered seizures. Conca and colleagues reported a patient who experienced a 'pseudoabsence seizure'. It is unclear if this was a true seizure (Conca, Konig et al. 2000). Bernabeu and colleagues reported on a patient who had a seizure during rTMS. In this case, there was a brief interstimulus interval (Bernabeu, Orient et al. 2004). The risk of seizures for rTMS treatment is less than 1%.

Immediately following an rTMS session similar to the ones proposed in this protocol, participants have been tested and do not show significant neurocognitive side effects. They are thus free to return to work or drive themselves home. One report found evidence of short-term hearing loss in participants who had been exposed to rTMS (Pascual-Leone, Houser et al. 1993). A study of single pulse rTMS in humans did not find any hearing loss (Pascual-Leone, Cohen et al. 1992). To our knowledge, there has been only one study of rTMS effects on hearing in rats (Counter, Borg et al. 1990). Further animal research is needed. Of more importance to this proposal, Loo and colleagues found mild changes in auditory threshold in two depressed patients following a 2-4 week treatment regimen.(Loo, Sachdev et al. 2001) This was mild and transient, however further safety testing appears warranted. However, in

general, participants in rTMS studies wear earplugs or earphones to minimize potential ear damage. Hearing protection will be provided to all participants in this study.

Zwanzger and colleagues reported one patient who developed new delusions during a 13 day treatment course with rTMS.(Zwanzger, Ella et al. 2002). The patient had never suffered from psychotic depression in prior episodes.

The VA has long been concerned with the issue of suicide in veterans and has funded a special MIRECC in VISN 19 to perform research on this issue and with whom this protocol has been developed. A major risk in treating seriously depressed patients is the risk of suicide. Even more difficult, many of these patients have a background of having made multiple attempts. Thus, monitoring suicide attempts, even the so-called less serious “gestures”, is of paramount importance. In the recently completed industry trial suicidal ideation as indexed by the HRSD Item 3 on suicidal ideation increased in 3% of sham patients over 6 weeks and did not increase in active rTMS patients. The findings of increased suicidal ideation in some sham patients as well as the fact that the population of TRMD patients as a whole are at elevated risk for suicide require that certain preventive measures be taken (Section X.B.8). Both suicidal ideation (Section VI.G.18) and behavior (Section VI.G.16) will be monitored.

Finally, since the previous review a new study examined the effects of large doses of rTMS in young normals (Anderson et al., 2006). As part of a study to examine the effects of rTMS on sleep deprivation, healthy men were exposed to 12,960 magnetic pulses a day for up to 3 days in one week or 38,880 magnetic pulses. No significant side effects were produced.

In summary, the short-term adverse events are mild discomfort at the site of stimulation, transient tension-type headaches on the day of stimulation, and concerns about high-frequency hearing loss. A risk exists for suicide in these patients, however, extensive precautions have been planned in collaboration with experts on suicide from the VISN 19 MIRECC and it is felt that inclusion of such patients in this protocol is consistent with providing new treatment options for these difficult patients.

G. Efficacy of rTMS and Meta-analyses

There have been a large number of published trials of rTMS for the treatment of depression (Avery 2001; Avery et al. 1999; Berman et al. 2000; Feinsod et al. 1998; Garcia-Toro et al.

2001; George et al. 2000; George et al. 1997; George et al. 1995; Grisaru et al. 1994; Hoflich et al. 1993; Janicak et al. 2002; Klein et al. 1999; Kolbinger et al. 1995; Loo et al. 1999; Nahas et al. 2003; Padberg et al. 2002a; Padberg et al. 2002b; Padberg et al. 1999; Szuba et al. 2001). Because small participant pools have been a frequent limitation, several meta-analyses have been conducted in order to assess the value of rTMS as a treatment for depression, each using different base references and statistical methods (Burt et al 2002; Holtzheimer et al. 2001; Kozel and George 2002; Martin JLR et al. 2002; McNamara et al. 2001). In the majority of these trials, the participants have failed prior medication trials. Thus, the participants represented in the published literature are a pre-selected group of more difficult-to-treat patients than those seen in typical studies of new antidepressant medications. Still, the conclusion of each of these five published meta-analyses has been the same: daily prefrontal rTMS delivered over several weeks has antidepressant effects greater than that obtained with placebo. In the meta-analysis by Burt et al., of 23 published comparisons for controlled rTMS prefrontal antidepressant trials, found that rTMS had a combined effect size of 0.67, considered to be a moderate to large antidepressant effect (Burt et al 2002). In a sub-analysis, rTMS was compared with ECT. The effect size for rTMS in these studies was greater than in the studies comparing rTMS to sham, which may indicate a participant selection bias. The authors infer that rTMS may be most effective in the patients who also satisfy clinical predictors for positive ECT response.

The most rigorous meta-analysis procedure to date was conducted using the Cochrane library guidelines (Martin JLR et al. 2002). This stringent meta-analysis included 14 trials suitable for analysis and found that left prefrontal rTMS at two weeks produced significantly greater improvements in the Hamilton Rating Scale than did placebo (Martin JLR et al. 2002).

To summarize, all five rTMS meta-analyses in the published literature concur that repeated daily prefrontal rTMS for at least two weeks has antidepressant effects greater than sham.

H. Overall Assessment of Effect Size and Assessment of Potential Clinical Impact

There is a general consensus that rTMS has a clinically significant antidepressant effect. The meta-analyses above have on average, an effect size of Cohen's d of about 0.65, (moderate effect) that is comparable with that of contemporary antidepressant medications. In

randomized controlled trials of new antidepressants, for example, a small to medium effect size (0.31-0.40) is common (Thase 2001).

On a clinical level, comparisons between rTMS and ECT are frequently made, since both are interventional procedures reserved chiefly for treatment resistant depression. To understand how comparable the two procedures are, several studies have been performed in which patients referred for ECT have been randomized to receive either ECT or rTMS. Grunhaus, et al. 2000 has reported on two cohorts of patients presenting for ECT treatment, which were randomized to receive either ECT or rTMS (Gershon et al. 2003; Grunhaus et al. 2000). In these cohorts, ECT proved to be superior to rTMS for the relief of psychotic depression; however, in the absence of psychotic features, the two treatments were statistically indistinguishable. Janicak, et al. has reported a small series, finding nearly equal effect sizes in the rTMS and ECT groups, with rTMS yielding a remission rate of 46% (Janicak et al. 2002). None of the studies explicitly evaluated cognitive side effect differences between rTMS and ECT, an area that remains important for future work. Dannon, et al. has recently reported similar relapse rates in the 6 months following ECT and rTMS (Dannon et al. 2002). Pridmore (2000) reported on the antidepressant effects of standard ECT 3 times per week versus one ECT per week followed by rTMS on the other four weekdays, and found that both techniques yielded similar rates of improvement, when the rTMS was continued through three weeks (Pridmore et al. 1998). Although no detailed neuropsychological testing was performed, it is likely that the rTMS and ECT group had fewer cognitive side effects than the ECT-only group.

In summary, the literature to date suggests that rTMS clinical antidepressant effects are in a range that is comparable with other antidepressant medications, and that the therapeutic effects persist as long as those that follow ECT. A crucial, yet unanswered, question remains: Are the antidepressant effects of rTMS clinically significant in the veteran population?

I. Justification of the Need within the VA

TRMD patients typical to the VA have been excluded from both large industry and NIH studies and their relevance to VA subjects is limited.

The proposed study is an advance and necessary for the VA because:

It will include patients with some suicidal ideation.

It will include typical VA dual-diagnosis TRMD patients.

It will provide an evaluation of economic barriers and accessibility of care issues that often prevent effective treatment of TRMD and suicidal ideation in VA patients.

1. Assessing Effect on Suicidality.

The VA has a special concern regarding treating potentially suicidal veterans. The VA needs new and effective treatments for potentially suicidal patients now. In the current VA environment, ECT is sometimes difficult to obtain and requires specialized services such as anesthesiology that are not available in many settings due to economic and accessibility of care issues. It would, therefore, be of benefit to the VA to determine if rTMS may be a useful tool for the reduction of suicidal ideation in veterans since it is likely to be more available to VA clinicians than ECT.

2. The Special VA Dual-Diagnoses Population.

Although the VA population is similar to the general population in many respects, there are important differences. It also differs significantly from the populations that have been included in prior trials.

- First of all, in the national veteran population that carries a diagnosis of a depressive disorder (N= 946,342 in 2005 outpatient file), over 80% have at least one additional psychiatric diagnosis. The two most common diagnoses are PTSD (39%) and substance abuse disorder (45%).
- Our patients have had military training. For most, as a result of basic training at a minimum, this involves a greater familiarity with firearms and how to use them in a lethal manner. Of all the methods of attempted suicide, using firearms is associated with the highest lethality.
- Having served in the military means that there is a greater risk of having been exposed to combat. Combat-related PTSD has been found to be much less responsive to treatment with selective serotonin reuptake inhibitors (SSRI) than non combat PTSD in civilians, which can require an adjunctive atypical antipsychotic. (Steine, Kline, and Matloff, 2002).

- It is important to note that 17.7% of completed suicides in the VA system have a comorbid diagnosis of anxiety disorder, most with PTSD (Lehmann, McCormick, McCracken 1995), and this is significantly more common than in the civilian population.

Commonly new antidepressant treatments are initially tested in highly selected patients, free from comorbid conditions, and not taking other antidepressant medications. Results found in these 'pure' groups may or may not translate into similar effects in actual practice settings.

An example of findings that did not translate from the nonveteran to the veteran population is the lack of response of male veterans with PTSD to SSRIs. A recent Cochrane Review showed that the clinical effects of SSRIs in PTSD were significantly smaller in studies containing veterans than in studies with relatively few veterans (Stein, Ipser & Seeday, 2006). The authors state that ("The finding of a difference in the reduction of symptom severity between trials with few war veterans versus those with many was not surprising, given the general characterization of the war trauma subgroup of PTSD sufferers as more treatment resistant than other subgroups") (p. 11)

Regarding depression, the over 20 randomized controlled trials to date with rTMS for depression have used selected groups, as do the two recent major studies by industry and the NIH. However, male veterans with depression may be quite different from the "clean" subjects used in the industry and NIH trials.

In sum, the typical TRMD veteran patient is not the typical patient likely to be seen in the ongoing rTMS trials. Such dual or multiple diagnoses veteran patients will not be fully considered in the NIH and industry trials and have been associated with relatively poor response to SSRIs in both PTSD and MDD. How will typical VA patients fare with rTMS? Even when the ongoing studies are completed, there will be no data about whether and to what degree rTMS will help to treat TRMD patients suffering from multiple comorbidities.

3. Economic Issues and Accessibility of Care.

rTMS could potentially generate substantial health benefits for VA patients. For severely depressed patients who do not fully respond to medication, the primary clinical alternative is electroconvulsive therapy (ECT). ECT has limited availability in the VA, in part due to its high cost and its substantial logistical requirements. Preliminary theoretical data suggest that there

is the potential for rTMS to have a significant and drastic cost advantage (Kozel et al. 2004) over ECT. Moreover, it could be disseminated and delivered to both urban as well as to rural facilities, and in VA Hospitals as well as Community Based Outpatient Clinics (CBOCs). In sum, rTMS has the potential to dramatically improve access to effective depression care for a large number of severely mentally ill VA patients.

However, if shown safe and effective, the budgetary cost of rTMS will likely be an important consideration relating to its subsequent evaluation and implementation. rTMS is a potentially expensive therapeutic intervention. The procedure itself is administered by a nurse practitioner or psychiatrist, and it is repeated daily over the course of several consecutive weeks; devices cost up to \$50,000 per unit; and infrequent but potentially serious adverse reactions to the treatment necessitate that candidate patients undergo precautionary screening and testing. A cost analysis that thoughtfully considers the budgetary and staffing implications of rTMS within the VA infrastructure, where resources for mental health are limited, will be needed to inform assessment of the net resource impacts of offering rTMS.

Currently ECT must be provided in hospital in a Recovery Room. rTMS may be performed in an outpatient setting in, for example, Community Based Outpatient Clinics (CBOCs). Thus, development of rTMS in the VA could potentially allow treatment in settings far from tertiary care centers, such as CBOCs, and increase accessibility of this care for veterans.

J. Summary Statement of Background and Rationale

Although meta-analyses suggest there is a moderate antidepressant effect of rTMS in patients with TRMD, the rationale for the proposed research is based on the unique needs of the VA population. A randomized, double-masked, placebo-controlled study with sufficient power, which evaluates rTMS in real-world VA patients with TRMD and dual psychiatric diagnoses being treated with antidepressants, is timely and clearly warranted. This may only be possible through the VA Cooperative Study Program. **Table 1**, Comparison of rTMS Studies, summarizes the unique characteristics of the proposed study in relation to other current work in the Industry-sponsored and NIH trials.

Table 1: Comparison of rTMS Studies

	PROPOSED CSP STUDY	VA	NIMH	INDUSTRY- SPONSORED
SAMPLE SIZE	360	240	301	
ON ANTIDEPRESSANT MEDICATIONS	YES	NO		NO
AGE	18-70	21-70		18-70
COMORBIDITIES	INCLUDED	EXCLUDED		EXCLUDED
SUICIDALITY	ASSESSED	NOT ASSESSED		NOT ASSESSED
HEALTH ECONOMICS	ASSESSED	NOT ASSESSED		NOT ASSESSED
AMOUNT OF TREATMENT	20-30 SESSIONS	15-30 SESSIONS		20 SESSIONS
PRIMARY ASSESSMENT FOR REMISSION	AT END OF TREATMENT PHASE	AT END OF TREATMENT PHASE		AFTER 4 WEEKS OF TREATMENT

II. STUDY OBJECTIVES

A. Primary Objective

To assess the efficacy of rTMS in veterans to bring about remission of TRMD.

B. Secondary Objectives

1. To evaluate the durability of benefit of rTMS in treatment of TRMD (patients receiving rTMS are more likely to remain in remission at 24 weeks post treatment than those receiving sham).

2. To evaluate the efficacy of rTMS in bringing about a significant decrease in depressive symptoms (a $\geq 50\%$ decrease in the Hamilton Rating Scale for Depression).
3. To determine whether depressive symptoms, suicidality, PTSD, substance abuse, cognitive function and quality of life improve with rTMS treatment.
4. To determine whether age, severity of symptoms at baseline, comorbidity with substance abuse or PTSD, duration of illness, and prior treatment resistance, predict differential treatment response.
5. To evaluate the cost effectiveness of rTMS in the treatment of depression in the VA Healthcare System.

III. OUTCOME MEASURES

A. Primary Outcome Measures

The proportion of participants achieving remission from depression based on the Hamilton Rating Scale for Depression of ≤ 10 at the end of the acute treatment phase.

B. Secondary Outcome Measures

The selection of secondary outcome measures is based on their use in previous studies in major depression, where appropriate.

1. Depression measured by Montgomery-Asberg Depression Rating Scales (MADRS)
2. Suicide Ideation measured by Beck Scale for Suicide Ideation (BSS)
3. Depression measured by Beck Depression Inventory (BDI)
4. Quality of Life measured by the VR-36
5. Cognitive Function as measured by a neuropsychological battery

IV. STUDY DESIGN

Our hypotheses will be tested in a three and a half year randomized double blind clinical trial of rTMS in TRMD. Three hundred and sixty participants will be recruited from 9 VA sites where they have been evaluated on a wide variety of measures including cognitive, neurological and functional parameters. All will meet DSM-IV criteria for Major Depression and all will have at least two failed pharmacological interventions as defined by the ATHF (Sackeim et al. 1990), i.e. they are TRMD patients. The primary dependent measure will be remission rate (HRSD24 \leq 10) at the end of the acute treatment phase, and secondary analyses will be conducted on other indices.

V. PATIENT POPULATION

The inclusion/exclusion criteria are designed to identify patients with TRMD who exhibit a full range of the manifestations of that condition. Furthermore, the population is intended to be representative of the VA's pool of patients with TRMD.

A. Inclusion Criteria

1. Between 18 and 80 years of age.
2. Using the Structured Clinical Interview for DSM Disorders (SCID) for DSM-IV-TR (First et al. 2002) patients will be diagnosed MDD.
3. Have a HRSD24 \geq 20 no more than 7 days prior to randomization.
4. Exhibit moderate level of resistance to antidepressant treatment defined, using the ATHF (Sackeim et al. 1990), as failure of at least two adequate medication trials.
5. Duration of current episode of MDD \leq 10 years.
6. Ability to obtain a Motor Threshold (MT) (should be determined at the end of the screening process).
7. Currently under the care of a VA psychiatrist.

8. If on a psychotropic medication regimen, that regimen will be stable for at least 4 weeks prior to randomization to the study and patient will be willing to remain on a stable regimen during the acute treatment phase.
9. Has an adequately stable condition and environment to enable attendance at scheduled clinic visits.
10. For female participants, agrees to use one of the following acceptable methods of birth control
 - Complete abstinence (not having sexual intercourse with anyone)
 - An oral contraceptive (birth control pills)
 - Norplant
 - Depo-Provera
 - A condom with spermicide
 - A cervical cap with spermicide
 - A diaphragm with spermicide
 - An Intrauterine device
 - Surgical sterilization (having your tubes tied)
11. Able to read, verbalize understanding and voluntarily sign the Informed Consent Form prior to performance of any study-specific procedures or assessments.

B. Exclusion Criteria

1. Pregnant or lactating female (This is an FDA-required exclusion. In the future, if rTMS becomes a proven treatment for major depression, its safety in the context of pregnancy should be studied separately (Nahas et al. 1999).
2. Unable to be safely withdrawn, at least two-weeks prior to treatment commencement, from medications that substantially increase the risk of having

seizures. For the purpose of this study, those medications are listed in Appendix H (for example, theophylline).

3. Have a cardiac pacemaker.
4. Have an implanted device (deep brain stimulation) or metal in the brain.
5. Have a cochlear implant.
6. Have a mass lesion, cerebral infarct, increased intracranial pressure, or other active CNS disease, including a seizure disorder.
7. Known current psychosis as determined by DSM-IV or SCID (axis I, psychotic disorder, schizophrenia) or a history of a non-mood psychotic disorder.
8. Known current Bipolar I disorder as determined by SCID or a History of Bipolar I disorder.
9. Current amnestic disorders, dementia, BOMC > 10, delirium, or other cognitive disorders.
10. Current substance abuse (not including caffeine or nicotine) as determined by positive toxicology screen, or by history via SCID, within 3 months prior to screening.
11. Patients with an elevated risk of seizure due to TBI.
12. Participation in another concurrent clinical trial.
13. Patients with prior exposure to rTMS.
14. Active current suicidal intent or plan as evidenced by a score of 4 or 5 on the suicidal ideation portion of the CSSRS or the endorsement of an actual attempt, interrupted attempt, or an aborted attempt in the past 6 months. All patients will be required to establish a written safety plan involving their primary VA psychiatrist and the treatment team before entering the clinical trial (See Section X.B.8).
15. Unstable cardiac disease or recent (< 3 months previous) myocardial infarction.
16. Patient refuses to sign consent for participation in the study.

VI. METHODOLOGY

A. Recruitment

1. Target: In order to meet the target of randomizing 360 participants within three years, the Study Chairman will select 9 potential VA sites for participation based on the availability of a large number of TRMD patients with relevant co-morbidities and the willingness and ability of the site to carry out the protocol. Each site will be expected to randomize at least 40 eligible patients over the three year recruitment period of the study. The VA sites that have expressed an interest in participating in this study and who treat a substantial number of relevant TRMD patients within a 3 year period can be found in Appendix N.

2. Methods: The Site Investigator (SI) and the Study Coordinator (SC) (hired at each site to work full-time on this project) will be responsible for patient recruitment. They will work closely with the site clinical staff to insure that the purpose and scope of the study, including eligibility criteria, are fully explained at the beginning of the study. Site staff will be told who to contact to refer a potential study participant. Study participants will be selected from the entire cohort of patients referred for outpatient or inpatient psychiatric treatment at the participating sites. In consultation with the SI, the patient's referring physician will continue to manage the general psychiatric care of each of the participants. The primary care physician and SI will work together with respect to management of the subject's care while participating in the study.

3. Patient Pool: The SIs and the SCs should expect to screen in person as many as 2-3 potential patients for every eligible consenting participant and will enroll (consent) 720-800 patients with concomitant disease at the local sites. The Human Studies Subcommittee and/or IRB will review any posters or advertisements used before being posted. It is essential to maintain a flow of patients for screening throughout the three year recruitment period.

4. Recruitment Plan: Potential participants will be recruited through a number of methods. These include, but are not limited to, referral by primary providers, referral by mental health providers, flyers posted in common areas such as canteens at VA hospitals, review of the VA administrative databases containing information for both outpatient and in-patient encounters which are housed in the Austin Information Technology Center, sending IRB approved messages to providers twice a year, and posting basic information about the study in local VA SharePoint sites.

a) Provider Referral: Local study staff will work with providers at their respective medical centers to identify veterans who may be appropriate for participation in this study. These providers will be in primary care and / or mental health clinics, residential treatment facilities, or inpatient psychiatry units. It is the responsibility of the provider to discuss the project with the veteran to determine interest in participation. Should the veteran be interested in learning more about the study, the provider will offer the veteran the options of either having study staff contact the veteran directly or the veteran contact the study staff. Additionally, the provider will be given a letter and response card they can send to their veteran patients informing them about the study and offering the option either for them to contact the study staff to learn more about the study, or have the study staff contact the patient. At no time will study staff contact veterans who have not expressed their desire to be contacted.

Study staff will be mindful of the constraints of recruiting from inpatient units, given that those who are involuntarily hospitalized cannot give consent, and, thus are ineligible to participate. However, should veterans be released and express interest in participating, s/he will be eligible for screening.

Study staff will conduct a basic though highly structured eligibility screen using the VA's Computerized Patient Record System (CPRS). This screen is based solely on our inclusion/exclusion criteria.

Veterans will be scheduled for the informed consent, initial screening procedure and baseline assessments.

- b) Advertisements, flyers, brochures: Approved media such as these will be placed in high visibility areas at each site to recruit possible participants.
- c) Review of VA Administrative Databases: The Chairman's Office will work with appropriate personnel with approved access to these databases to identify potential participants. This identification will occur through a searching of relevant diagnostic and procedure codes that are drawn from our inclusion /exclusion criteria. These lists will be provided to the appropriate local study staff who will be responsible for a more focused evaluation of these records in CPRS. For those veterans passing this level of review, study staff will contact the veteran's primary provider who may then discuss project with

the veteran. Just as in the provider referral situations, the provider will offer interested veterans the options of either having study staff contact them directly or they can contact the study staff. Again, at no time will study staff contact veterans who have not expressed their desire to be contacted. If passing initial eligibility, will be scheduled for the informed consent, initial screening procedure and baseline assessments.

d) Sending messages to providers: E-mails sharing basic study information may be sent to providers twice a year. Model language includes, “Are you looking for an alternate option for your patients with Major Depression Disorder (MDD) who have failed at least 2 drug therapies? Consider referring your patient to the TMS Depression Study (CSP 556: *The Effectiveness of rTMS (repetitive transcranial magnetic stimulation) in Depressed Patients.*”

For details, go to <http://clinicaltrials.gov/ct2/show/NCT01191333> or contact [insert name(s) and title(s) of study team member(s) and their contact information]

e) Posting study information on SharePoint sites: Basic information about the study as in 4d above may be placed in local VA SharePoint sites such as Mental Health, General Medicine and Women’s Health.

f) Recruitment postcards will be sent by a direct marketing company, who will generate a mailing list of veterans who live near the study sites. Interested veterans will contact either their Mental Health Provider or the VA rTMS study team for questions or more information.

5. Minorities and Women: Because the VA population is largely male, the proportion of females enrolled will not be representative of actual prevalence rates. Although most recruitment will occur in mental health clinics, recruitment within women’s health clinics will be used to try to maximize the enrollment of eligible women. Ethnic and racial minorities are well-represented in the VA population and study staff will be trained to recognize the variations in symptom presentation characteristic of ethnic and racial minorities so that potential participants from these groups will not be excluded.

B. Screening Assessments

Patients who are screened for possible eligibility for the study will be listed on the Patient Screening Log. After the patient signs the Informed Consent Form, the screening procedures and assessments can be initiated. A template of the Informed Consent Form can be found in Appendix A. The screening phase will last between two and four weeks to allow adequate time for all of the assessments to be completed, to assure the patient's capacity and willingness to participate in the study and to ensure that all patients have HRSD24 scores above entry criteria for the study within seven days prior to randomization. If the SI feels that the patient may not be capable of giving informed consent, the SI may request a competency evaluation using the VA standard clinical protocol. All assessments and their frequencies of administration are listed in Table 2 in Protocol section VI.G. Although screening data will not be used in the primary analysis, it will be retained to determine if participants who entered the study were comparable to those who were excluded.

C. Randomization to Treatment

Patients who sign the Informed Consent Form and meet the study eligibility criteria will be enrolled into the study and will be randomized into one of 2 treatment groups: rTMS or sham rTMS. Patients who fail screening may be re-screened at a later time at the discretion of the site investigator.

To randomize a patient into the study, the SI or the SC will submit the electronic randomization form. This computerized system, after verifying eligibility, will randomize a patient to either the rTMS or to the sham rTMS treatment group. A non-sequential treatment number will be assigned. This unique treatment number will be key entered into the device which will be associated with a treatment assignment and will enable the rTMS device to deliver the appropriate treatment (active or sham) to each patient. Every attempt will be made to randomize a participant so that he/she will receive his/her first rTMS treatment as soon as possible after randomization. Non-sequential treatment numbers will be assigned to ensure that investigators cannot initiate a participant on treatment before randomization. An adaptive randomization scheme will be used so that approximately equal numbers of patients will be randomized to each treatment group within several important subsets. These subsets include patients with a substance abuse disorder and patients with PTSD. Enrolling site will also be

incorporated into the adaptive randomization scheme. A “biased coin” procedure will be used to make an assignment that will improve overall balance more likely than an assignment that will not (Efron 1971). Imbalance will be calculated by summing the marginal totals for these three factors for each treatment group and calculating the difference, D. If the imbalance is less than three, assignments will be made with equal probability; otherwise, the probability of assigning to the group that will increase imbalance will be $1/D$. This approach will be incorporated within the electronic data capture system.

D. Duration of the Study

The duration of the study will be three and a half years, with a three year enrollment period. Each participant will be in the trial for a total of approximately 29-39 weeks (2-4 weeks screening, 4-11 weeks acute treatment phase and 24 week follow-up phase).

E. Intervention Procedure

The overview of the experimental design and procedures is presented in Figure 2.

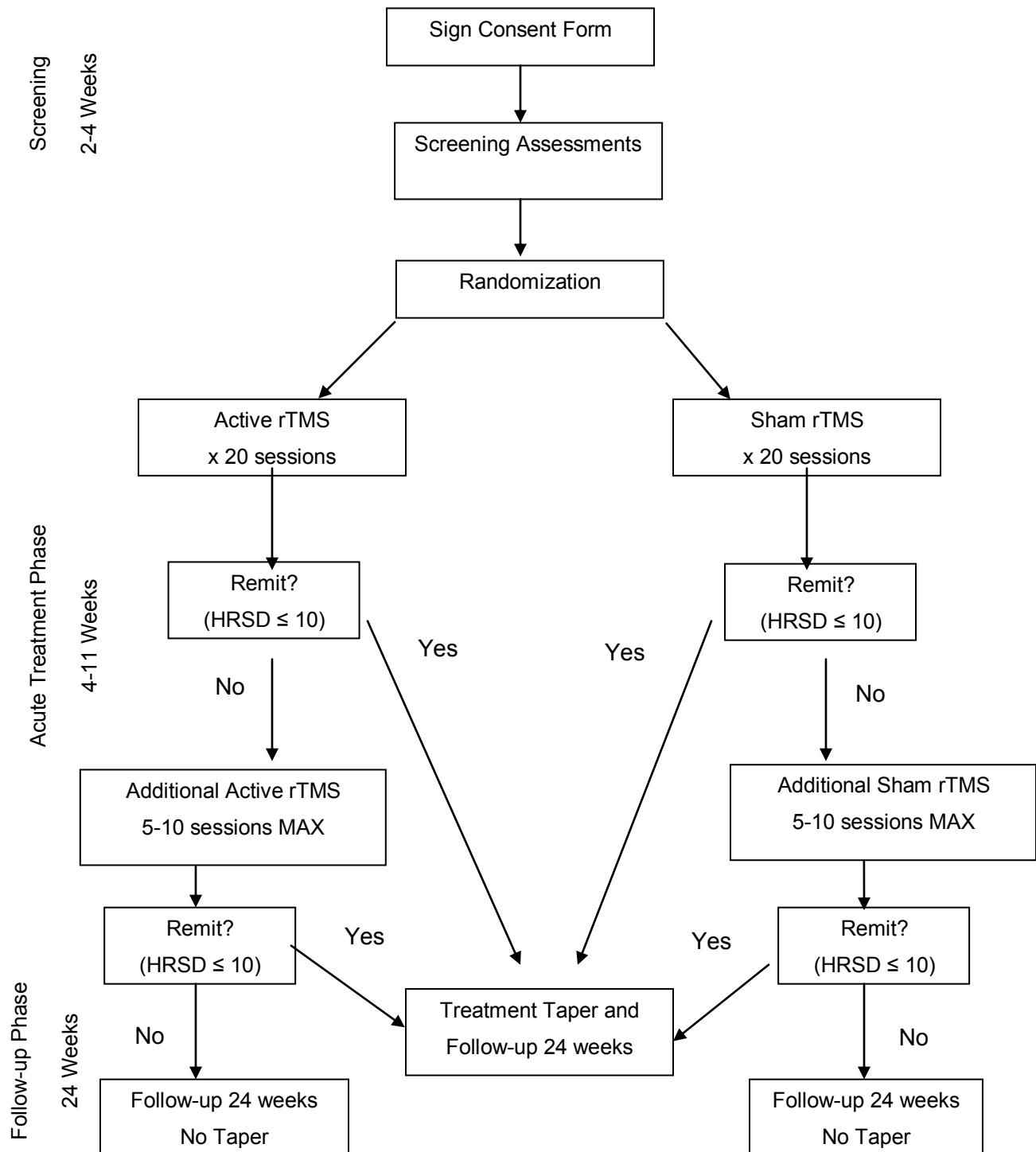


Figure 2: Overview of Research Design

Acute Treatment Phase. After randomization, and on the first day of each block of treatment, the administrator will determine the motor threshold (MT). The administrator will then deliver left prefrontal active rTMS treatment or Sham (Control) rTMS treatment for 20 to 30 sessions in blocks of 5 sessions. Patients are first tested for “remission” after the first 20 sessions of treatment and then again at the 25th and 30th sessions. “Remission” is defined as a decrease in Hamilton Rating Scale for Depression to 10 or less. **Patients will be retested for remission following the last treatment in each 5-session block.**

- If a participant remits after the first 20 sessions, the participant will enter the 24 week follow-up phase; all participants will receive a minimum of 20 treatments before being evaluated for remission;
- If a participant does not remit after the first 20 sessions of treatment, the participant will be offered an additional 5 or 10 sessions of treatment and retested for “remission” after 25 or 30 sessions. This procedure may continue for a maximum of 30 sessions total treatment.
- If the participant remits, he/she will enter the 24 week follow-up phase during which they will receive a “taper” of treatments over three weeks. The taper will include 3 treatment sessions in the first week, 2 in the second week and 1 in the last week of the taper;
- If a participant does not remit at the end of 30 sessions of treatment or drops out during treatment, the participant will be considered a treatment “failure” for the purpose of the primary analyses. The participant will enter the 24 week follow-up phase. Patients who are treatment “failures” will not receive a “taper” of treatments.

Units of 5 sessions will normally be delivered over one week’s time. As is the case with other somatic treatments such as electroconvulsive therapy, some consideration of scheduling flexibility must be made to accommodate holidays and other events. These units of 5 sessions can be delivered over a minimum of 5 calendar days and should be delivered within 12 calendar days. Thus, the entire acute treatment phase would normally take between 4 weeks to 11 weeks. At the end of each treatment block, study staff will enter progress notes for each participant in CPRS. These progress notes will be very brief in nature and contain no results or scores of assessments and will serve simply as records of treatment and assessment. The participant’s primary mental health provider will be listed as an additional signer on these

CSP #556 “The Effectiveness of rTMS in Depressed VA Patients”

Version 4.6, February 2016

Main Section of Protocol

notes. This is to ensure that providers are aware of the veterans progress throughout the study and to maintain an open line of communication with study staff.

Follow-up Phase. After the acute treatment phase ends, all patients will enter a 24 week follow-up period. Taper treatments are considered part of the Follow-up Phase. Follow-up visits will occur approximately monthly during the follow-up phase. These visits should be face-to-face but, in unusual circumstances, telephonic visits may be allowed. Appropriate assessments to measure treatment effects after the acute and follow-up phases will be collected as described in Table 2, Assessments and Frequencies of Administration, in Protocol section VI.G. At the end of each follow-up visit, study staff will enter progress notes for each participant in CPRS. These progress notes will be very brief in nature and contain no results or scores of assessments and serve simply as records of assessment. As on the notes in the acute phase, the participant's primary mental health provider will be listed as an additional signer on these notes.

F. Treatment Regimen

1. Rationale for Selection of rTMS Stimulation Parameters

The Planning Committee's decision regarding the choice of rTMS stimulation parameters in this trial was made in a systematic way with data from three sources.

- a. First, the Planning Committee members performed a thorough literature review of the rTMS antidepressant trials performed over the last 15 years (n=70 trials as of 12/06).
- b. These data were then presented and discussed at a planning meeting attended by the rTMS experts on the CSP Planning Committee, and were re-examined in light of current neurobiology data.
- c. Finally, the potential list of parameters were then filtered by the committee in light of practicality, safety and feasibility, specifically with respect to use in the VA population and whether deviation from parameters used in prior studies would potentially jeopardize the other goals of the study, i.e. to maximize comparability with other studies.

d. Treatment parameters were reviewed by the Study's Executive Committee prior to the start of the study and were revised to incorporate the most current information.

The Planning and Executive Committees then settled on the following dose:

- Power: 120% of motor threshold as separately determined for each patient prior to treatment/sham sessions
- Pulse frequency: 10 Hz
- Length of each pulse train: 4 seconds
- Time between pulse trains: 10 seconds
- Length of treatment: 25 minutes
- Total 4000 pulses per session, 5 days/week, 4 weeks/20 session minimum
- 120,000 pulses total for 30 sessions or 80,000 pulses total for 20 sessions.

There are **two major points** to be emphasized about these proposed parameters:

Major Point 1: The proposed parameters are the most likely, based on current knowledge, to be potentially effective in the VA population.

The dosing parameters involve the choice of coil and type of coil, location of stimulation, intensity, frequency, daily dose, and total number of pulses. Each was discussed briefly.

Location – 66 of the 70 published studies of rTMS as an antidepressant have chosen to stimulate over the LDLPFC, following on the initial finding of antidepressant efficacy at this site (George et al., 1995). Although other prefrontal cortex sites have been examined and have found antidepressant effects, the total literature at any other site is limited in terms of subjects studied and the number of studies. The LDLPFC site is clearly the most likely region to be effective, based on prior studies. (See Section 2 below for a more detailed discussion about how to best position the coil to stimulate the prefrontal cortex.)

Intensity – rTMS antidepressant studies have ranged from dose of 80% MT to 120% MT. Older studies used lower intensity stimulation because of safety concerns at the time which

have now been relaxed with greater experience. There have been no studies at intensities higher than those proposed in this trial. In several recent studies, 120% MT is sufficient to stimulate the prefrontal cortex in all subjects under age 70, even those with prefrontal atrophy (Nahas et al., 2004). It is both tolerable and safe. Higher intensity stimulation would be risky and potentially have more patient dropouts due to pain.

Frequency – The frequency of stimulation has ranged from less than 1 Hz to 20 Hz. All other factors being equal, higher frequency stimulation is more likely to cause a seizure, and is more painful. Many neurobiological effects of rTMS and brain stimulation are frequency dependent (e.g. speech arrest only occurs at 6Hz or faster, Epstein et al., 1996). Although other dosing parameters do appear to matter with respect to antidepressant efficacy, the frequency of stimulation has not been shown to matter (Gershon et al., 2003). We thus chose 10 Hz based on the safety and tolerability data in the published literature, and because it has recently shown effects in the industry clinical trial.

Daily Dose – The daily dose appears to matter, with more stimulation per day being better (Gerson et al., 2003) and (Jorge et al., 2008). The daily dose in our study is similar to the most recent industry trial and the 2006 study by Avery and associates. However, given the clear trend that higher doses are more likely effective, and the recent effectiveness trial at the Medical University of South Carolina (MUSC) in depressed patients on medications who received 6000 stimuli/day (Hadley et al, in Press, JECT), we have decided to increase the number of stimuli given per day from 3000 as was originally proposed and used in the industry and NIMH trials, to 4000 stimuli per day. This is much less than was shown safe in the MUSC effectiveness trial but nevertheless is a proper modest increase in the number of stimuli over the trial. This increase reflects the ever growing safety database with TMS and current scientific trends.

Length of Treatment – Initial studies with rTMS had short exposure times (2 weeks) and were likely under treating. More recent studies show that most patients respond by 4 weeks (20 sessions), with up to 6 weeks (30 sessions) needed for full response in those showing some clinical effects.

Summary on Parameter Choice – The proposed parameters have shown efficacy in many prior studies, and represent the best choice of parameters that would be able to test the

hypothesis of whether rTMS works in the VA population. They essentially are the same parameters that were used in the recent NIH trial and in the major industry trial. The only difference is that with accumulating comfort with these parameters, the recent safety revisions from Sienna 2008, and several trials where patients were given 6000 stimuli/day or more, we have increased the total daily dose to 4000 stimuli.

Major Point 2: Although there may be improvements in parameters over the next 5-10 years, these are likely to be minor and not revolutionary.

rTMS is a relatively new form of therapy, with first reports beginning in the early 1990's. Over the past 5 years, there have been only minimal changes in the dosing parameters. Although there will likely be continued minor improvements, these will likely not be radical and negate the results of a VA CSP study.

There are some basic limitations in pushing the dose much greater than the parameters we propose. We are at the upper limit of where one can safely stimulate with respect to causing seizures. Any higher frequencies or longer trains and there is a high risk of producing seizures (Wassermann, 1997). Although one could safely double or triple the number of stimuli given in a day (Anderson et al., 2006), this would be infeasible in terms of one person essentially spending 5-6 hours in a chair every day for several weeks. We have benefited from the recent safety guidelines revisions, where the safe time between TMS trains should be at least twice the TMS train. As originally proposed, we stimulated for 4 sec and had 26 seconds rest between trains. This was highly inefficient and not needed. We have reduced the intertrain interval to 10 seconds, which allows us to safely give more stimuli without extending the length of time in the chair for a full session. These more efficient intertrain interval times were shown safe and well-tolerated in the MUSC effectiveness trial.

2. Rationale for Selection of rTMS Stimulation Coil Location

In the early days of rTMS, some researchers developed the '5 cm rule' as a quick and efficient method of placing the coil over the LDLPFC (George et al., 1995; 1996). Basically, one finds the best scalp location for stimulating the thumb through a functional search method. After finding this location, one moves 5 cm anterior and in a parasagittal line to find the stimulation location for the prefrontal cortex. This quick method, based on published anatomical atlases, works well in clinical settings and obviates the need for costly MRI or CT scans. It has been

used in 65 of the 70 published rTMS antidepressant studies. The problem with this method is that it fails to account for differences in the location of motor cortex (some subjects may have motor cortex farther back in their skull), and it does not account for variation in overall brain or skull size. A group elegantly showed that using this algorithm in adults results in actual stimulation over premotor cortex in 1/3 of subjects, with the others being stimulated in Brodmann areas 9 and 46 (Herwig et al., 2001). A different approach would be to use a system, like that used in EEG electrode placement, which compensates for variations in skull size (Herwig et al., 2003). An even more scientifically rigorous approach would be to use brain imaging and individually select the scalp location based on either structural or functional anatomy. While these other systems are more anatomically precise, we do not know the intended target within the prefrontal cortex that is maximum for treating depression (if it exists as a single well-defined region). Thus, in the absence of new compelling data showing a better system, the study Planning Committee concluded that we should use the 5cm rule, which has worked in prior trials. More recent data has demonstrated that a 6 cm rule results in better coil placement and this rule will be used in this study.

A summary of the acute treatment (intervention phase) regimen can be found in **Appendix K**.

G. Study Assessments

The assessments and their frequencies of administration are described in **Table 2** in Protocol section VI.G. Following **Table 2** is a description of each assessment.

Table 2: Assessments and Frequencies of Administration

Assessment		2-4 weeks	Acute Treatment Phase						Follow-up Phase									
			4 - 11 weeks						24 weeks (6 months)									
			End of Session Number ¹						PRN Taper weeks			Weeks						
			Screening/ Baseline	5	10	15	20	[25]	[30/ last]	1	2	3	4	8	12	16	20	24
86	Consent	S*																
01	Screening Form	S																
02	Randomization Form	B*																
03	Baseline	S																
04	Medical History	S																
05	Physical Exam	S							x									
06	Labs	S																
07	Structured Clinical Interview for DSM-IV-TR (SCID-I)	S																
08	Current/Past ATHF	S																
09	Lifetime Drinking History	B																
10	Clinician Administered PTSD Scale (CAPS)	B							x									x
11	Trauma History Questionnaire (THQ)	B																
12	Life Stressor Checklist-revised (LSC-R)	B																
13	Six-Item Blessed Orientation-Memory-Concentration (BOMC)	S																
14	Pregnancy Test	S ²	Every 4 weeks															
15	Medication Use	S	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
16	Study Visit Form		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
17	Audiometry: REMOVED																	
18	rTMS Treatment Log		x	x	x	x	x	x	x									
19	rTMS Taper Log									x	x	x						
20	Hamilton Rating Scale for Depression (HRSD) and MADRS	S ²	x	x	x	x	x	x	x				x	x	x	x	x	x
21	Beck Depression Inventory (BDI)	B	x	x	x	x	x	x	x				x	x	x	x	x	x
22	Quick Inventory of Depressive Symptomatology (QIDS-C16)	B	x	x	x	x	x	x	x				x	x	x	x	x	x
23	Columbia-Suicide Severity Rating Scale (C-SSRS)	S																
24	Columbia-Suicide Severity Rating Scale (C-SSRS) F/U		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
25	Beck Scale for Suicidal Ideation (BSS)	S	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
26	Beck Hopelessness Scale	S	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
27	Quality of Life (VR 36)	B							x									x

Assessment		Screening/ Baseline	Acute Treatment Phase						Follow-up Phase								
			4 - 11 weeks						24 weeks (6 months)								
			2-4 weeks		End of Session Number ¹				PRN Taper weeks		Weeks						
			5	10	15	20	[25]	[30/ last]	1	2	3	4	8	12	16	20	24
28	Neuropsychological Battery	B						x									x
29	DAST	S						x									x
30	PTSD Checklist (PCL)	B						x									x
31	MAST	S						x									x
32	STAXI-2	S	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
TLFB	Alcohol/Drug Timeline Followback (TLFB)		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
33	Urine Tox Screen/Alcohol Test	S		x		x		X		x		x	x	x		x	
34	Termination Form ³																x
35	Control Questionnaire	Before and after the 1 st treatment															x
36	Protocol Deviation	As required															
37	Adverse Events (AE) and ADE and Serious Adverse Events (SAEs) and UADE	As required															

***B= Baseline**

***S= Screening**

¹ Sessions 21-25 and 26-30 may not be required if patient goes into remission earlier

² Must be conducted within 7 days prior to randomization

³ Termination Form will be completed at the end of the study OR when a patient decides to end study participation prior to the study completion date; i.e., a patient decides to withdraw or leave the study for any reason, withdraws consent, or is suspended from the study.

1. Demographics, Medical History, Physical Exam, Laboratory, Toxicology, Pregnancy

Test and Medication Use. Relevant demographics will be collected as to age, gender, racial/ethnic grouping, military history and income. In addition, a standard Medical History and Physical Exam will be completed as well as laboratory tests including a Complete Blood Count (CBC), electrolytes (chemistry), thyroid panel and a liver function test. An alcohol test and urine drug toxicology screen will be conducted prior to randomization and also randomly during the following time points of study participation:

- Acute Treatment Phase: 2nd, 4th, and 6th (if still in acute treatment) weeks
- Taper Phase: 2nd week
- Follow-up Phase: 1st, 3rd, and 5th months

A pregnancy test will be conducted on all female patients of childbearing potential (that is, all women except for those who are post menopause for > 2 years or who have a history of hysterectomy or surgical sterilization) prior to randomization and every four weeks during the study. Information on medication use (prescription, natural food products, and “over the counter”) will be collected at screening and updated after each block of five sessions during the treatment phase and every four weeks during the follow-up phase.

2. Structured Clinical Interview for DSM-IV (SCID) (First et al., 2002). The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) is a semi-structured interview that is used to make the major DSM-IV Axis I diagnoses in the most uniform manner possible.

3. Antidepressant Treatment History Form (ATHF) (Sackeim et al., 1990). The ATHF provides a uniform and rigorous method of eliciting and recording a patient’s past experience using antidepressant medications. The ATHF provides detailed information about which treatments the patient has received during the index episode and over his/her lifetime. Specific criteria are used to evaluate the adequacy (e.g., dose and duration) of each treatment trial, and a determination is made, for each trial, whether the patient manifested treatment resistance (did not satisfactorily respond at adequate dose and duration) or whether the stringent dose and duration requirements could not be met (treatment intolerance).

Measures of Substance Abuse and Post-traumatic Stress

To perform moderator analyses determining if these comorbid conditions are associated with differential response to treatment, relevant measures will be collected. Since all subjects, at the time of the protocol, will not be abusing substances, the most relevant measures will be history of duration and severity of substance abuse, in particular alcohol abuse. Additional measures will quantify relevant aspects of PTSD.

4. Lifetime Drinking History (Skinner & Sheu, 1982). Lifetime alcohol consumption will be assessed using the Lifetime Drinking History (LDH) instrument as designed by Skinner and Sheu (1982) and refined by Sobell and colleagues (1988, 1990). LDH is the state-of-the-art validated assessment instrument for obtaining quantitative data on the frequency, amount, duration, and pattern of lifetime alcohol consumption beginning from the onset of regular drinking. Aggregate indices for total lifetime drinking can be assessed with moderate to high reliability (Skinner & Sheu, 1982; Sobell et al., 1990, 1988). It is recognized that the pattern of

drinking behavior (i.e. chronic regular drinking vs. binge drinking) may affect outcome measures. Therefore, drinking assessment will include measures of total alcohol consumption, typical and maximum alcohol consumption per occasion, average daily and average monthly intake (measures of drinking intensity reflecting both frequency of drinking occasions and dose per occasion), both for the last six months (current drinking) and for lifetime (lifetime drinking history).

5. Michigan Alcohol Screening Test (MAST). The MAST is self-report measure for the detection of alcoholism. It consists of 25 yes-no questions that are differentially weighted depending on the severity of the symptom addressed in each item. The score ranges for interpretation of the MAST are as follows: 0-4 = absence of alcoholism; 5-6 = possible alcoholism; 7 and up = probable alcoholism. The measure will be used to assess alcohol abuse at baseline and then at the end of acute treatment (intervention) and the follow-up phase.

6. Drug Abuse Screening Test (DAST) (Skinner, 1982). The DAST is a self-report measure for the detection of drug abuse or dependence on a range of psychoactive substances, other than alcohol. The DAST was adapted from the MAST and shares a similar item structure. A score of 5 or higher is indicative of a possible drug use disorder.

7. Clinician Administered PTSD Scale (CAPS) (Blake et al., 1995). CAPS will determine lifetime and current PTSD. The CAPS measures frequency and intensity of PTSD-related symptoms. Possible scores range from 0 to 136. In a recent review of studies utilizing the CAPS, (Weathers et al., 2001) propose the following severity score ranges for interpreting the CAPS, which are as follows: 0-19 = Asymptomatic/few symptoms; 20-39 = Mild PTSD/subthreshold; 40-59 = Moderate PTSD/threshold; 60-79 = Severe PTSD symptomatology; > 80 = Extreme PTSD. Using these recommendations, in the proposed study, PTSD positive subjects will be positive for lifetime PTSD, related to any lifetime traumatic experience, and will meet CAPS criteria for current, chronic PTSD if they have a current CAPS score of > 40; PTSD negative subjects will be those with a current CAPS score of < 20.

8. Trauma History Questionnaire (THQ) (Green, 1996). This is a 24-item self report inventory which has been modified to provide data on childhood trauma such as sexual or

physical assault. This scale will be used to determine the presence or absence of childhood sexual or physical abuse prior to age 13 and to better characterize the trauma histories of our participants. Responses to items 18-23 focus specifically on the age of occurrence of sexual and physical assault. The Trauma History Questionnaire has been shown to have good test-retest stability (Green, 1996).

9. Life Stressor Checklist-Revised (LSC-R) (Wolfe & Kimerling, 1997). This is a 30-item structured clinical interview for lifetime exposure to stressful life events. The scale emphasizes a number of different potentially traumatic events and assesses the participant's emotional reaction to the stressors and the time period in which the stressors occurred. The LSC-R is reported to have sound psychometric qualities within various PTSD populations (Wolfe & Kimerling, 1997). This measure along with the Trauma History Questionnaire will be used to assess the trauma histories of our participants.

10. PTSD Checklist (PCL) (Blanchard et al., 1996). This is a 17 item self report. Its limitation is that it is keyed to a single traumatic event; e.g., the patient's worst experience in the military. Nonetheless, it has adequate reliability and has been shown to correlate well with scores from the CAPS. It will be used for follow-up of symptoms to assess change with treatment.

11. Pure Tone Audiometry. Section Removed

12. Hamilton Rating Scale for Depression (HRSD). This measure is the primary outcome measure and is completed after each block of 5 sessions throughout the study. The HRSD is the "gold standard" of randomized clinical trials for depression, and the primary measure of most rTMS studies to date. This study will utilize the 24-item version of this instrument (HRSD24) to evaluate depressed mood, vegetative and cognitive symptoms of depression, and comorbid anxiety symptoms. It provides ratings on current DSM-IV symptoms of depression, with the exceptions of hypersomnia, increased appetite, and concentration/indecision.

The Planning Committee, in making this recommendation, examined the outcome measures used in current NIH and industry trials as well as the ACNP criteria for "remission" (Rush et al., 2006). The ACNP recommends that outcome measures reflect all major criteria used in the diagnosis of MDD. Neither the HRSD or the MADRS include all criteria however, they are

widely used in clinical trials and the ACNP report notes that the field has not followed this recommendation and that if one were to use these measures for reasons of comparability (as this Planning Committee recommends), the ACNP report suggests the use of other metrics to assure that remission is complete. For that reason, the Planning Committee recommended additional use of the Quick Inventory of Depressive Symptomatology (QIDS-C16), which meets the ACNP criteria.

Certification of Ratings of HRSD: We plan to follow the NIH protocol procedures for administration and certification of the HRSD ratings. This will include the use of a prepared script to help administer the HRSD. Certification of all raters at a participating site will be verified prior to enrollment. This will be done by shipping recordings of mock interviews (non-patient) to the sites where trained raters have determined a “gold standard HRSD score”. Site raters will then submit their scores. Following NIH procedures, large deviations will be noted, and a rater can have an additional test. This can be repeated for a total of 3 times until the site is told they must find another rater.

Longitudinal Quality Control for HRSD: Following NIH procedures, to ensure that HRSD do not “drift” over time, one HRSD recording will be circulated to evaluators at all participating sites every 6 months. The evaluators will be asked to rate this recording and to return their ratings. Evaluators who drift greater than 3 points on the HRSD total score will receive telephone consultation followed by one additional HRSD recording.

13. Montgomery Asberg Depression Rating Scale (MADRS). As another measure of depression, the Montgomery-Asberg Depression Rating Scale (MADRS) has been used with increasing frequency in recent years to measure outcome in antidepressant efficacy trials. It offers an alternative view of depressive illness, and may be sensitive to depressive symptoms that are not easily captured in the context of the HRSD, such as hypersomnia, increased appetite, and concentration/indecision.

14. Beck Depression Inventory (BDI). This measure is a 21-item self-report test presented in a multiple choice format which measures presence and extent of depression. Each of the 21 items addresses a specific symptom or attitude that pertains to depressed patients, and which are consistent with descriptions of the depression within the peer-reviewed literature. While generally deemed less reliable than scales score by a trained rater (for example, the HRSD),

the Beck scale is easy to administer, and provides convenient means by which patients can effectively communicate their own perception of their mood state.

15. Quick Inventory of Depressive Symptomatology (QIDS-C16). The ACNP recommends that outcome measures reflect all major criteria used in the diagnosis of MDD. For that reason the Planning Committee recommended additional use of the Quick Inventory of Depressive Symptomatology (QIDS-C16), which meets the ACNP criteria (Rush et al., 2003). The HRSD does not measure hypersomnia, weight gain or problems with concentration or decision making.

16. Columbia – Suicide Severity Rating Scale (C-SSRS). Suicide is a rare event. As such, suicide rates cannot be used as an outcome measure for an rTMS study. Similarly, the study is of too short a duration to expect to find a significant difference in numbers or lethality of suicide attempts between treatment and placebo (sham rTMS) groups. Nonetheless, there are two areas that can be expected to change with successful rTMS treatment: preoccupation with suicidal ideations or plans. Because this study uses both a lead in period prior to treatment and a sham rTMS treatment group, we will be able to compare the rate of parasuicidal behavior in these patients, who are at more serious risk of a suicide completion. One of the newer methods of monitoring patients at risk for suicide is the C-SSRS. The C-SSRS assesses suicidal ideation as well suicidal behavior over a specified time period and is frequently employed by the Food and Drug Administration in research to determine if suicidality is an adverse effect. The form will be collected at multiple timepoints in during the course of the study. Initially, it will be collected at baseline to serve as a screener for persons reporting suicidal ideation or behaviors in the past six months. It will also be completed weekly during acute treatment and then monthly during the follow-up phase to monitor for the presence of suicidal ideation or behaviors. The sensitivity of this instrument will allow us to identify even “minor” suicide “gestures” as well as more serious attempts.

17. Beck Hopelessness Scale (BHS) (Beck et al., 1974). The Beck Hopelessness Scale is a self-report measure consisting of 20 “yes/no” items. A total severity of hopelessness is calculated from summing the 20 items and guidelines for interpretation for scores are as follows: 0-3 = minimal hopelessness; 4-8 = mild hopelessness; 9-14 = moderate hopelessness; and 15-20 = severe hopelessness. The BHS will be given at screening, weekly during acute treatment and taper phases and then monthly during the follow-up phase.

18. Beck Scale for Suicide Ideation (BSS). To help clinicians screen psychiatric patients for suicidal ideation, the Beck Scale for Suicide Ideation (Beck and Steer, 1991) was developed, and is herein referred to as the BSS. This self-report measure consists of 21 items and is one of the most thorough assessments of both active and passive suicidal ideation. Respondents are asked to rate the severity of each item on a 3-point scale with scores ranging from 0 to 2. The first five items on the BSS are regarded as a screener for suicidal ideation and assess one's desire to live, desire to die, reasons to live and reasons to die, and suicidal ideation. The remainder of the BSS assesses the duration and frequency of suicidal ideation, ambivalence regarding suicidal ideation, reasons for living / deterrents for suicide, suicide plan / opportunity to enact plan, expectations for following through after an attempt, preparations that have been made to ready for a suicide, past suicide attempts, and wish to die during past suicide attempts. It should be noted that the psychiatrist responsible for the assessment of the patient is responsible for performing a more detailed assessment of any patient showing an increase in BSS score. The BSS will be given at screening, weekly during acute treatment and taper phases and then monthly during the follow-up phase.

Suicidal ideation, hopelessness, agitation, aggression, and depressive symptoms can also be derived from the HRSD and the MADRS, which is also being rated on each patient. The advantages of the HRSD and the MADRS are that they are interviewer-scored scales that focus not only on ideation, but also on psychotic symptoms, and somatic symptoms. Thus, this study, in contrast to the other multisite trials of rTMS, will not only be different because of the population (veterans with TRMD) that it treats, but also because it incorporates five scales that enable evaluation of both ideation and intent (CSSRS and BSS), hopelessness (BHS), and mood, psychotic, and somatic symptoms (HRSD, MADRS).

19. Health Services: Veterans RAND 36 Item Health Survey (VR-36). The VR-36 (formerly known as the SF-36V) is a self-administered survey that measures eight dimensions of health: physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health. It yields scale scores for each of these eight health domains, and two summary measures of physical and mental health: the Physical Component Summary (PCS) and Mental Component Summary (MCS). The VR-36 includes two additional items that assess how much physical and emotional health have changed over the previous year. The VR-36 is a generic measure, as opposed to one that targets a specific age, disease, or treatment group. Thus, it

CSP #556 "The Effectiveness of rTMS in Depressed VA Patients"

Version 4.6, February 2016

Main Section of Protocol

has been useful in assessing the health of general and specific populations, comparing the relative burden of diseases, differentiating the health benefits produced by a wide range of treatments, and screening individual patients. The applicability of the VR-36 is apparent from its widespread use.

20. State-Trait Anger Expression Inventory -2 (STAXI-2). The STAXI-2 is a 57-item self-report measure of the experience, expression, and control of anger. The measure consists of six scale, five subscales, and Anger Expression Index which provides a measure of total anger expression. The STAXI-2 is frequently included in risk assessments for violence and will be used as such in the current protocol.

21. Blessed Orientation Memory Concentration Test (BOMC). The BOMC (Katzman, Brown, Fuld, Peck, Schechter, & Schimmel, 1983) is a 6-item screening measure of cognitive impairment which takes approximately 5 minutes to administer. The measure consists of 3 orientation questions, listing months backwards, a name and address memory phrase, and counting backwards from 20 to 1. This measure is fairly sensitive to milder levels of cognitive impairment.

22. Neuropsychological Battery. We propose to use a battery that is sensitive to the potential cognitive effects of rTMS. rTMS may improve cognitive function as depression is lifted, or it could have the potential for impairing function. A battery has been designed to be sensitive to such potential effects and has been used in previous studies of the effectiveness of rTMS. We propose to use measures that have been used in previous studies of rTMS as they have proven to be sensitive and it will also provide a basis for comparison of the VA patients entering this study with patients who have participated in other studies of rTMS.

The cognitive assessments will be administered at screening, at the end of the acute treatment phase and at the end of the 24 week follow-up phase. These measures are widely used in the literature and have been shown to be effective when working with severely depressed patients

Testing will include measures of Executive Function, Attention, Memory, Visuospatial Ability, Processing Speed, Psychomotor Function, and premorbid intelligence.

Executive functioning will be assessed using the **Controlled Oral Word Association (COWA) Test**, which is a test of verbal fluency. Participants are asked to produce as many words that

begin with a specific letter (F, A, or S) as they can within one minute. The participant is then asked to name as many animal names as possible within one minute (Spreen and Strauss, 2006).

Attention will be assessed using the **Stroop Color and Word test** (Golden, 1978). This measure consists of three pages: a Word page with 100 color words printed in black ink; a Color page with 100 X's printed in colored ink; and a Color-Word page that contains words from the Word page printed in colors (the word and the color do not match). Participants are asked to read as many words or name as many colors as possible in 45 seconds.

The Rey Auditory-Verbal Learning Test (RAVLT; Rey, 1964; Lezak et al., 2004) will be used to assess verbal learning and memory. The measure consists of 15 nouns that are read aloud for five trials. After each trial, the participant is asked to recall as many words as they can from the list. Another list of words, an interference list, will be read after the fifth trial and the participant will be asked to recall the words from that list. Immediately after that recall, the participant will be asked to recall as many words from the original list of 15 nouns. This is then followed by a 20 minute delay, during which other measures of the cognitive assessment will be administered. The participant will be asked to recall the original list of 15 words after this 20 minute delay. Finally the participant will be asked to identify the original 15 words after being a read a story that contains all of the original 15 words.

The Judgment of Line Orientation (JLO; Benton et al., 1994) will be used to assess visuospatial ability. There are two alternate forms that each consist of 30 items with an additional 5 practice items. Items are presented in a spiral bound booklet with stimuli appearing in the upper part of the booklet and the multiple choice card appearing in the lower part. The participant is asked to indicate on the multiple choice card the lines that match the direction of the lines on the stimulus card.

Processing speed will be assessed using the **Symbol Digit Modalities Test (SDMT; Smith, 1991)**. Participants are presented with a coding key consisting of nine abstract symbols. They must scan the coding key and record the corresponding number as quickly as possible. The participants are given 90 seconds to complete the task.

Psychomotor functioning will be assessed using the **Trail Making Test: Parts A and B (TMT; Reitan & Wolfson, 1993)**. In Part A, the participant is asked to connect, in order, 25 encircled

numbers that are dispersed randomly on a page. The participant is then asked to connect 25 encircled numbers and letters in an alternating order in Part B. Both Part A and Part B include practice exercises to ensure the participant understands the nature of the task. All tasks are timed.

The **North American National Adult Reading Test** (NAART; Blair & Spreen, 1989) will be used as an estimate of premorbid intellectual functioning. This measure consists of 61 items that are presented in two columns on a page for the participant to read. Participants are asked to read each word aloud as the examiner marks the errors on a score card.

All of the measures in the cognitive assessment are paper and pencil measures that will be administered by research staff. Staff will be trained in the proper administration and scoring of the cognitive assessment.

The cognitive assessment is expected to last approximately one hour at screening as well as at each follow-up.

23. Control Questionnaire. A questionnaire will be used before and after the first treatment session, and at the end of the final study visit to elicit patient perception of whether they were on active or sham rTMS treatment.

H. Adverse Events (AEs) and Adverse Device Effects (ADEs)

1. Adverse Device Effect (ADE) and Adverse Event (AE)

Definitions

An Adverse Device Effect (ADE) is defined by 21 CFR 812.3(s) and CSP Global Standard Operating Procedure (SOP) 3.6 as any adverse effect/event caused by or associated with the use of a device.

An Adverse Event (AE) is defined by the ICH for Clinical Safety Data Management and CSP Global SOP 3.6 as any untoward physical or psychological occurrence in a human subject participating in research. The AE does not necessarily have to have a causal relationship with the pharmacological product, study intervention or assessment. An AE can, therefore, be any unfavorable or unintended sign (including an abnormal laboratory finding), symptom or disease associated with the use of a medicinal (investigational) product.

Reporting

In CSP #556, collecting and recording all ADEs and AEs will begin at the time the patient signs the informed consent form and will continue throughout the follow-up phase. All events will be recorded on the appropriate case report form.

Relatedness involves an assessment of the degree of causality between the study intervention and the event. Site investigators will be asked to provide an assessment of relatedness. The assessment provided by the site investigator is part of the information used by the sponsor to determine if the adverse event or effect presents a patient safety concern. Pursuant to CSP Global SOP 3.6, an ADE is deemed to be associated with the use of the study device if there is “a reasonable possibility that the experience may have been caused by the device or by participation in the trial.” Thus, all adverse events or effects with a reasonable causal relationship to the rTMS treatment should be considered “related”. A definite relationship does not need to be established. The following levels of relatedness will be used in CSP #556:

Not attributed to the rTMS treatment

Possibly attributed to the rTMS treatment

Attributed to the rTMS treatment

2. Serious Adverse Events (SAEs) and Unanticipated Adverse Device Effects (UADEs)

Definitions

Serious Adverse Events (SAEs) are a subset of adverse events and are defined by the ICH for Clinical Safety Data Management and CSP Global SOP 3.6 as any untoward medical occurrence that;

Results in death

Is life-threatening

Requires inpatient hospitalization or prolongation of existing hospitalization

Results in persistent or significant disability or incapacity

Is a congenital anomaly/birth defect or

Any other condition that, based upon medical judgment, may jeopardize the subject and require medical or surgical treatment to prevent one of the above outcomes

In addition, due to the potential increased risk of rTMS among depressed patients, seizures (not including syncope), suicide attempts, and any patient reports of significant hearing loss are considered Serious Adverse Events for the purpose of CSP #556 regardless of whether these events meet any of the above criteria. Participants will be assessed for subjective hearing problems during Screening, near midpoint of Acute Treatment Phase, End of Acute Treatment, and at the Final Follow-up Visit.

An Unanticipated Adverse Device Effect (UADE) is defined by CSP Global SOP 3.6 as: "Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of patients". For this study an UADE is considered a category of SAE, which will be reported on the same form.

Collecting and Recording

For CSP #556, all SAEs and UADEs will be recorded on the SAE form, regardless of cause. The site investigator will be asked to determine whether the serious adverse event is related to:

rTMS Device

rTMS treatment

Disease progression of depression

Medications used to treat depression

Collecting and recording SAEs/UADEs will begin at the time the patient signs the informed consent form and will continue throughout the follow-up phase. For a patient who ends study participation prior to the study's completion date, unresolved SAEs will be monitored and

reported for 30 days after the “End of Study” date for that patient. In addition, the investigator must collect all SAEs reported to them for a period of 30 days after the study’s completion.

There are additional reporting requirements beyond using the CSP #556 policy and forms. Sites are responsible for submitting all information required by VA Central IRB policy. Please visit the VA CIRB website at <http://www.research.va.gov/vacentralirb/> for current policies, instructions and forms.

Specific VA Central IRB links

- a. What must be reported to the VA Central IRB:

<http://www.research.va.gov/vacentralirb/policies.cfm#4>

- b. Table of Reporting Requirements to the VA Central IRB:

<http://www.research.va.gov/programs/pride/cirb/CIRB-Table-of-Reporting-Requirements.pdf>

3. Expedited Reporting of Serious Adverse Events (SAEs) and Unanticipated Adverse Device Effects (UADEs)

The CSP Clinical Research Pharmacy Coordinating Center (CSPCRPCC or PCC) will be responsible for initially evaluating all serious adverse events for patient safety concerns and will confer with the Study Chair (or another physician member of the Executive Committee if the Study Chair is unavailable) as required during this evaluation process. After being reviewed by the Study Chair, the PCC Director and the CSPCC Director, any event deemed to be related, serious and unexpected will be reported to CRADO, study investigators, and FDA.

Expedited Reporting by sites to the Study Sponsor (CSP): All Serious Adverse Events (SAEs) which includes Unanticipated Adverse Device Effects (UADEs) require prompt reporting, within 72 hours of the site investigator being made aware of the event. The SAE reports will be forwarded within 72 hours of discovery of an SAE by the study site to Perry Point CSPCC who will immediately notify the CSPCRPCC and the Chairman’s Office. If the SAE is not resolved at the time the event is reported, the site must monitor and provide SAE follow-up information at least every 30 days until the SAE becomes resolved. The site must handle requests for SAE Follow-up information in the same prompt manner that the original SAE reports are handled

Expedited Reporting by the Sponsor to the FDA: The Chairman and Study Pharmacist will review the SAE report to assess completeness of documentation and to determine whether the SAE requires expedited reporting to the FDA.

Specifically, if an event meets the criteria for unexpectedness (i.e., not previously reported), seriousness (by definitions in section H.2.), and relatedness, it will be reported to the FDA within 10 working days for UADEs and within 7 calendar days for unexpected SAEs (Safety Reports) of the sponsor (Cooperative Studies Program) receiving the report as required by regulation.

4. Data Monitoring Committee (DMC) Reporting of Adverse Events, Adverse Device Effects, Serious Adverse Events, and Unanticipated Adverse Device Effects. The Clinical Research Pharmacist and the Study Biostatistician will generate tabulations of AEs and SAEs and present a summary of these to the DMC on a schedule set by the DMC. The DMC will also determine when they should be unblinded to treatment assignment for the reviewing of adverse event data. The DMC will advise the CSP Director concerning whether the study should continue or be stopped for safety reasons.

5. Role of the Site Investigator in Adverse Event Monitoring

The site investigator (as well as other site personnel) will be responsible for following adverse event and adverse device effects reporting requirements. These responsibilities include:

- a. Reviewing the accuracy and completeness of all adverse events/device reports;
- b. Knowing and complying with the VA CIRB (accessible at <http://www.research.va.gov/vacentralirb/>) and VHA Handbook 1058.01 Research Reporting Compliance Requirements section 6 (accessible at http://www1.va.gov/vhapublications/ViewPublication.asp?pub_ID=3116) reporting requirements for unanticipated problems. The VA Central IRB has reporting requirements separate from and beyond Sponsor reporting requirements. See the link above for the Table of Reporting Requirements in Section VI.H.2;
- c. Reporting to the VA Central IRB safety issues reported to the site by the sponsor;

- d. Closely monitoring research participants at each study assessment visit for any new Adverse Events (AEs), Adverse Device Effects (ADEs), Serious Adverse Events (SAEs) which includes Unanticipated Adverse Device Effect (UADE).
- 6. The Study Sponsor (Perry Point CSPCC, CSPCRPCC, and Study Chair) is responsible for the following procedures:
 - a. The Study Pharmacist promptly reviews newly submitted SAE reports to assess completeness of documentation and to determine whether the SAE requires expedited reporting to FDA. SAE reports which may require further reporting to FDA are brought to the attention of the Chair's Office for further medical advice.
 - b. The Perry Point CSPCC tracks receipt of follow-up reports of unresolved SAEs.
 - c. SAE reports that warrant immediate notification to VA Central Office are handled CSPCRPCC forwarded through the Directors of the Perry Point CSPCC and CSPCRPCC to VA Central Office.
 - d. The CSPCRPCC is sent electronic files of adverse events reported semiannually and serious adverse events reported quarterly for assignment of MedDRA codes.
 - e. Tracking of unresolved SAEs by the Sponsor ceases 30 days after the patient completes the study or withdraws consent to be followed.

I. Dropouts and Follow-up Procedures

This is an “intent-to-treat” protocol and any data of patients who are randomized to treatment will be retained for data analyses. As patients will remain under the care of their primary VA psychiatrist before, during and after participation in this study, the patient’s primary VA psychiatrist will remain central to the recruitment, participation and follow-up processes. Throughout a patient’s participation in the study, the site investigator will communicate with the patient’s primary VA psychiatrist to discuss the patient’s condition, reactions and any clinically significant adverse events. If a patient drops out or leaves the study for any reason or is suspended from the study for breaking study rules, every attempt will be made to contact the patient and complete a Termination Form.

J. Missed Visits and Study Termination

If a patient decides to withdraw their consent, a Termination Form will be completed. The Termination Form will include questions regarding the reason for termination and the patient's impression of the efficacy of the treatment to that point. If a patient is lost to follow-up or fails to come to clinic, the patient's primary VA psychiatrist will be informed.

The patient may be terminated from the study at any time if the SI deems that the patient has not been following the protocol. This will generally be done only when the protocol violation significantly increases the risk associated with continuing to participate in the study. A Termination Form will be completed. Patients who are terminated prior to the end of the acute treatment phase will be considered treatment failures.

Any female participant who becomes pregnant during the acute treatment phase of the study will discontinue the study treatments for safety reasons as the effects of rTMS on unborn fetuses is not known at this time and she will immediately enter the follow-up phase. Any female participant who gets pregnant during the follow-up phase of the study will continue to be followed-up in accordance with the protocol and complete all assessments. Women who become pregnant at any time during the study will be asked to sign a release of information in order for the study staff to access the medical records for the outcome of the pregnancy. Women who become pregnant during participation will be referred to an OB/GYN clinic.

K. Follow-up Procedures for Non-remitters and Non-responders

Following the 4-11 week acute phase, all non-remitting and non-responding rTMS patients (defined as HRSD score percent change from screening less than 50%) will be provided 24 weeks of follow-up. Patients will remain under the care of their primary VA psychiatrist before, during and after participation in this study. Their primary VA psychiatrist will adjust medications in compliance with the protocol, which allow adjustments by the psychiatrist as clinically indicated after the acute treatment phase.

L. Protocol Violations

All protocol violations will be promptly reported to the study sponsor on the form developed for such reporting. In addition, protocol violations which meet the CIRB's criteria for reporting (see

VA CIRB Form 129 Report of Protocol Deviations, Violations, and/or Noncompliance) must be reported to the CIRB as specified in that document.

M. Participant Compensation

Participants are compensated for the purpose of their time and effort put forth. Participants involved at any point up to week 1 of treatment reach payment #1 of \$40, treatment week's 2-6 participation are payment #2 of \$300, follow-up visits 1-6 equal payment #3 of \$60 for a total of up to \$400 per participant. Participants may reach a follow up stage after only 4 weeks of treatment; they will still earn the payment 2 of \$300 and will then go into the follow up phase. Some individuals will reach follow up at earlier stages than others, which will not vary the amount of payment.

If a subject terminates early from one of the three stages, they will be paid the amount equivalent to the stage they are in, i.e., if they are in treatment week 3 and terminate, they will receive payment #1 and payment #2.

N. Genetics

Section Removed.

VII. DATA MANAGEMENT AND CASE REPORT FORMS

A. Assessments, Case Report Forms (CRFs) and their Frequency of Administration and Collection

Please refer to Table 2 in Protocol section VI.G for a list of assessments, CRFs, and their frequencies of administration and collection.

B. Data Collection and Data Entry

Based on source documents collected at the study sites, data will be collected and then entered at the site using electronic data capture (EDC). The VA Cooperative Studies Program Coordinating Center (CSPCC) at Perry Point will develop the EDC templates. CSPCC will function as the centralized data management center for the study. The medical record, laboratory reports and all related documents will be the source of verification of data entered. Data should be entered on an ongoing and regular basis throughout the study and in

accordance with the instructions in the study operations manual. The SI is responsible for maintaining accurate, complete and up-to-date records for each participant. The SI is also responsible for maintaining any source documentation related to the study, including any films, tracings, computer discs or tapes.

CSPCC will be responsible for the validation of the clinical database, ensuring data integrity, and for the training of all participating staff on applicable data management procedures. InfoPath will be utilized in this clinical trial. Any discrepancies (i.e., missing data, range validation, cross check) that are discovered during the verification process will be flagged with quality control notes and clinical sites will be required to either correct or confirm flagged entries. The CSPCC will send Quality Control Reports to the Chairman's Office and to the participating sites on a monthly basis. These reports will summarize the quality and quantity of the data that each site has submitted.

When the study is completed and all data have been entered into the clinical database and the database has been checked for quality assurance and is locked, the CSPCC statisticians, in accordance with the Analytical Plan Section of this protocol, will perform statistical analysis of the data. Periodically, during the study, CSPCC will prepare various types of summary reports of the data so that progress of the study can be monitored. These reports will be prepared for the Data Monitoring Committee (DMC) and others, as appropriate.

C. Study Documentation and Records Retention

Study documentation includes all CRFs, quality control notes, workbooks, source documents, monitoring logs and appointment schedules, sponsor-investigator correspondence and regulatory documents (e.g., signed protocol and amendments, IRB correspondence and approved consent form and signed informed consent forms, Statement of Investigator form, and clinical supplies receipt and distribution records).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the study. Thus, source documents include, but are not limited to laboratory reports, audiology reports, patient diaries and progress notes, hospital charts or pharmacy records and any other reports or records of any procedure performed in accordance with the protocol.

Whenever possible, the original recording of an observation should be retained as the source document; however, a photocopy is acceptable provided that it is a clear, legible, and exact duplication of the original document.

Research records for all study participants including medical history and physical findings, laboratory data, and results of consultations with the primary care VA psychiatrist are to be maintained by the investigator in a secure storage facility for 3 years after the end of the study or until notified by CSPCC. These records are to be maintained in compliance with IRB, State and Federal requirements, whichever is longest. Exceptions to the 3-year retention requirement can be found in 45 CFR 74.53 and 92.42 (e.g., if any litigation, claim, financial management review, or audit is started before the expiration of the 3-year period, the records must be retained until all litigation, claims, or audit findings involving the records have been resolved and final action taken). It is the investigator's responsibility to retain copies of the completed CRFs until notified in writing by CSPCC that they can be destroyed. In all instances, the site must get permission from CSPCC prior to disposition of any study documentation and materials.

All records with identifiers will be stored indefinitely in accordance with the VA Records Control Schedule.

D. Data Security Plan

All data collected for this study will be handled and used in compliance with both the CSP and the Perry Point CSPCC data security plans. All patient level data will be treated as protected health information. Data will be transmitted from participating sites using secure servers. Study personnel at CSPCC, CRPCC, and at participating sites will be required to complete annual training courses. These courses will cover good clinical practices, human subjects' protection, cyber security, and privacy policy. Any data security breaches will be immediately reported. Access to patient level data at CSPCC or CRPCC, will be obtained through user accounts which will be protected by strong passwords. File protections will be used to limit access to members of the study group. Patient level data will never be stored on portable storage devices unless it is encrypted, explicitly authorized, and use specific.

VIII. BIOSTATISTICAL CONSIDERATIONS

A. Sample Size

The primary hypothesis of the study is that in VA patients with TRMD, rTMS will result in a greater remission rate at the end of acute treatment than sham rTMS. The primary outcome measure in this study is success or failure to achieve remission from depression as defined by a score on the Hamilton Rating Scale for Depression (HRSD24) of 10 or less. The primary analysis will be done as an “intent-to-treat” analysis, i.e. patients will be analyzed in the groups to which they were randomized and drop-outs will be considered treatment failures. The primary hypothesis will be addressed using a logistic regression model with PTSD diagnosis, history of substance abuse, and site as covariates.

Based on review of the studies reported in the Introduction Section, the Planning Committee felt that a 10% difference between treatments would be of clinical relevance given the severity of the illness. With a sample size of 180 per group, the proposed study will have a power of 81% to detect an absolute difference between groups of 10% in the percentage of those participants who remit (6% sham and 16% rTMS). Thus, a total of 360 patients will be randomized. This goal of 360 patients, larger than any previous study, also provides a measure of protection should some assumptions be wrong.

B. Analysis Plan

1. Site Effects and Baseline Comparability

Site effects will be tested using a logistic regression analysis examining the effect for Treatment in a model that includes Site and Site x Treatment interaction. Baseline comparability among the treatment groups will be evaluated with respect to such variables as demographics (e.g., age, gender, race), baseline values of outcome measures (e.g., the HRSD, QOL measure(s), suicidality, etc.), antidepressant currently being used, etc. Chi-square and analysis of variance techniques, as appropriate, will be used to determine any differences in distribution of the variables across the treatment groups. Any variable that appears to be different between the groups ($p < 0.10$) will be evaluated to determine whether such imbalances had any effect on conclusions.

2. Analysis of Primary Outcome Measure

The primary outcome measure in this study is success or failure to achieve remission from depression after a maximum of 30 sessions of rTMS or sham treatment. “Remission” is defined by a score on the HRSD24 of 10 or less after a maximum of 30 sessions of treatment. The primary analysis will be done as an “intent-to-treat” analysis, i.e. patients will be analyzed in the groups to which they were randomized, and patients who dropout before completing the Acute Treatment Phase will be considered treatment failures for the primary analysis on remission rates. The primary analyses and several secondary analyses will be conducted on outcome measures such as “remission” and “response” which are binary and defined by specific criteria. Logistic regression models with PTSD diagnosis, history of substance abuse, and site as covariates will be used for these analyses.

C. Additional Analyses

In addition to the main analysis using the entire randomized or “intent-to-treat” cohort, logistic regression models will be used for “completers” and also for “fully compliant” subjects to provide further information about treatment effects. For example, it would be expected that if rTMS had a significant clinical effect, its effect would appear greater in “completer” and “totally compliant” cohorts, than in the entire randomized cohort. Other analyses will be performed on secondary measures to further provide useful clinical information.

Some secondary outcome measures, such as sustained response rate (“recovery”) and response on secondary outcome measures, can also be analyzed using logistic regression models. Other potential secondary analyses include continuous variables such as: change in suicidality, change in cognitive function and change in quality of life (QOL). The effect of rTMS on such continuous measures will be determined using random regression and similar techniques that maximize the use of available data in repeated measures designs.

Potential moderators of treatment response also will be analyzed using multivariate analysis of variance or regression techniques. In addition, exploratory analyses will be performed using signal detection techniques (Receiver Operator Characteristics or ROC) to attempt to identify novel moderators predictors of response. The following gives examples of some potential

analyses that may be carried out that use random regression techniques, which may be more sensitive to change than the logistic regression analyses.

a. Random regression approach to efficacy analyses

Random regression models will be used to test and evaluate treatment efficacy (see e.g., Gibbons et al., 1993). Such models trace the individual trajectories over time and, in effect, use available information to impute any missing data for comparable subjects. They thus compare the groups on a parameter describing the trajectory (e.g., the subject's response rate over time). This method not only minimizes loss of power and bias due to dropouts (for analytical purposes there are none), but also amplifies the reliability of measures using repeated measures per subject and thus usually increases power.

Short-Term Efficacy (Baseline to End of Acute Treatment). This approach can be used to replicate and enhance the understanding of the main analyses. Data to be entered into the random regression analyses will include those collected at baseline and after sessions 10, 20 or possibly 30 if the patient receives treatment at that time. We will use a linear model on $\ln(t+1)$ to model the typical “fish hook” shape of the response trajectory, assuming an autoregressive covariance structure within individuals with treatment group as the independent variable. The primary outcome measure will be the slope of HRSD change. This random regression parallel of the primary analyses will provide complementary information to assess if rTMS is superior to sham rTMS. Secondary random regression analyses also will be performed on each of the other outcome measures. The effect of site will also be examined as in the primary analyses.

Longer-term efficacy (End of Treatment to End of Follow-up). Data to be entered into analyses will include those collected from weeks 4 to 24 of follow-up, and analytic techniques will parallel those described above. This will allow a comparison of loss of treatment effect from the end of the treatment to the end of follow-up, i.e. it will address questions of pattern of “recovery” and “recurrence.”

**b. Random regression approach to individual differences in response
(Moderators)**

Multiple regression analyses will be performed to determine if, as hypothesized, there will be individual differences in the efficacy of treatment depending upon specific predictors. This analysis will be done by adding the predictor variable and its interaction with treatment to the Random Regression Model used above. A significant interaction indicates a differential effect size depending on predictor status. Separate predictor of response analyses will be performed for each set of outcome data. These analyses are used to determine in whom or under what conditions improvement occurs. For example, we expect that younger age will predict a better response to rTMS than to sham rTMS. The initial measures to be used in these analyses will be severity of symptoms at baseline, type of comorbidity (PTSD, substance abuse, or both), duration of illness and prior treatment resistance.

In these exploratory analyses, alternative measures might prove to have different abilities to predict response to rTMS. Our consultant, Dr. Kraemer is an expert in the use of signal-detection methods to make such determinations (Kraemer, 1992). Because of the potential that collinearity may be a problem among potential moderators and mediators, Dr. Kraemer proposes that any examination of effects of the proposed predictor variables be corrected for the potential effect of initial level of severity of depression.

D. Assessing Size of Treatment Effect

Although data analyses can indicate the statistical significance of results, a statistically significant result does not in and of itself imply that a finding is useful in a practical sense. Therefore, in addition to testing for statistical significance, we will convey practical significance by reporting treatment effect sizes and their confidence intervals (Kraemer & Kupfer, 2006). We believe that such evaluations will yield conclusions that are directly relevant to the development of treatment programs of the type proposed here.

E. Supplemental Statistical Analyses

We will examine the degree of convergent validity between depression measures that are gathered on the same days. The analyses proposed are not presented as a complete list of all analyses likely to be performed. They simply provide a brief outline of the major statistics that will be obtained.

F. Economic Analysis

We will collect and report information on the incremental health care cost of rTMS based on its implementation at multiple VA medical centers (see **Appendix M**). Specifically, we will estimate the incremental per patient program (or direct) cost of rTMS relative to usual care over the course of an rTMS treatment (lasting no more than 11 weeks for most study participants) in our proposed implementation). Sensitivity analyses will be used to derive upper and lower estimates of resource use and incremental costs.

Although the costs and benefits of rTMS could be substantial in magnitude, we believe a full cost, cost-effectiveness, or cost-benefit study would be premature during this initial phase of effectiveness testing. rTMS could either increase or decrease specialty mental health treatment costs depending on the magnitude of any cost-offset. It also could bring about significant societal benefits by preventing suicide and lowering depression-related morbidity. In a full evaluation, these and other potential benefits of rTMS would be weighed against direct and indirect costs. The sham control design does not allow for natural economic comparison to treatment as usual, and many of the economic benefits (or costs) resulting from treatment may emerge beyond the proposed study period (9 to 17 weeks). Therefore, in the current study, economic analyses will focus primarily on the direct treatment and implementation costs and cost-consequences. We will, however, conduct a preliminary and limited study of its incremental effects on cost per sustained remission using comparisons of clinical outcome at 24-weeks post-treatment across the two treatment arms as our measures of incremental effectiveness (see **Appendix M**). We believe these estimates will provide important preliminary evidence on the potential cost-effectiveness of rTMS treatment.

IX. QUALITY ASSURANCE PROCEDURES

A. Rater Training

To insure the validity and the integrity of this research study, a formalized training program will be provided to the appropriate staff who will be conducting key assessments and for the staff who will be administering the rTMS treatments. Both pre-study and annual certification will be required.

B. Good Clinical Practices (GCP)

The Site Monitoring, Auditing and Resource Team (SMART) is responsible to assure that participating sites conduct the study in compliance with Good Clinical Practices. SMART consists of the Good Clinical Practices (GCP) Monitoring Group (GCPMG) and the GCP Standards and Resource Group (GCPSRG). GCP Monitors will visit participating sites annually to monitor investigator records and practices as described in the Monitoring Plan to be prepared for this trial. To promote GCP in the trial, SMART will also develop written GCP guidance and tools specifically for the trial and provide training in the use of these materials and in the principles of GCP at the start of the trial. Training is provided at the kick-off meeting and during GCP implementation visits made by SMART to each site at the start of subject enrollment. Finally, GCP Auditors may visit sites at any time throughout the trial to assess GCP compliance as requested by Perry Point CSPCC, or other members of the study management and monitoring teams.

In summary, SMART will accomplish the following:

1. Prepare a written Monitoring Plan for review and concurrence of Perry Point CSPCC Director and Study Chairman.
2. Prepare and provide sites with GCP tools and guidance to aide in organizing files and maintaining records in compliance with the protocol and GCP.
3. Present GCP training at the study kick-off meeting.
4. Conduct site GCP implementation visits to participating sites to aid in implementing the training, practices and tools provided by Perry Point CSPCC and SMART.

5. Conduct routine monitoring visits to each participating site at least annually as directed by the study's Monitoring Plan.
6. Conduct a closeout-monitoring visit to each site at the end of the study to assure completion of all study tasks and appropriate archiving of study records.
7. Perform independent quality assurance audits at selected sites as requested by Perry Point CSPCC and other members of the study management and monitoring teams if approved by the Directors of CSPCC and CSPCRPCC.

X. STUDY MANAGEMENT, MONITORING AND TRAINING

A. Study Management

The Site Investigator, the TMS Treater and the Study Coordinator at each of the participating sites will conduct the daily activities of the study. The Study Chairman's Office, the Cooperative Studies Program Coordinating Center (CSPCC), and the Cooperative Studies Program Clinical Research Pharmacy Coordinating Center (CSPCRPCC) will provide leadership and guidance to the local sites, as well as performing their assigned tasks, as described below:

1. Office of the Chairman. The Chairman's Office, located at the Palo Alto VA Medical Center, will coordinate and administer all aspects of the study and will closely monitor the progress of the study. This office will provide leadership for the study and will be in routine contact with the participating sites to ensure that the study is performed in accordance with the protocol and to encourage the local study team to keep enrollment and visit activities on schedule. The Chairman will preside over all Study Group Meetings and will represent the study, along with the Study Biostatistician and the pharmacist (as needed) at all meetings of outside review committees.

2. CSPCC. The CSPCC, located in Perry Point, Maryland, will provide administrative, data management and statistical support for the study. CSPCC staff will provide guidance on completion of forms and data quality queries. They will develop editing software and manage the study database. All reports generated during the ongoing phase of the study and the final statistical analyses will be the responsibility of the CSPCC. In tandem with the Chairman, CSPCC will monitor study progress to ensure

that the study is proceeding as scheduled. A CSPC study team dedicated to this study has already been established. This team is headed by the Study Biostatistician and will include the Project Manager, the Statistical Programmer, the Database Programmer and two Computer Assistants.

3. CSPCRPCC. The CSP Clinical Research Pharmacy Coordinating Center (CSPCRPCC) manages the pharmaceutical aspects of multi-center pharmaceutical and device clinical trials including patient safety monitoring. CSPCRPCC acts as a liaison between the study participants, the FDA and the manufacturers of the study drug(s) or device(s) in all VA Cooperative Studies that involve drugs or devices. The CSPCRPCC develops Drug or Device Treatment and Handling Procedures: obtains and distributes the study drug(s) or device(s); prepares a Drug or Device Information Report for each of the study drugs to assist in the Human Rights Committee Review; and provides advice and consultation about drug or device-related matters during the study. CSPCRPCC is responsible for monitoring and reporting the safety of trial participants through the review, assessment, and communication of adverse events and serious adverse events reported by study personnel with reviewing responsibilities occur through ongoing communication with the Study Chairman, Executive Committee, Data Coordinating Center, and CSP Central Office. The reporting activities include the filing of regulatory documents involving adverse events with the FDA and manufacturers to meet federal regulations and CSP policies. In conjunction with the Data Coordinating Center, the CSPCRPCC trends and analyzes safety data in order to prepare reports for various committees including the Data Monitoring Committee (DMC), Institutional Review Boards (IRBs), Study Executive Committee(s), and study investigator meetings.

4. Participating Sites. All participating sites must be a VA Health Care System facility that agrees to adhere to the study protocol, meet the recruitment target of the study and provide full administrative support, including adequate clinic space and any necessary equipment. Each site is expected to be able to enroll at least 40 patients during the three year enrollment period or until full study enrollment is achieved.

5. Site Investigator (SI). The SI from each of the participating sites must enthusiastically support the study and be willing to devote sufficient time and energy to ensure that the study's goals are met. The SI must have at least a 5/8 VA appointment

and be a physician in good standing and be board-certified in Psychiatry and/or Neurology. The SI will assume responsibility for the following aspects of the study:

Meet recruitment goals and ensure timely follow-up of participants.

Ensure the integrity of the study protocol and the data collected from his/her site.

Provide ongoing supervision to study staff and ensure that the study staff is sufficiently trained to administer the assessment tools as well as the rTMS device.

Provide for adequate coverage for the study in the absence of any study staff.

Obtain initial and continuing reviews by the local Human Subjects Subcommittee/IRB and the local Research and Development (R&D) Office; will submit all written approvals to the CSPCC in a timely manner.

TMS Treater (TT): Nurse Practitioner (NP), Registered Nurse (RN), or Physician Assistant (PA). A full-time NP, RN or PA, preferably one experienced in mental health and/or research, will be recruited for the study and will function under the supervision of the SI. The NP, RN, or PA will screen patients, obtain medical histories, perform physical examinations, and conduct structured assessments including the ATHF. The NP, RN, or PA will be BCLS certified and will be trained and fully credentialed to administer the rTMS treatments. If a site is unable to recruit or retain a NP, RN, or PA for this study, the SI will contact the Study Chairman to discuss other potential staff who would possess the appropriate skills and credentials for this position.

Study Coordinator (SC). A full-time SC, preferably one who is experienced in TRMD and clinical trials, will be recruited for the study and will be under the direct supervision of the SI. The SC will recruit and randomize patients into the study, perform assessments including the SCID, HRSD, the MADRS, the CSSRS, the BSS, the BHS, the BDI, the neuropsychological battery and the Health Services assessments. The SC will perform other administrative tasks including completion of case report forms, correction of edits and data clarification requests. The SC will also contact study participants with appointment reminders and for follow-up as needed.

B. Monitoring

A number of groups will be charged with monitoring the various aspects of the study. These groups include the Study Group, the Executive Committee, Data Monitoring Committee, the Site Monitoring, Auditing and Resource Team (SMART) and the Cooperative Studies Scientific Evaluation Committee (CSSEC). With the exception of CSSEC, each of these committees will meet at the beginning of patient intake, six to nine months later, and yearly thereafter. CSSEC may review the study at its midpoint. This monitoring will not preclude the annual monitoring that the local R&D Committee and Human Subjects Subcommittee/IRB must also perform.

1. Study Group

The study group consists of all participating SIs, TTs and SCs as well as staff from the Chairman's Office, CSPCC, and CSPCRPCC. This group meets annually to discuss the plans/progress of the study, as well as to identify any problems encountered during the conduct of the trial. No outcome data are presented to this group.

2. Executive Committee

The Executive Committee is the management and decision-making body for the operational aspects of the study. This committee is chaired by Dr. Jerome Yesavage, and includes the Study Biostatistician, the CRP, a minimum of three SIs and outside consultants, if necessary. This committee monitors the performance of participating sites and quality of data collected. The Executive Committee formulates plans for publications and oversees the publication and presentation of all data from the study. Permission from this committee must be granted before any study data may be used for presentation or publication. This group also does not receive outcome data during the course of the study. Executive Committee decisions that need to be made between regularly scheduled meetings will be made during periodic phone conferences.

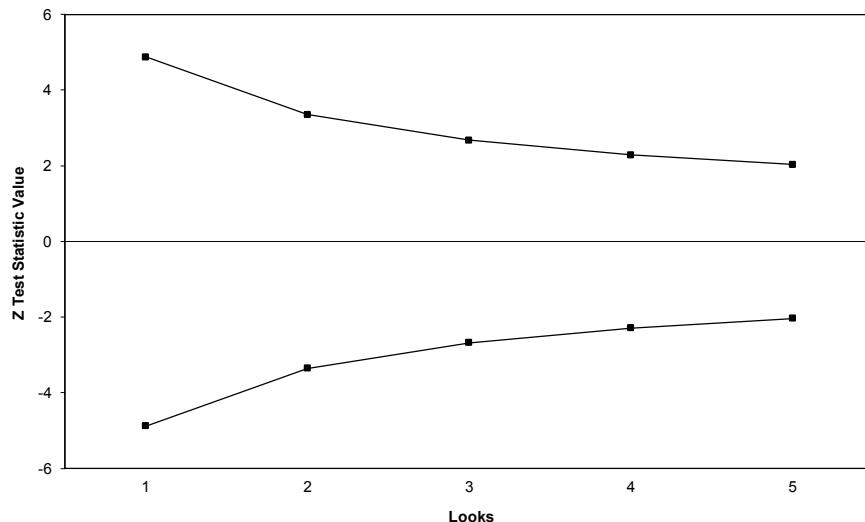
3. Data Monitoring Committee (DMC)

The DMC is a group of outside experts in the area of TRMD, clinical trials and biostatistics that reviews the progress of the study and monitors patient enrollment, outcomes, adverse events, and other issues related to patient safety. The DMC makes recommendations to the CSP Director as to whether the study should continue or be

modified or terminated. The DMC can consider patient safety or other circumstances as grounds for early termination, including either compelling internal or external evidence of treatment differences or infeasibility of addressing the study hypotheses (e.g., poor patient intake, poor adherence to the protocol). The DMC will meet annually to review data reports prepared by the CSPCC. At the six-month interval between the annual meetings, the DMC will receive a data report for their review. Any member of the DMC can ask for a meeting of the group if he/she feels that it is necessary, based upon the data. This group will receive outcome data during the course of the study.

In order for the DMC to make its recommendation for continuation of the study, it will be necessary for them to see the analyses for the primary outcome measure every time that the report is run and it is possible to calculate the primary outcome measure. Periodic monitoring of interim results can significantly affect the probability of making an incorrect decision. A number of formal techniques have been developed for interpreting interim results. At the organizational meeting, the DMC will select the technique that it wants to use to monitor the study. Suggested techniques are the Haybittle-Peto and Lan-DeMets group sequential boundaries. For the Haybittle-Peto method, a constant z-statistic is used as the monitoring boundary. The Lan-DeMets procedure produces decision boundaries that are quite conservative over the first several looks and then gradually converges to the nominal alpha levels as the final look is approached. Figure 3 gives an example of the Lan-DeMets boundaries for five looks at an alpha level of 0.05.

Figure 3. Lan De - Mets Group Sequential Monitoring Boundaries



4. Human Rights Committee (HRC)

The Human Rights Committee (HRC) will conduct annual site visits to ensure that patients' rights and safety are being properly protected.

5. Internal Reviews

The Study Chairman, the Study Biostatistician, the CRP and the CSPCC Project Manager will communicate regularly and frequently to review study status. Discussion items will include overall and site-specific enrollment, regulatory issues, protocol compliance and data completeness and quality. Action plans to deal with identified problems will be developed.

6. Site Monitoring, Auditing and Resource Team (SMART)

The Site Monitoring, Auditing and Resource Team (SMART) will conduct monitoring visits to each participating site to monitor investigative records and practices to ensure sites are in compliance with both the study protocol and GCP. These site visits will occur annually or more frequently if directed by the study's Monitoring Plan. Independent quality assurance audits will also be conducted at selected sites, if needed.

7. Special Procedures for Monitoring of Substance Abuse

Under the exclusion criteria, we have listed substance abuse within the previous 90 days because evaluating withdrawal symptoms or cravings in the context of a depression study complicates the evaluation. Furthermore, alcohol withdrawal, cocaine and stimulant abuse, and barbiturate withdrawal are all associated with an increased risk of seizures. More critically, actively abusing drugs or alcohol is associated with a higher risk of completed suicide. Thus, beginning to abuse alcohol or drugs could well be a prelude to a completed suicide and must be immediately addressed.

Prior to study randomization, all potential participants will submit to both an alcohol test and a urine drug toxicology screen. Those that have positive results on either of these tests will be excluded from participation. For those that are eligible for participation, they must also complete alcohol tests and urine drug toxicology screens at randomly at the following time points:

- 1) Acute Treatment Phase: 2nd, 4th, and 6th (if still in acute treatment) weeks
- 2) Taper Phase: 2nd week
- 3) Follow-Up Phase: 1st, 3rd, and 5th months

Throughout the study, site staff will also monitor participants' use of substances including alcohol, OTC medication, opiates, and street drugs for possible abuse through the use of self-report measures. Prior to each treatment session, study staff will ask participants if they have used any substances in the past 24 hours and if so, how much was used. Study staff will further monitor participants' alcohol and other substance use with weekly administrations of the Alcohol / Drug of Choice Timeline Followback Method (TLFB) (Sobell and Sobell, 1992) during the acute and taper phases of treatment, and monthly administrations of the TLFB during the follow-up phase. The TLFB is a self-report measure of recent drinking behavior or substance abuse. Using a calendar, the patients will retrospectively estimate their daily consumption of alcohol and other substances over the past 7 days prior to the interview. This will enable the study staff to quantify the amount of substances patients are using, therefore tracking changes in

these amounts and addressing problematic substance use at the earliest possible instance. This tool is used for monitoring purposes during the study, not for enrollment.

Participants will also complete the MAST and DAST during screening, at the end of acute treatment, and at the end of the follow-up phase.

Use of substances is not prohibited during study participation; however, participants are discouraged from consuming more than one alcoholic drink per day during their participation. If it is determined that a participant is abusing substances, study staff will alert the SI. At that time, the SI will evaluate the situation and determine if it is appropriate for the participant to continue. The Site PI will use the “VA/DoD Clinical Practice Guideline for Management of Substance Use Disorders” (The Management of Substance Use Disorders Working Group, 2009) as a reference in the evaluation of the situation.

Additionally, during the informed consent process, participants must agree to allow study staff to contact their primary mental health provider should the participant begin to abuse substances during the course of their participation in the treatment trial. Potential participants that do not agree to this portion of the informed consent will not be allowed to enroll.

If at any point someone presents for treatment and is visibly intoxicated, study staff will follow their local VA policy regarding the assessment of intoxication and behavior risk. From that point forward, the participant will be excluded from participation in the study and coded as a treatment failure.

To summarize, stopping criteria for treatment will include:

1. Alcohol use greater than one glass of wine/day or equivalent. Use of alcohol when patient has been warned of serious medication/alcohol interactions, will also fit this criteria. If patients are found to be noncompliant with this, the Site Investigator will decide whether to administer treatment and evaluate the patient's appropriateness for continued participation.
2. Abuse of illegal drugs. If patients are found to be noncompliant with this, the Site Investigator will decide whether to administer treatment and evaluate the

patient's appropriateness for continued participation. An exception to this will be patients who used marijuana up until the past 30 days. Ongoing THC abuse will change the status to "discontinued from the study".

3. Abuse or misuse of prescribed psychiatric medications will also result in either withdrawal from the study or inclusion as a noncompliant patient.

8. Special Procedures for Safety of Potentially Suicidal or Dangerous Patients

Appropriate and frequent assessment of suicidality is important when working with severely depressed individuals. Our approach to this is comprehensive in nature and includes multiple clinical interviews (CSSRS and HRSD) as well as self-report measures (BSS and BHS) that are given at baseline, weekly during acute treatment and the taper phases, and monthly during the follow-up phase. The following criteria will be used for the assessment of suicidality:

Baseline

- a) CSSRS: the endorsement of items 4 or 5, indicating Active Suicidal Ideation with Some Intent to Act, without Specific Plan or Active Suicidal Ideation with Specific Plan and Intent, OR the endorsement of an Actual Attempt, an Interrupted Attempt, an Aborted Attempt, or Preparatory Acts or Behaviors in the 6 months prior to assessment will trigger a clinical evaluation by the Site Investigator, the patient's primary mental health provider, or a mental health emergency clinician.
- b) HRSD: a score of 2 or greater on items 10 (Anxiety-Psychic) or 11 (Anxiety-Somatic) or a score of 4 on item 9 (Agitation) IN combination with a score of 3 or greater on item 3 (Suicide) will trigger a clinical evaluation by the Site Investigator, the patient's primary mental health provider, or a mental health emergency clinician.
- c) MADRS: A score of 4 or greater on item 10 (Suicide Intent) of the MADRS will trigger a clinical evaluation by the Site Investigator, the patient's primary mental health provider, or a mental health emergency clinician.

- d) BSS: any positive response to an item on the BSS could indicate suicidal ideation thus triggering a clinical evaluation by the Site Investigator, the patient's primary mental health provider, or a mental health emergency clinician.
- e) BHS: A score of 9 or greater indicating moderate hopelessness on the BHS will trigger a clinical evaluation by the Site Investigator, the patient's primary mental health provider, or a mental health emergency clinician.
- f) STAXI-2: Scores above the 75th percentile or below the 25th percentile on the STAXI-2 will trigger an assessment of danger to self or danger to others.

Acute Treatment and Taper Phases

- a) CSSRS: the endorsement of items 4 or 5, indicating Active Suicidal Ideation with Some Intent to Act, without Specific Plan or Active Suicidal Ideation with Specific Plan and Intent, OR the endorsement of an Actual Attempt, an Interrupted Attempt, an Aborted Attempt, or Preparatory Acts or Behaviors since the last assessment will trigger a clinical evaluation by the Site Investigator, the patient's primary mental health provider, or a mental health emergency clinician.
- b) HRSD: a score of 2 or greater on items 10 (Anxiety-Psychic) or 11 (Anxiety-Somatic) or a score of 4 on item 9 (Agitation) IN combination with a score of 3 or greater on item 3 (Suicide) will trigger a clinical evaluation by the Site Investigator, the patient's primary mental health provider, or a mental health emergency clinician.
- c) MADRS: A score of 4 or greater on item 10 (Suicide Intent) of the MADRS will trigger a clinical evaluation by the Site Investigator, the patient's primary mental health provider, or a mental health emergency clinician.
- d) BSS: any positive response to an item on the BSS could indicate suicidal ideation thus triggering a clinical evaluation by the Site Investigator, the patient's primary mental health provider, or a mental health emergency clinician.
- e) BHS: A score of 9 or greater indicating moderate hopelessness on the BHS will trigger a clinical evaluation by the Site Investigator, the patient's primary mental health provider, or a mental health emergency clinician.

f) STAXI-2: Scores above the 75th percentile or below the 25th percentile on the STAXI-2 will trigger an assessment of danger to self or danger to others.

Follow-up Phase

a) CSSRS: the endorsement of items 4 or 5, indicating Active Suicidal Ideation with Some Intent to Act, without Specific Plan or Active Suicidal Ideation with Specific Plan and Intent, OR the endorsement of an Actual Attempt, an Interrupted Attempt, an Aborted Attempt, or Preparatory Acts or Behaviors since the last assessment will trigger a clinical evaluation by the Site Investigator, the patient's primary mental health provider, or a mental health emergency clinician.

b) HRSD: a score of 2 or greater on items 10 (Anxiety-Psychic) or 11 (Anxiety-Somatic) or a score of 4 on item 9 (Agitation) IN combination with a score of 3 or greater on item 3 (Suicide) will trigger a clinical evaluation by the Site Investigator, the patient's primary mental health provider, or a mental health emergency clinician.

c) MADRS: A score of 4 or greater on item 10 (Suicide Intent) of the MADRS will trigger a clinical evaluation by the Site Investigator, the patient's primary mental health provider, or a mental health emergency clinician.

d) BSS: any positive response to an item on the BSS could indicate suicidal ideation thus triggering a clinical evaluation by the Site Investigator, the patient's primary mental health provider, or a mental health emergency clinician.

e) BHS: A score of 9 or greater indicating moderate hopelessness on the BHS will trigger a clinical evaluation by the Site Investigator, the patient's primary mental health provider, or a mental health emergency clinician.

f) STAXI-2: Scores above the 75th percentile or below the 25th percentile on the STAXI-2 will trigger an assessment of danger to self or danger to others.

If a patient is determined to be suicidal, either based on the CSSRS, HRSD, MADRS, BSS, BHS, STAXI-2, clinical evaluation, or by statements made by the patient, a clinical evaluation will be immediately conducted by the Site Investigator, by the patient's individual mental health provider, or a mental health emergency clinician. The patient

will not be left alone until the evaluation has been completed and a decision made about disposition in conjunction with the Chief of Mental Health Outpatient Clinic or the Mental Health Emergency clinician.

A common practice is to stop a treatment if a patient makes a suicide attempt. Because this may occur early in treatment, before a patient is adequately treated, we would elect to continue treatment with the patient in an inpatient unit if the patient agrees to continue the trial. Discharge would be based on the patient's ability to adhere to a modified safety plan (listing behaviors and strategies in the event of increasing suicidal impulses, including returning to the ER). Monitoring of suicidal behavior within the VA is subject to national and local medical center directives. This protocol is designed to follow all such directives and not to preclude any. The suicide assessment and management plan must follow the established written plan of the site institution's guide from their mental health service.

For all patients enrolled in the study, we will develop a safety plan agreed upon with the primary mental health provider and the patient as a condition of participation in the study. All safety plans will be created according to the VA manual, "Safety Plan Treatment Manual to Reduce Suicide Risk: Veteran Version" (Stanley and Brown, 2008). This plan will include support from the VA, family contacts and friends, and other people the patient trusts. The safety plan will also incorporate the VA national suicide hotline resource phone number: 1-800-273-TALK (8255) as a support outlet. Failure of the patient to comply with the safety plan will require stopping study treatments and aggressively treating the suicidality.

Similarly, as a condition of participation, we will insist that patients with a history of suicidality have all firearms either removed from their residence or placed under lock and key, including trigger locks, with guns and ammunition locked separately and the keys given to another family member or friend. Suicide is an impulsive act and since our patients know how to use firearms effectively, the decision to make a suicide attempt will more likely be fatal if a firearm is available. Thus, another stopping point for persons with a history of suicidality will be a violation of the firearms agreement and/or the procurement of a new firearm during the study.

A certain percentage of seriously depressed patients will actually have a bipolar II or even bipolar I disorder which is undiagnosed, often because the patient sees the hypomania as “normal” or even optimum functioning. The onset of acute mania or a mixed state, both of which carry a significant risk of suicide, will also necessitate discontinuing study treatments and beginning appropriate treatment for bipolar disorder.

Another way we are attempting to decrease the suicide risk to the patient is to enable the patient to continue in treatment with his/her primary mental health provider and to continue taking all medication except those which would convey an increased risk of seizures (which would likely have resulted in the patient’s having been excluded). Should the patient drop out of outpatient treatment or if we receive information from the primary mental health provider that the patient is imminently suicidal, we will institute appropriate safety measures and discontinue study treatments if a major change in medication or treatment is necessary. Similarly, any patient who is so imminently suicidal (or homicidal) that s/he would require involuntary treatment, would no longer meet criteria for continuing study treatments. Once the suicidal patient has regained capacity (i.e., is no longer involuntarily hospitalized), if the patient so desires and treatment is not contraindicated, s/he may be re-consented and may resume treatment sessions.

If after 100 patients are enrolled 3% of the total enrolled participants have a completed suicide or 6% have attempted suicide, enrollment will be suspended pending an analysis of the SAE data by the DMC. The DMC will review all reports of suicides and suicide attempts carefully to determine whether suicide risks are excessive. If so, recommendations for restart of study enrollment may entail modifications to procedures which would be subject to IRB and FDA approval. If risk of suicide is not deemed excessive, the study will be restarted without modifications. All suicide attempts and completions will be considered SAEs, and as such, will be reported to the study executive committee, Central IRB, and the DMC by the Clinical Research Pharmacist and Study Biostatistician. The DMC will monitor all SAEs regularly (at least every 6 months) throughout the study and assess potential for increased risks to patients. The DMC may also impose requirements for more frequent monitoring of SAEs. We recognize that study termination or modification based on serious adverse events, such as suicide attempts, ultimately rests with the DMC, the Central IRB, and the study

executive committee and that more stringent stopping points may be initiated during the study.

9. Special Procedures for the Monitoring of Seizures

If at any point during study participation, a participant has a seizure (not including syncope), that participant will be withdrawn from the study treatments immediately (they will still be followed for protocol assessments). All seizures (not including syncope) will be considered serious adverse events, and as such, will be reported to the DMC by the Clinical Research Pharmacist and Study Biostatistician. We will suspend enrollment if 10 participants experience a seizure (not including syncope) during study participation, and request that the DMC evaluate the SAE data, to determine if enrollment of new patients should be resumed without protocol changes, if protocol modifications should be made before resuming enrollment, or if the study should be terminated. In the event a patient on bupropion has a seizure associated with TMS treatment, enrollment and treatment of patients on any dose of bupropion will be suspended pending evaluation by the study Executive Committee and DMC as to (a) whether the event was a true seizure or merely syncope (b) whether the patient was receiving active treatment and (c) other circumstances that might have contributed to the seizure. Bupropion use could be reinstated if the Executive Committee, DMC, CIRB, and FDA agree that such action is appropriate. We recognize that study termination or modification based on serious adverse events, such as seizures, ultimately rests with the DMC and the study executive committee and that more stringent stopping points may be initiated during the study.

C. Training

Prior to the initiation of the study, a kick off meeting of the Study Group will be held. This meeting will include discussions of the study protocol, clinical and administrative details of the study, the roles/responsibilities of the SI and of the participating sites, assessment of workload, the informed consent process, regulatory issues and recruitment goals.

In conjunction with the kick-off meeting, training sessions will be held for the study staff. Training will include the correct use of all data collection forms, study definitions, recruitment strategies, and techniques of conducting patient assessments and rTMS treatment

administrations (Appendix O). Particular problems and unique features of evaluating and following patients with TRMD will be discussed. Potential barriers to successful study implementation will be identified as well as resolution techniques. The goal of this meeting is to ensure that all staff is thoroughly familiar and comfortable with the essential aspects of the study. A GCP training course will also be held in conjunction with the kick-off meeting to ensure all study personnel are familiar with the principles of good clinical practices.

XI. RESEARCH RESULTS & CONFIDENTIALITY

A. Confidentiality

During this research study, personal information (name, address, social security number, date of birth) and health information, will be collected by VA research personnel, and used for the scientific goals of the research study. The information collected will be kept confidential as required by law. This does not prevent the researchers from disclosing voluntarily, without the patient's consent, information that would identify the patient if there is reason to believe they are experiencing suicidal or homicidal tendencies. Any reports or publications resulting from this study will not include any information that could identify the patient. Study codes will be used for all study reports generated to help maintain confidentiality.

A Certificate of Confidentiality has been obtained from the Food and Drug Administration (FDA). This helps protect participant privacy by allowing investigators to refuse to release personal and other research information outside of the research study, even by a court order. By law, information can still be released in cases of suspect child abuse, elder abuse, intent to harm oneself or others, or if the participant has an infectious disease for which State or Federal law requires reporting. The Certificate of Confidentiality does not prevent the participant or a participant's family from releasing data about the participant or his/her involvement in this study.

B. Publication of Research Results

The policy of the Cooperative Studies Program is that outcome data will not be revealed to the participating investigators until the data collection phase of the study is completed. This policy safeguards against possible biases affecting the data collection. The regular and ex-officio members of the Data Monitoring Committee will be reviewing the outcome results to ensure

that the study will be terminated if a definitive answer is reached earlier than the scheduled end of the study.

All presentations and publications from this study will follow CSP policy as stated in the CSP Guidelines. The presentation or publication of any or all data collected by participating investigators on patients entered into the Department of Veterans Affairs Cooperative Study is under the direct control of the study's Executive Committee. This is true whether the publication or presentation is concerned with the results of the principal undertaking or is associated with the study in some other way. No individual participating investigator has any inherent right to perform analyses or interpretations or to make public presentations or seek publication of any or all of the data other than under the approval of the Executive Committee.

The Executive Committee has the authority to establish one or more publication committees, usually comprised of subgroups of participating investigators and some members of the Executive Committee, for the purpose of producing manuscripts for presentation and publication. Any presentation or publication, when formulated by the Executive Committee or its authorized representatives, should be circulated to all participating investigators for review, comments, and suggestions, at least four weeks prior to submission of the manuscript to the presenting or publishing body.

All publications must give proper recognition to the Study's funding source, and should list all participants in the study. If an investigator's major salary support and/or commitment are from the VA, it is obligatory that investigators list the VA as his/her primary institutional affiliation. Submission of manuscripts or abstracts must follow the usual VA policy; ideally, a subtitle states, "A Department of Veterans Affairs Cooperative Study." The CSP also requires that every manuscript be reviewed and approved by the CSPCC Director prior to submission as a final quality control step. Mechanisms for appeal by a dissatisfied investigator will follow procedures defined by the VA Office of Research and Development.

Participation in Department of Veterans Affairs Cooperative Studies is voluntary. Any investigator who cannot accept these operation guidelines regarding publication policy should not volunteer to participate in the study.

C. Planned Publications

Following completion of the study, a manuscript will be prepared for the primary outcome. This manuscript will describe the effect of rTMS on various measures of depressive symptoms. Additional manuscripts may be prepared to report on secondary outcome findings, including effects of rTMS on suicidality, cognitive function and quality of life.

XII. REFERENCES

Alegria M, Chatterji P, Wells K, Cao Z, Chen C, Takeuchi D, Jackson J, & Meng XL. (2008). Disparity in depression treatment among racial and ethnic minority populations in the United States. *Psychiatric Services*, 59: 1264-1272.

Anderson B, Mishory A, Nahas Z, et al. (2006): Tolerability and safety of high daily doses of repetitive transcranial magnetic stimulation in healthy young men. *J ECT* 22(1):49-53.

Anderson B, Kavanagh K, et al. (2009): Decreasing procedural pain over time of left prefrontal rTMS for depression: Initial results from the open-label phase of a multisite trial (OPT-TMS). *Brain Stimulation*, Volume 2 (2): 88-92.

Anonymous (2002): Refractory Depression: Current Strategies and Future Directions. In Nolen WA ZJ, Roose SP, Amsterdam JD (ed). New York: Wiley.

Avery DH (2001): Transcranial magnetic stimulation in the treatment of depression. *Essent Psychopharmacol* 4:37-48.

Avery DH, Claypoole K, Robinson L, et al. (1999): Repetitive transcranial magnetic stimulation in the treatment of medication-resistant depression: preliminary data. *J Nerv Ment Dis* 187:114-7.

Barker AF, IL; Jarratt, JA; Jalinous, R (1989): Magnetic stimulation of the human nervous system: an introduction and basic principles. In Chokroverty S (ed), *Magnetic Stimulation in Clinical Neurophysiology*. Boston: Butterworth's, pp 55-72.

Barker AT, Freeston IL, Jalinous R, Jarratt JA (1987): Magnetic stimulation of the human brain and peripheral nervous system: an introduction and the results of an initial clinical evaluation. *Neurosurgery* 20:100-9.

Barker AT, Jalinous R, Freeston IL (1985): Non-invasive magnetic stimulation of human motor cortex. *Lancet* 1:1106-7.

Beck AT, Steer RA (1991): Manual for Beck scale for suicide ideation. San Antonio, TX: Psychological Corporation.

Beck A, Weissman A, Lester D, Trexler L. (1974). The measurement of pessimism: the hopelessness scale. *Journal of Consulting and Clinical Psychology* 42:861-865.

Benton, A.L., Sivan, A. B., Hamsher, K. deS., Varney, N. R., & Spreen, O. (1994). Contributions to neuropsychological assessment (2nd ed.). Orlando, FL: Psychological Assessment Resources.

Berman RM, Narasimhan M, Sanacora G, et al. (2000): A randomized clinical trial of repetitive transcranial magnetic stimulation in the treatment of major depression. *Biol Psychiatry* 47:332-7.

Bernabeu M, Orient F, Tormos JM, Pascual-Leone A (2004): Seizure induced by fast repetitive transcranial magnetic stimulation. *Clin Neurophysiol* 115:1714-5.

Blair, JR. & Spreen, O. (1989). Predicting premorbid IQ: A revision of the National Adult Reading Test. *The Clinical Neuropsychologist* 3, 129-136.

Blake DD, Weathers FW, Nagy LM, et al. (1995). The development of a Clinician-Administered PTSD Scale. *Journal of Traumatic Stress*, 8:75-90.

Blanchard EB, Jones-Alexander J, Buckley TC, Forneris CA. (1996). Psychometric properties of the PTSD Checklist (PCL). *Behav Res Ther* 34:669-73.

Bohning DE (2000): Introduction and Overview of TMS Physics. In George MSB, R.H. (ed), *Transcranial Magnetic Stimulation in Neuropsychiatry*. Washington, DC: American Psychiatric Press, pp 13-44.

Bohning DE, Pecheny AP, Epstein CM, et al. (1997): In-Vivo Three Dimensional Transcranial Magnetic Stimulation (TMS) Field Mapping with MRI. *Neuroimage* 5:S522.

Brown GK, NIMH Report, 2000, pages 83-86, unpublished.

Burt T, Lisanby SH, Sackeim HA (2002): Neuropsychiatric applications of transcranial magnetic stimulation: a meta analysis. *Int J Neuropsychopharmacol* 5:73-103.

Chen R, Gerloff C, Classen J, et al. (1997): Safety of different inter-train intervals for repetitive transcranial magnetic stimulation and recommendations for safe ranges of stimulation parameters. *Electroencephalogr Clin Neurophysiol* 105:415-21.

Conca A, Konig P, Hausmann A (2000): Transcranial magnetic stimulation induces 'pseudoabsence seizure'. *Acta Psychiatr Scand* 101:246-8; discussion 248-9.

Counter SA, Borg E, Lofqvist L, Brismar T (1990): Hearing loss from the acoustic artifact of the coil used in extracranial magnetic stimulation. *Neurology* 40:1159-62.

Dannon PN, Dolberg OT, Schreiber S, Grunhaus L (2002): Three and six-month outcome following courses of either ECT or rTMS in a population of severely depressed individuals--preliminary report. *Biol Psychiatry* 51:687-90.

Davey KR, Cheng CH, Epstein CM (1991): Prediction of magnetically induced electric fields in biological tissue. *IEEE Trans Biomed Eng* 38:418-22.

Davis TM, Bush KR, Kivlahan DR, et al. (2003): Screening for substance abuse and psychiatric disorders among women patients in a VA Health Care System. *Psychiatric Serv.* 54:214-18.

Delanty N, Vaughan CJ, French JA (1998): Medical causes of seizures. *Lancet* 352:383-90.

Efron B (1971): Forcing a sequential experiment to be balanced. *Biometrika* 58:403-17.

Epstein CM, Lah JJ, Meador K, et al. (1996): Optimum stimulus parameters for lateralized suppression of speech with magnetic brain stimulation. *Neurology* 47:1590-93.

Feinsod M, Kreinin B, Chistyakov A, Klein E (1998): Preliminary evidence for a beneficial effect of low-frequency, repetitive transcranial magnetic stimulation in patients with major depression and schizophrenia. *Depress Anxiety* 7:65-8.

Figiel GS, Epstein C, McDonald WM, et al. (1998): The use of rapid-rate transcranial magnetic stimulation (rTMS) in refractory depressed patients. *J Neuropsychiatry Clin Neurosci* 10:20-5.

Fireman M, Indest DW, Blackwell A, et al. (2005): Addressing Tri-morbidity (Hepatitis C, Psychiatric Diagnosis, and Substance Use): The importance of routine mental health screening as a component of a comanagement model of care. *Clinical Infectious Diseases* 40:S286-S291.

First M, Spitzer R, Gibbon M, Williams J (2002): Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Non-Patient Edition. (SCID-I/NP). New York: Biometrics Research, New York State Psychiatric Institute.

Garcia-Toro M, Pascual-Leone A, Romera M, et al. (2001): Prefrontal repetitive transcranial magnetic stimulation as add-on treatment in depression. *Journal of Neurology, Neurosurgery & Psychiatry* 71:546-48.

Gavin, A. R., Walton, E., Chae, D. H., Alegria, M., Jackson, J. S., and Takeuchi (2010). The associations between socioeconomic status and major depressive disorder among Blacks, Latinos, Asians, and Non-Hispanic Whites: Findings from The Collaborative Psychiatric Epidemiology Studies, *Psychol Med* 40: 51-61.

George MS, Wassermann EM, Williams WA, et al. (1995): Daily repetitive transcranial magnetic stimulation (rTMS) improves mood in depression. *Neuroreport* 6:1853-6.

George MS, Wassermann EM, Williams WA, et al. (1996). Changes in mood and hormone levels after rapid-rate transcranial magnetic stimulation (rTMS) of the prefrontal cortex. *J Neuropsychiatry Clin Neurosci* 8:172-80.

George MS, Wassermann EM, Kimbrell TA, et al. (1997): Mood improvement following daily left prefrontal repetitive transcranial magnetic stimulation in patients with depression: a placebo-controlled crossover trial. *Am J Psychiatry* 154:1752-6.

George MS, Nahas Z, Molloy M, et al. (2000): A controlled trial of daily left prefrontal cortex TMS for treating depression. *Biol Psychiatry* 48:962-70.

Gershon AA, Dannon PN, Grunhaus L (2003): Transcranial magnetic stimulation in the treatment of depression. *Am J Psychiatry* 160:835-45.

Gibbons RD, Hedeker DR, Elkin I, Wateraux C, Kraemer HC, Greenhouse JB, Shea MT, Imber SD, Sotsky SM, and Watkins JT.(1993): Some conceptual and statistical issues in analysis of longitudinal psychiatric data. *Arch of Gen Psychiatry* 50:739-50

Golden, CJ. (1978). Stroop Color and Word Test: A manual for clinical and experimental uses. Chicago, IL: Stoelting Co.

Golier JA, Yehuda R, Schmeidler J, Siever LJ (2001): Variability and severity of depression and anxiety in post traumatic stress disorder and. major depressive disorder. *Depression and anxiety* 13:97-100

Green BL (1996): Trauma History Questionnaire. In Stamm BH (Ed.), *Measurement of stress, trauma, and adaptation* (pp. 366-369). Lutherville, MD: Sidran Press.

Grisaru N, Yarovslavsky U, Arbarbanel J, et al. (1994): Transcranial magnetic stimulation in depression and schizophrenia. *European Neuropsychopharmacology* 4:287-88.

Grunhaus L, Dannon PN, Schreiber S, et al. (2000): Repetitive transcranial magnetic stimulation is as effective as electroconvulsive therapy in the treatment of nondelusional major depressive disorder: an open study. *Biol Psychiatry* 47:314-24.

Hadley D, Anderson B, Borckardt, et al. (2010): Safety, Tolerability and Effectiveness of High Doses of Adjunctive Left Prefrontal Daily rTMS for Treatment Resistant Depression in an Academic Clinical Setting. *Journal of ECT* (in press).

Herwig U, Padberg F, Unger J, (2001). Transcranial magnetic stimulation in therapy studies: examination of the reliability of "standard" coil positioning by neuronavigation. *Biological Psychiatry* 50:58-61.

Herwig U, Satrapi P, Schonfeldt-Lecuona C. (2003). Using the international 10-20 EEG system for positioning of transcranial magnetic stimulation. *Brain Topography* 16:95-99.

Hoflich G, Kasper S, Hufnagel A, et al. (1993): Application of transcranial magnetic stimulation in the treatment of drug-resistant major depression. *Human Psychopharmacology* 8:361-65.

Holtzheimer PE, 3rd, Russo J, Avery DH (2001): A meta-analysis of repetitive transcranial magnetic stimulation in the treatment of depression. *Psychopharmacol Bull* 35:149-69.

Janicak PG, Dowd SM, Martis B, et al. (2002): Repetitive transcranial magnetic stimulation versus electroconvulsive therapy for major depression: preliminary results of a randomized trial. *Biol Psychiatry* 51:659-67.

Jorge R, Moser D, et al. (2008): Treatment of vascular depression using transcranial magnetic stimulation. *Arch Gen Psychiatry* 65(3): 268-276.

Kaplan H, Sadock B (1996): Concise Textbook of Clinical Psychiatry. Baltimore: William & Wilkins. Validation of a short orientation-memory-concentration test of cognitive impairment. *American Journal of Psychiatry*, 140, 734-739.

Keller MB, Lavori PW, Mueller TI, et al. (1992): Time to recovery, chronicity, and levels of psychopathology in major depression. A 5-year prospective follow-up of 431 subjects. *Arch Gen Psychiatry* 49:809-16.

Kiers L, Cros D, Chiappa KH, Fang J (1993): Variability of motor potentials evoked by transcranial magnetic stimulation. *Electroencephalogr Clin Neurophysiol* 89:415-23.

Klein E, Kreinin I, Chistyakov A, et al. (1999): Therapeutic efficacy of right prefrontal slow repetitive transcranial magnetic stimulation in major depression: a double-blind controlled study. *Arch Gen Psychiatry* 56:315-20.

Kraemer HC (1992) Evaluating Medical Tests: Objective and Quantitative Guidelines. Newbury Park (CA): Sage.

Kraemer HC, Kupfer DJ (2006): Size of treatment effects and their importance to clinical research and practice. *Biol Psychiatry* 59(11):990-6.

Kolbinger HM, Hoflich G, Hufnagel A, et al. (1995): Transcranial magnetic stimulation (TMS) in the treatment of major depression: a pilot study. *Human Psychopharmacology* 10:305-10.

Kozel FA, George MS (2002): Meta-analysis of left prefrontal repetitive transcranial magnetic stimulation (rTMS) to treat depression. *Journal of Psychiatric Practice* 8:270-75.

Kozel FA, George MS, Simpson KN (2004): Decision analysis of the cost-effectiveness of repetitive transcranial magnetic stimulation versus electroconvulsive therapy for treatment of nonpsychotic severe depression. *CNS Spectr* 9:476-82.

Lehmann L, McCormick RA, McCracken L (1995): Suicidal behavior in the VA health care system. *Psychiatr. Serv.* 46:1069-71.

Lezak, MD, Howieson, DB, Loring, DW, Hannay, HJ, & Fischer, JS (2004). *Neuropsychological Assessment* (4th ed.). New York: Oxford University Press.

Lisanby SH, Gutman D, Luber B, et al. (2001) Sham TMS: Intracerebral measurement of the induced electrical field and the induction of motor-evoked potentials. *Biological Psychiatry* 49:460-63.

Little JT, Kimbrell TA, Wassermann EM, et al. (2000): Cognitive effects of 1- and 20-hertz repetitive transcranial magnetic stimulation in depression: preliminary report. *Neuropsychiatry Neuropsychol Behav Neurol* 13:119-24.

Loo C, Mitchell P, Sachdev P, et al. (1999): Double-blind controlled investigation of transcranial magnetic stimulation for the treatment of resistant major depression. *Am J Psychiatry* 156:946-8.

Loo C, Taylor JL, Gandevia SC, et al. (2000): Transcranial magnetic stimulation (TMS) in controlled treatment studies: Are some "sham" forms active? *Biological Psychiatry* 47:325-31.

Loo C, Sachdev P, Elsayed H, et al. (2001): Effects of a 2- to 4-week course of repetitive transcranial magnetic stimulation (rTMS) on neuropsychologic functioning, electroencephalogram, and auditory threshold in depressed patients. *Biol Psychiatry* 49:615-23.

Marcus SM, Young EA, Kerber KB, Kornstein S, Farabaugh AH, Mitchell J, Wisniewski SR, Balasubramani GK, Trivedi MH, and Rush AJ (2005). Gender differences in depression: Findings from the STAR*D study. *Journal of Affective Disorders*, 87:141-150.

Martin JL, Barbanjo MJ, Schlaepfer TE, et al. (2003): Repetitive transcranial magnetic stimulation for the treatment of depression. Systematic review and meta-analysis. *Br J Psychiatry* 182:480-91.

Martin JLR, Barbanjo MJ, Schlaepfer TE, et al. (2002): Transcranial magnetic stimulation for treating depression (Cochrane Review). In (eds.): The Cochrane Library. Oxford: Update Software: The Cochrane Library. Oxford: Update Software.

McDonald WM, Greenberg BD (2000): Electroconvulsive therapy in the treatment of neuropsychiatric conditions and transcranial magnetic stimulation as a pathophysiological probe in neuropsychiatry. *Depress Anxiety* 12:135-43.

McNamara B, Ray JL, Arthurs OJ, Boniface S (2001): Transcranial magnetic stimulation for depression and other psychiatric disorders. *Psychol Med* 31:1141-6.

Mishory A, Molnar C, et al. (2004): The Maximum-likelihood Strategy for Determining Transcranial Magnetic Stimulation Motor Threshold, Using Parameter Estimation by Sequential Testing Is Faster Than Conventional Methods With Similar Precision. *J ECT* 20:160-165.

Nahas Z, Bohning DE, Molloy MA, et al. (1999): Safety and feasibility of repetitive transcranial magnetic stimulation in the treatment of anxious depression in pregnancy: a case report. *J Clin Psychiatry* 60:50-2.

Nahas Z, DeBrux C, Chandler V, et al. (2000): Lack of significant changes on magnetic resonance scans before and after 2 weeks of daily left prefrontal repetitive transcranial magnetic stimulation for depression. *Journal of ECT*:380-90.

Nahas Z, Kozel FA, Li X, et al. (2003): Left prefrontal transcranial magnetic stimulation (TMS) treatment of depression in bipolar affective disorder: a pilot study of acute safety and efficacy. *Bipolar Disord* 5:40-7.

Nahas Z, Li X, Kozel FA, et al. (2004): Safety and benefits of distance-adjusted prefrontal transcranial magnetic stimulation in depressed patients 55-75 years of age: a pilot study. *Depress Anxiety* 19:249-56.

Olfson M, Marcus S, Sackeim HA, et al. (1998): Use of ECT for the inpatient treatment of recurrent major depression. *Am J Psychiatry* 155:22-9.

Padberg F, Schule C, Zwanzger P, et al. (2002a): Relation between responses to repetitive transcranial magnetic stimulation and partial sleep deprivation in major depression. *Journal of Psychiatric Research* 36:131-5.

Padberg F, Zwanzger P, Keck ME, et al. (2002b): Repetitive transcranial magnetic stimulation (rTMS) in major depression: relation between efficacy and stimulation intensity. *Neuropsychopharmacology* 27:638-45.

Padberg F, Zwanzger P, Thoma H, et al. (1999): Repetitive transcranial magnetic stimulation (rTMS) in pharmacotherapy-refractory major depression: comparative study of fast, slow and sham rTMS. *Psychiatry Res* 88:163-71.

Pascual-Leone A, Cohen LG, Shotland LI, et al. (1992): No evidence of hearing loss in humans due to transcranial magnetic stimulation. *Neurology*:647-51.

Pascual-Leone A, Houser CM, Reese K, et al. (1993): Safety of rapid-rate transcranial magnetic stimulation in normal volunteers. *Electroencephalogr Clin Neurophysiol* 89:120-30.

Pridmore S, Fernandes Filho JA, Nahas Z, et al. (1998): Motor threshold in transcranial magnetic stimulation: a comparison of a neurophysiological method and a visualization of movement method. *J Ect* 14:25-7.

Pridmore S, Bruno R, Turnier-Shea Y, Reid P, Rybak M. Comparison of unlimited numbers of rapid transcranial magnetic stimulation (rTMS) and ECT treatment sessions in major depressive episode. *Int J Neuropsychopharmacol* 2000;3:129-34.

Reitan, R. M. & Wolfson, D. (1993). The Halstead-Reitan Neuropsychological Test Battery: Theory and Clinical Interpretation. (2nd ed.). Neuropsychological Press, Tucson, AZ.

Rey, A. (1964). *L'examen clinique en psychologie*. Presses Universitaires de France: Paris.

Rossi S, Hallett M, Rossini PM, Pascual-Leone (2009): A. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clin Neurophysiol* 120:2008-39.

Roth BJ, Cohen LG, Hallett M (1991): The electric field induced during magnetic stimulation. *Electroencephalogr Clin Neurophysiol Suppl* 43:268-78.

Roth BJ, Momen S, Turner R (1994): Algorithm for the design of magnetic stimulation coils. *Med Biol Eng Comput* 32:214-6.

Roth Y, Zangen A, Hallett M (2002): A coil design for transcranial magnetic stimulation of deep brain regions. *J Clin Neurophysiol* 19:361-70.

Rush AJ, Trivedi MH, Ibrahim HM, et al. (2003): The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. *Biol Psychiatry*. 54:573-83.

Rush AJ, Kraemer HC, Sackeim HA, et al. (2006): Report by the ACNP Task Force on response and remission in major depressive disorder. *Neuropsychopharmacology*. 31:1841-53.

Sackeim HA, Prudic J, Devanand DP, et al. (1990): The impact of medication resistance and continuation pharmacotherapy on relapse following response to electroconvulsive therapy in major depression. *J Clin Psychopharmacol* 10:96-104.

Sackeim HA, Roose SP, Lavori PW (2006): Determining the duration of antidepressant treatment: application of signal detection methodology and the need for Duration Adaptive Designs (DAD). *Biological Psychiatry* 59:483-92

Skinner H A, Sheu W J (1982): Reliability of alcohol use indices. The Lifetime Drinking History and the MAST. *Journal of Studies on Alcohol* 43:1157-70.

Smith, A. (1991). Symbol Digit Modalities Test. Los Angeles, CA: Western Psychological Services.

Sobell L C, Sobell M B (1990): Self-reports issues in alcohol abuse: State of the art and future directions. *Behavioral Assessment* 12:77-90.

Sobell L C, Sobell M B, Riley D M, et al. (1988): The reliability of alcohol abusers' self-reports of drinking and life events that occurred in the distant past. *Journal of Studies on Alcohol* 49:225-32.

Sobell M B, Sobell L C (1994): Controlled drinking research. *Addiction* 89:483-84.

Spreen, O. & Strauss, E. (2006). *A Compendium of Neuropsychological Tests: Administration, Norms and Commentary*. (3rd ed.). Oxford University Press, New York.

Stein M, Kline MA, Matloff JL (2002): Adjunctive olanzapine for SSRI-resistant combat-related PTSD: a double-blind, placebo-controlled study. *Am J Psychiatry* 159:1777-9.

Stein DJ, Ipser JC, Seedat S (2006): Pharmacotherapy for post traumatic stress disorder (PTSD) (Review) The Cochrane Library 2006, Issue 2.

Stewart LM, Walsh V, Rothwell JC (2001): Motor and phosphene thresholds: a transcranial magnetic stimulation correlation study. *Neuropsychologia* 39:415-9.

Szuba MP, O'Reardon JP, Rai AS, et al. (2001): Acute mood and thyroid stimulating hormone effects of transcranial magnetic stimulation in major depression. *Biol Psychiatry* 50:22-7.

Thase ME (2001): The need for clinically relevant research on treatment-resistant depression. *J Clin Psychiatry* 62:221-4.

Thase ME (2004): Therapeutic alternatives for difficult-to-treat depression: a narrative review of the state of the evidence. *CNS Spectr* 9:808-16, 818-21.

Triggs WJ, McCoy KJ, Greer R, et al. (1999): Effects of left frontal transcranial magnetic stimulation on depressed mood, cognition, and corticomotor threshold. *Biol Psychiatry* 45:1440-6.

U.S. Department of Health and Human Services. (2001). Mental Health: Culture, Race, and Ethnicity—A Supplement to Mental Health: A Report of the Surgeon General. Rockville, MD: U.S. Department of Health and Human Services, Substance Abuse and Mental Health Services Administration, Center for Mental Health Services

Wassermann EM (1997): Report on risk and safety of repetitive transcranial magnetic stimulation (rTMS): Suggested guidelines from the International Workshop on Risk and Safety of rTMS (June 1996). *Electroencephalo Clin Neuro*. 108:1-16

Weathers F W, Keane T M, Davidson J R (2001): Clinician-administered PTSD scale: a review of the first ten years of research. *Depression and anxiety* 13:132-56.

Wolfe J, Kimerling R (1997): Gender issues in the assessment of posttraumatic stress disorder. In J. P. Wilson & T. M. Keane (Eds.), *Assessing psychology trauma and PTSD* (pp. 192-238). New York, NY: Guilford Press.

Zwanzger P, Ella R, Keck ME, Rupprecht R, Padberg F (2002): Occurrence of delusions during repetitive transcranial magnetic stimulation (rTMS) in major depression. Biol Psychiatry 51:602-3.

APPENDIX A

HUMAN RIGHTS ISSUES

HUMAN RIGHTS COMMITTEE MINUTES and INFORMED CONSENT FORMS

HRC Minutes dated 08/11/2005

HRC Minutes dated 09/16/2005

HRC Minutes dated 09/28/2005

HRC Minutes dated 03/20/2007

HRC Minutes dated 05/15/2007

HRC Minutes dated 03/19/2009

A Comment on Informed Consent

It is the responsibility of study staff to protect veterans and ensure that their participation is based upon an sufficient understanding of the study. Thus, informed consent is one of the pillars of ethical human subjects research. Study staff are obligated to work with veterans so that they have the opportunity to make an informed decision as to whether or not to participate in research. A key component in the informed consent process is the dialogue between the study staff and the veteran.

As an additional safeguard to ensure that all participants are making an informed decision is the inclusion of a quiz at the conclusion of the informed consent document. This **Attachment** item, true/false quiz addresses major points from the informed consent document and serves as a point of discussion between study staff and the veteran. Should a veteran answer any of the items incorrectly, study staff must use this opportunity to more fully discuss that information from the informed consent with the veteran. This discussion should continue until study staff are satisfied that the veteran is clear on the issue at hand. Thus this is not a pass/fail test and no data will be collected from this document.

There may be instances when study staff question a “consent capacity.” Should this occur, study staff are to follow their local VAs guidelines for the assessment of capacity to consent to participate in research. If the local VA does not have such guidelines, study staff will receive guidance from the Chairman’s Office as to how to proceed with

such an evaluation. Key components of consent capacity assessment including components of the research such as the study purpose, experimental components, associated risks and benefits, voluntary nature of participation and alternatives to participation. The determination of whether a prospective subject is capable of providing informed consent is based on a consideration of relevant study factors and an individual's consent capacity.

**COOPERATIVE STUDIES PROGRAM COORDINATING CENTER
PERRY POINT, MARYLAND
HUMAN RIGHTS COMMITTEE MEETING
Sheraton BWI (7032 Elm Road)
August 11, 2005**

A meeting of the Human Rights Committee occurred on August 11, 2005 with the following in attendance:

Eli Perencevich, M.D., M.S.
Teresa Berman
Edward Hobson
Adele M. Gilpin, Ph.D., J.D.
Rose Kurz, Ph.D.
Clint McSherry, Ph.D.

ABSENT:

Lisa Dixon, M.D., M.P.H.
Alan Fix, M.D., M.S.
Lettie Carr, J.D.
James Crothers

Non-Committee members:
CSPCC: Joseph Collins, Sc.D.
Susan Stinnett
Frances McSherry
Barbara Yndo
Eric Washburn
Karen Jones, M.S.

Study Representatives (Palo Alto VA):
Jerome Yesavage, M.D.
Brett Schneider, M.D.

The committee met for the initial review of the protocol and informed consent for CS #556, "The Effectiveness of rTMS in Depressed VA Patients" which will be submitted to the CSSMRB in November 2005.

The following materials were provided to the committee:

- Protocol (included the following documents):
 - Executive Summary (Abstract) – pages 3-4
 - Informed Consent Materials (Version 2.0, dated August 9, 2005)
- Consent Form Checklist

Dr. Collins gave an overview of the study to the committee. The purpose of this study is to evaluate the efficacy, safety, durability of benefits and cost-effectiveness of repetitive Transcranial Magnetic Stimulation (rTMS) in the resolution of treatment-resistant major depression (TRMD). Two hundred and forty veterans diagnosed with TRMD will be enrolled at 8 VA Medical Centers over a 2 ½ year period. Participants will be randomized into a double blind clinical trial to left prefrontal rTMS treatment or to sham (control) rTMS treatment for up to 30 treatment sessions. The primary outcome measure is to assess the efficacy of rTMS in veterans to bring about remission of TRMD.

The committee members reviewed both the protocol and informed consent and formulated a list of recommendations/concerns. The study Chairman, Dr. Jerome Yesavage, and Dr. Brett Schneider were then asked to join to committee meeting. Dr. Yesavage provided a concise summary of the study indicating that the major risk of the study was the possibility of seizures. Other side effects include tension headaches and/or the possibility of hearing loss. He also informed the committee that the sham will deliver the same noise as the active rTMS coil, but that neither would produce warmth or the possibility of a burn. Both Dr. Yesavage and Dr. Schneider fielded questions from the committee members. They were:

- Safety (Risk of Seizures): The protocol states that 8 seizures have been reported secondary to rTMS. The committee requested information regarding the overall numbers of individuals treated. Dr. Yesavage indicated that the literature does not provide firm numbers, but his estimate would be upwards around 100,000.

- Genetics Subprotocol: There is very little information in the protocol regarding this portion of the study. Dr. Collins indicated that all genetics subprotocols are handled by the Palo Alto Coordinating Center and once it is received at Perry Point it will be presented to the Human Rights Committee to review. There will be a separate informed consent for this subprotocol.

- Depression Rating Scale: The committee suggested that a patient depression rating scale be included in this study. Dr. Yesavage agreed that this could be done.

- Independent Assessment of Subjects. The committee expressed concern about the ability of severely depressed subjects being able to comprehend and sign an informed consent. Dr. Yesavage indicated that the protocol will be revised to state that if the physician feels that the subject may not be capable of understanding the protocol or informed consent that an independent assessment of the subject will be requested.

The committee suggested the following changes be made to the informed consent.

General

1. Lower reading level of informed consent.
2. Remove the term “non-invasive” throughout informed consent.
3. Authoritative language throughout informed consent should be softened. In other words, phrases such as “you will be required” should be changed to “you will provide.”
4. The term “feelings of suicide” which is used throughout informed consent should be changed to read “thoughts or feelings of suicide.”

Specific

Page 1 (Terms Section)

- Under rTMS. The sentence reads, “A repetitive Transcranial Magnetic Stimulation machine is an experimental device that is capable of delivering a higher number of stimuli per second.” Change the word “higher” to “high”.

Page 2 (Purpose and Background of the Study)

- The last sentence of the last paragraph, “Your duration in the study will last 11 to 21 weeks.” needs to be further explained. Perhaps the sentence could read, “Your participation in the study will be a maximum of 21 weeks.”

Page 3 (Screening Phase)

- Fifth bullet from end. Last sentence of that paragraph should be inserted after first sentence.

Page 3 (Acute Treatment Phase)

- Last sentence of first paragraph reads, "The final treatment session may occur after 15, 20, 25 or 30 sessions and will require approximately 3 hours of your time." An explanation needs to be included as to "why" the final treatment sessions may occur at any of these time intervals. Perhaps it should read, "At the end of the 15th session you will be evaluated to determine the need for future sessions."

Page 4 (Description of Study Treatment)

- Last sentence of first bullet reads, "Your head will be placed in a rigid holder so that the rTMS coil is correctly positioned on your head." It should be changed to read, "Your head will be placed in a **fixed (or stationary)** holder...."

Page 5 (Description of Study Treatment)

- Last bullet. Take out reference to the 3,200 pulses.

Page 5 (Follow-Up Phase)

- 3rd bullet. This information says that the subject will be asked about any suicidal feelings at follow-up week 6. The committee suggested that this occur throughout the study. Dr. Yesavage indicated that this would be added to the protocol.

- Last bullet. Change last bullet to read as follows: "At your final follow-up visit, you will be asked whether you believe you received the active treatment or the sham (inactive) treatment."

Page 7 (Potential Risks and Discomforts)

General Comment for this section: The committee suggested that more detail than necessary is provided in this section. It is recommended that many of the details can be removed and the section should clearly list the possible risks.

- 3rd bullet: This bullet should concentrate on why there is a potential for hearing loss and why the subject should wear earphones. The information regarding "minor burns" should be removed since the coil technology has changed and there is no risk for burns. The description of the sound under this bullet (light tapping sound) is inconsistent with the description of the sound as presented in bullet # 8.

- 4th bullet: The sentence reading, "rTMS is frequently uncomfortable for patients because the magnetic pulses cause facial and scalp muscles to contract." should be combined with bullet # 9. A comment should be made that the feelings of numbness in the face are temporary.

- 5th bullet: The following two sentences under this bullet contradict one another:
“Since that time, there have been two reports of what may have been seizures.”
“There have been no treatment-related seizures reported in current ongoing clinical trials.”
Also, the term “treatment-related” needs to be defined.

Page 8 (Potential Risks and Discomforts)

- 3rd bullet from end. Take out the reference to the study assessments being “frustrating and time-consuming.”

Page 8 (Pregnancy)

- Combine this section with the “For Women Only” section.

Page 8 (Anticipated Benefits of the Study)

- Include any known benefits of rTMS.

Page 9 (Withdrawal From the Study)

- Last bullet. Last portion of sentence should read, “...might influence your willingness to continue participating.”

RECOMMENDATION: The committee suggested that the recommendations be incorporated into a revised protocol and informed consent and presented to the committee for final approval at its next meeting.



CLINT MCSHERRY, Ph.D.
Acting Chairperson, Human Rights Committee

Department of Veterans Affairs

Memorandum

Date: September 16, 2005

From: Director, Cooperative Studies Program
Coordinating Center, Perry Point, MD 21902

Subj: Response – CSP #556, “The Effectiveness of rTMS in Depressed VA Patients”

To: Human Rights Committee Members

1. On August 11, 2005, the Human Rights Committee (HRC) met to review CSP #556, “The Effectiveness of rTMS in Depressed VA Patients”.

Following this review, your committee identified several areas in the **STUDY PROTOCOL** that required further clarification. Below is a brief description of each issue and the corrective action taken:

a. **Recommendation:** Clarify the risk of seizures.

Corrective Action: “The risk of seizures for rTMS treatment is less than 1%” (page 15 of revised protocol).

b. **Recommendation:** In addition to the Beck Scale for Suicidal Ideation (BSS), include a self-administered depression rating scale in the protocol that will be conducted at screening and on a weekly basis.

Corrective Action: The Beck Depression Inventory (BDI) has been added as a secondary outcome measurement tool. Both the BDI and the BSS are self-administered assessment tools that will be conducted at screening, during sessions 1 through the end of the final acute treatment phase and during follow-up weeks 1 through 6 (pages 23, 32 and 35 of revised protocol).

c. **Recommendation:** Clarify if there is a need for an independent assessment of a severely depressed patient’s ability to comprehend and sign an informed consent.

Corrective Action: “If the SI feels that the patient may not be capable of giving informed consent, the SI may request a competency evaluation” (page 27 of the revised protocol).

The changes cited above have been incorporated into the revised protocol (dated September 16, 2005) and references have been consistently integrated throughout the document.

2. Your committee also identified several significant issues with the **INFORMED CONSENT**. After carefully reviewing your recommendations, the following corrective actions were initiated:

- a. The definition of the rTMS machine has been revised to say: "A repetitive Transcranial Magnetic Stimulation machine is an experimental device that is capable of delivering a high number of magnetic pulses per second" (page 1 of the revised consent).
- b. Clarified the participant's duration in the study to be a maximum of 21 weeks (page 2 of the revised consent).
- c. Clarified the description of the Acute Treatment Phase to read: "Each treatment session will last approximately one hour of which 38 minutes will consist of the actual rTMS treatment. After every fifth treatment, you will meet with a member of the study staff to complete various study assessments that will last up to an additional hour. After the 15th session, you will be evaluated to determine if there has been any improvement in your symptoms of depression. This evaluation will determine if any future sessions are needed. Your final treatment session will require approximately 3 hours of your time" (page 3 of the revised consent).
- d. Replaced the term "feelings of suicide" with "thoughts or feelings of suicide" throughout the document.
- e. Added an additional self-assessment for depression that will be conducted throughout the study (pages 4 and 5 of the revised consent).
- f. Edited the Potential Risks and Discomforts section for organization, content and terminology. Side effects of hearing loss, headaches, muscle twitching, temporary numbness in the face and seizures have been clarified (page 6 of the revised consent).
- g. Various sections throughout the document have been thoroughly reorganized and edited. The language has been softened and, whenever possible, technical passages have been replaced with layman's terms. Per the Lix Readability Scale, this document is rated at an 8th grade reading level.
- h. Enhanced the "Anticipated Benefits of the Study" section to reflect the potential QOL benefits and the greater accessibility of this treatment to our veterans (page 7 of the revised consent).

3. Please note that since the August 11th HRC meeting, several **MODIFICATIONS** have been made to the CSP #556 protocol. The changes are as follows:

- A TSH, T₃ and T₄ have been added to the laboratory studies performed at screening (see page 33 of the revised protocol).
- An electrocardiogram (ECG) will be performed at screening (pages 32 and 33 of the revised protocol and page 3 of the revised consent).

- A short videotape of an actual rTMS treatment will be provided to each site for the patients to view (page 1 of the revised consent).
- The "review of medication use" has been expanded to include "natural food products" (page 33 of the revised protocol and page 2 of the revised consent).
- A brief description of scalp electrodes has been added to the "Description of Study Treatment" (page 4 of the revised consent).
- A section has been added to the "Use of Research Results" section for the patient to agree to the use of their social security number to access VA and HCFA databases (pages 8 and 9 of the revised consent).
- With the addition of the BDI as a self-administered assessment for depression, the HUI will no longer be required and has been deleted from the protocol. Also, the "Economic Issues" and the "Economic Analysis" sections of the protocol have been expanded (pages 20, 49 and 50 of the revised protocol).

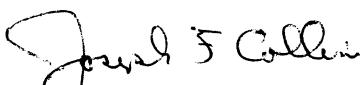
I am enclosing a copy of the revised protocol and the informed consent with the above cited changes highlighted in YELLOW. Also enclosed is a copy of the Human Rights Committee minutes for the August 11th meeting that itemizes your recommended changes.

As you can see, the CSP #556 study team has very carefully reviewed your comments/recommendations and has initiated appropriate corrective actions. The team remains very committed to this research study and will make every effort to ensure that it is a success.

If you feel that the human rights issues have been satisfactorily resolved, please indicate your approval below. You may contact me if you have any questions or concerns that you would like to discuss. I can be reached at 410-642-2411, ext 5288.

We appreciate your time in reviewing these revised documents and we look forward to the results of your second review.

Sincerely,



JOSEPH F. COLLINS, Sc.D.
Director, Cooperative Studies
Program Coordinating Center
Perry Point, Maryland 21902

APPROVE:	Date
Lisa Dixon, MD., MPH Chairman, Human Rights Committee	

Enclosures (5) Study Abstract
 Minutes of HRC meeting of August 11, 2005
 Revised Study Protocol, dated September 16, 2005
 Revised Informed Consent, Version 3.0, dated September 16, 2005 (See Appendix A)
 Original Informed Consent, Version 2.0, dated August 9, 2005 (reviewed at 8/11/05 HRC)

**COOPERATIVE STUDIES PROGRAM COORDINATING CENTER
PERRY POINT, MARYLAND
HUMAN RIGHTS COMMITTEE MEETING
Sheraton BWI (7032 Elm Road)
September 28, 2005**

A meeting of the Human Rights Committee occurred on September 28, 2005 with the following in attendance:

Eli Perencevich, M.D., M.S.
Teresa Berman
Edward Hobson
Adele M. Gilpin, Ph.D., J.D.
Alan Fix, M.D., M.S.

Non-Committee members:
CSPCC: Joseph Collins, Sc.D.
Susan Stinnett
Cindy Howell
Kousick Biswas, Ph.D.
Eric Washburn
Karen Jones, M.S.

ABSENT:

Lisa Dixon, M.D., M.P.H.
Clint McSherry, Ph.D.
Lettie Carr, J.D.
James Crothers
Rose Kurz, Ph.D.

The committee met to review a revised protocol and informed consent for **CS #556**, “The Effectiveness of rTMS in Depressed VA Patients.”

Materials provided:

- Memo to Human Rights Committee Members (dated 9/16/05). This memo provides further explanation/clarifications to the protocol and informed consent.
- Study Abstract
- Minutes of HRC meeting of August 11, 2005
- Revised Study Protocol, dated September 16, 2005 (Note: Changes highlighted in yellow)
- Revised Informed Consent, Version 3.0, dated September 16, 2005 (see Appendix A) (Note: Changes highlighted in yellow)
- Original Informed Consent, Version 2.0, dated August 9, 2005 (reviewed at 8/11/05 HRC meeting)
- Appendix F (Device Handling Procedures) and Appendix G (Device Information (provided in a separate packet)
- Informed Consent Checklist

Dr. Fix was unable to be at the last Human Rights Committee meeting when this study was reviewed, so an overview of the study was provided by the biostatistician, Karen Jones.

The committee felt their previous concerns had been addressed in both the protocol and informed consent, but did make two suggestions as follows:

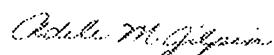
1. Pages A-10 and A-11 (Use of Research Results Section). The last two paragraphs of this section should remain together on one page rather than divided between two pages. By these paragraphs remaining together it will more clearly identify to the patient why he/she is giving authorization for administrative access to databases, using social security numbers.

2. Potential Risks and Discomforts Section

- It was suggested that information which was in the original informed consent that indicated what would be done if a seizure occurred, should remain in the informed consent, rather than be removed.
- Also, there should be more clarification of the statement, "The risk of seizures for rTMS treatment is less than 1%." One percent was a number generated in older studies using different technology, but because more current technology has not generated reliable data as of yet it is thought that 1% represents a worst case scenario.

Minor modifications had been made to both the protocol and informed consent, all which were approved by the committee.

RECOMMENDATION: The Committee approved the revised protocol and informed consent with the above suggestions to be incorporated into the informed consent.



ADELE M. GILPIN, Ph.D., J.D.
Acting Chairperson, Human Rights Committee

**COOPERATIVE STUDIES PROGRAM COORDINATING CENTER
PERRY POINT, MARYLAND
HUMAN RIGHTS COMMITTEE MEETING
Sheraton BWI (7032 Elm Road)
March 20, 2007**

A meeting of the Human Rights Committee occurred on March 20, 2007 with the following in attendance:

Clint McSherry, Ph.D.
Thomas Murtaugh, Ph.D.
Edward Hobson
Joseph Liberto, M.D.
Teresa Berman, J.D.
Toni Pollin, Ph.D.
Adele M. Gilpin, Ph.D., J.D.
Lettie Carr, J.D.

Non-Committee members:
CSPCC: Joseph Collins, Sc.D.
Susan Stinnett
David Weiss, Ph.D.
Stephen Bingham, Ph.D.
Philip Connor

ABSENT:

Eli Perencevich, M.D., M.S.

The committee met to review **CS #556** – “The Effectiveness of rTMS in Depressed VA Patients.” This study was previously reviewed by the Human Rights Committee in preparation for the November 2005 Cooperative Studies Scientific Merit Review Board (CSSMRB) meeting. At that meeting the Board recommended that the study be revised and resubmitted at a later date.

Materials provided to the committee were as follows:

- Abstract (Page A-1 of document)
- Prior HRC minutes (8/11/05 and 9/28/05)
- Protocol (Version HRC_3 dated 3/8/07)
- Informed Consent (Version HRC_3 dated 3/8/07)

Dr. Stephen Bingham, Biostatistician for the study, provided a brief overview. Three hundred and sixty veterans diagnosed with Treatment-Resistant Major Depression (TRMD) will be enrolled at 11 VA Medical Centers over a three year period. Participants will be randomized into a double blind clinical trial to left prefrontal repetitive Transcranial Magnetic Stimulation (rTMS) treatment or to sham (control) rTMS treatment (180 participants each group) for up to 30 treatment sessions. This study will evaluate the efficacy, safety, durability of benefits and cost-effectiveness of rTMS in the resolution of TRMD with emphasis on the unique VA population of depressed patients that are commonly co-morbid for substance abuse and/or Post-Traumatic Stress Disorder (PTSD).

The Committee was informed that the Study Chairperson, Dr. Yesavage, would be available by conference call if required to answer any questions.

The Committee had the following recommended revisions to the Informed Consent:

Page C-2: PURPOSE AND BACKGROUND OF THE STUDY

- The first sentence in the first paragraph of this section states, “The purpose of this study is to evaluate the effectiveness of a new technology for treating patients with treatment resistant major depression. The Committee recommends that the words, “treatment resistant major depression” be further defined in terms that are more understandable for someone reading the informed consent.

Page C-2: 1. SCREENING PHASE

- Third bullet. Information here talks about a subject being tested with an rTMS coil to determine how much power is required to make the right thumb move by stimulating a spot on the left side of the brain. The Committee recommends that this test be conducted at the end of the screening process as other screening processes may exclude subjects before this type of testing is required.

Page C-3: 1. SCREENING PHASE

- The third bullet says, “If you have an abnormal liver function test, you may need to return for additional health assessments.” This sentence needs to be reworded as the words “abnormal liver function test” may need further explanation.

Page C-6: COMPENSATION

- The amount of \$25.00 to be provided to subjects for completing the required assessments seems to be quite low. Please evaluate.

Page C-6: POTENTIAL RISKS AND DISCOMFORTS

- Second bullet says, “If you are taking any medication thought by the study investigator to greatly increase the risk of having a seizure, you will need to be taken off that medication before you can participate.” Subjects should be instructed to work with their doctor should they need to be taken off any medication.
- Third bullet. Suggested that no brand names be used here.
- Fifth bullet. Last sentence says, “The risk of seizures for rTMS treatment is less than 1%.” Committee is requesting that clarification be provided here, i.e., what is estimated denominator?
- Sixth bullet. First sentence says, “There is a possible risk of hearing loss due to the light tapping sounds made by the device.” Exactly what is the possibility? If earphones are used how much of the possibility is removed? Please quantify.

Page C-7: ANTICIPATED BENEFITS OF THE STUDY

- First paragraph, second sentence should be changed to read, “However, the treatment may provide relief **from depression** and improve your quality of life.”
- First paragraph, third sentence should be changed to read, “In the research literature to date, rTMS does appear to be an effective treatment in patients with depression who do not respond **adequately** to antidepressant medications.”
- Paragraphs one and three of this section could be combined.

- Second paragraph, last sentence says, "Study staff will refer you for additional treatment if such problems are identified." Need to indicate here who is responsible for paying for additional treatment.

Page C-7: ALTERNATIVES TO PARTICIPATION

- Last sentence says, "Alternative treatments include antidepressant medications and electroconvulsive therapy (ECT)." This needs to be explained in lay language.

Page C-8: EMERGENCY CARE AND COMPENSATION FOR INJURY

- Second paragraph should include some language regarding what a subject should do should they experience suicidal thoughts. Who should be called?
- Consider adding additional language as follows as part of this section:

In general, no long-term medical care or financial compensation for research-related injuries or illness will be provided. The costs of such treatment will be paid for by you or by your health insurance carrier. You also have the right to pursue legal remedy if you believe that your injuries justify such action. Compensation for injury/illness may be payable under the Federal Tort Claims Act. The availability of this compensation may vary depending upon the circumstances involved and there are certain limitations.

GENERAL: Consider adding the following language to the informed consent:

Some veterans are required to pay co-payments for medical care and services provided by the VA. These co-payment requirements will continue to apply to medical care and services provided by VA that are not part of the study.

RECOMMENDATION: The Human Rights Committee suggested that the recommendations to the informed consent be made and presented to the committee for final approval.
(Total = 8; Vote: For – 0, Opposed – 0, Deferred – 8)



CLINT MCSHERRY, Ph.D.
Chairperson, Human Rights Committee

**COOPERATIVE STUDIES PROGRAM COORDINATING CENTER
PERRY POINT, MARYLAND
HUMAN RIGHTS COMMITTEE MEETING
CONFERENCE CALL
May 15, 2007**

A conference call of the Human Rights Committee occurred on May 15, 2007 with the following in attendance:

Clint McSherry, Ph.D.
Thomas Murtaugh, Ph.D.
Edward Hobson
Joseph Liberto, M.D.
Teresa Berman, J.D.
Toni Pollin, Ph.D.
Lettie Carr, J.D.
Candace Rosen, J.D.

Non-Committee members:
CSPCC: Joseph Collins, Sc.D.
Susan Stinnett
Barbara Yndo
Stephen Bingham, Ph.D.
Tara Burke

ABSENT:

Eli Perencevich, M.D., M.S.
Adele M. Gilpin, Ph.D., J.D.

Two studies are scheduled for review:

CS #535 – “Anabolic Steroid Therapy on Pressure Ulcer Healing in Persons with SCI” (Annual Review plus Review of Two Protocol Amendments)

CS #556 – “The Effectiveness of rTMS in Depressed VA Patients” (Review of revised informed consent)


CLINT MCSHERRY, Ph.D.

Chairperson, Human Rights Committee

**COOPERATIVE STUDIES PROGRAM COORDINATING CENTER
PERRY POINT, MARYLAND
HUMAN RIGHTS COMMITTEE MEETING
CONFERENCE CALL
May 15, 2007**

A conference call of the Human Rights Committee occurred on May 15, 2007 with the following in attendance:

Clint McSherry, Ph.D.
Thomas Murtaugh, Ph.D.
Edward Hobson
Joseph Liberto, M.D.
Teresa Berman, J.D.
Toni Pollin, Ph.D.
Lettie Carr, J.D.
Candace Rosen, J.D.

Non-Committee members:
CSPCC: Joseph Collins, Sc.D.
Susan Stinnett
Barbara Yndo
Stephen Bingham, Ph.D.
Tara Burke

ABSENT:

Eli Perencevich, M.D., M.S.
Adele M. Gilpin, Ph.D., J.D.

The committee convened by conference call for the annual review of CS #535 – “Anabolic Steroid Therapy on Pressure Ulcer Healing in Persons with SCI.” The Committee also was asked to review a Memo of Clarification, a Data Monitoring Committee amendment, as well as an amendment proposed by the Chairman.

The following materials were provided to the Human Rights Committee:

- Memo to HRC dated 5/4/07
- Data and Safety Monitoring Board Report (DSMB) (dated 3/20/07)
- Additional Materials
 - o DSMB Minutes (dated 3/20/07)
 - o Memo of Clarification (dated 3/27/07)
 - o Chair Proposed Protocol Amendment
 - o DSMB Proposed Protocol Amendment
 - o HRC Minutes – 3/20/07, 3/29/06 and 3/10/05
 - o Latest Version of Screening and Treatment Informed Consents (dated 3/2006)
 - o Protocol (dated 6/2007) plus supporting documents
- Informed Consent Checklist

Dr. Collins, biostatistician for this study, provided a brief overview. The primary objective of this study is to determine whether spinal cord injury inpatients with a chronic Stage III or IV pressure ulcer of the pelvic region who are randomized to receive 24 weeks of optimized clinical care and an oral anabolic steroid agent (oxandrolone) will have a greater percent of healed pressure ulcers than those who receive placebo under the same standards of care. This is a five-year prospective, randomized, double blind, placebo-controlled clinical trial. There will be 400 patients entered over a 4-year enrollment period at 15 VA Medical Centers.

Recruitment for the study is below expected and options are being considered to remedy this issue. Another problem seems to be emerging. Patients are not remaining in treatment for the entire study period. The Chairman has proposed an amendment to the protocol which would allow patients who have been discharged from the hospital to continue to participate in the study as an outpatient.

The Committee reviewed the materials provided and several questions were raised and answered by Dr. Collins. These issues were mainly those of clarification.

The following documents were reviewed and approved by the Committee:

1. **Memo of Clarification** – Elevated Liver Function Tests (dated March 27, 2007)
 - This Memo of Clarification further explained that subjects with LFT levels \geq 2.5 times the upper normal limit at a participating site are required to stop study drug. At that point in time a specialist would be requested and follow-up tests performed. Only with the concurrence of the specialty consult may study drug be restarted.
2. **Chair Proposed Protocol Amendment**
 - This amendment was approved at the March 20, 2007 meeting of the DSMB; will also need approval by the Acting Director, Clinical Science R&D Service in VA Headquarters. Basically the amendment would allow subjects who have been discharged from the hospital to continue to participate in the study as an outpatient. For subjects who are discharged, every attempt should be made to maintain the complete study protocol.
3. **DSMB Protocol Amendment**
 - This amendment requires that any subject randomized to the study would have 4 week and 8 week post study drug follow-up lab tests. At the time of each follow-up visit, the healed wound site would be examined, body weight would be obtained, required blood studies would be collected on all subjects, healed or not and miscellaneous evaluations would be performed. Blood studies would be conducted on all randomized subjects regardless of wound healing status.

RECOMMENDATION: The Human Rights Committee approved the continuation of this study. The Memo of Clarification, Chair Proposed Protocol Amendment and the DSMB Protocol Amendment were also approved as presented. (Total = 8; Vote: For – 8, Opposed – 0, Deferred – 0).



CLINT MCSHERRY, Ph.D.
Chairperson, Human Rights Committee

HUMAN RIGHTS COMMITTEE VOTE

MEETING DATE: 5/15/07

CSP NO. 535

	FOR	AGAINST	ABSTAIN	ABSENT
JOSEPH LIBERTO, M.D.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
CANDACE ROSEN, J.D.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
LETTIE CARR	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
THOMAS MURTAUGH, Ph.D.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
ADELE M. GILPIN, Ph.D., J.D.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
ELI PERENCEVICH, M.D., M.S.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
TONI POLLIN, Ph.D.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
TERESA BERMAN	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
EDWARD HOBSON	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
WILLIAM C. MCSHERRY, Ph.D.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>


Signature of HR Committee Chairperson

**COOPERATIVE STUDIES PROGRAM COORDINATING CENTER
PERRY POINT, MARYLAND
HUMAN RIGHTS COMMITTEE MEETING
CONFERENCE CALL
May 15, 2007**

A conference call of the Human Rights Committee occurred on May 15, 2007 with the following in attendance:

Clint McSherry, Ph.D.
Thomas Murtaugh, Ph.D.
Edward Hobson
Joseph Liberto, M.D.
Teresa Berman, J.D.
Toni Pollin, Ph.D.
Lettie Carr, J.D.
Candace Rosen, J.D.

Non-Committee members:
CSPCC: Joseph Collins, Sc.D.
Susan Stinnett
Barbara Yndo
Stephen Bingham, Ph.D.
Tara Burke

ABSENT:

Eli Perencevich, M.D., M.S.
Adele M. Gilpin, Ph.D., J.D.

The committee convened by conference call to review CS #556 – “The Effectiveness of rTMS in Depressed VA Patients.” This study was previously reviewed by the Human Rights Committee at its March 20, 2007 meeting. The Committee suggested that recommendations to the informed consent be made and presented for final approval.

Materials provided to the committee were as follows:

- Memo to HRC dated 4/16/07
- Informed Consent dated 4/21/07 (Identifies Changes)
- Abstract
- Prior HRC Minutes (3/20/07, 9/28/05 and 8/11/05)
- Protocol (Version CSSMRB 2nd Submitted – 4/26/07)
- Informed Consent Checklist

Dr. Stephen Bingham, Biostatistician for the study, provided a brief overview for the benefit of the new Committee members. Three hundred and sixty veterans diagnosed with Treatment-Resistant Major Depression (TRMD) will be enrolled at 10 VA Medical Centers over a three year period. Participants will be randomized into a double blind clinical trial to left prefrontal repetitive Transcranial Magnetic Stimulation (rTMS) treatment or to sham (control) rTMS treatment (180 participants each group) for up to 30 treatment sessions.

The Committee had the following recommended revisions to the Informed Consent:

PURPOSE AND BACKGROUND OF THE STUDY

- The Committee recommended that the first sentence of this section be revised to read, "The purpose of this study is to evaluate the effectiveness of a new technology for treating patients with major depression who have not responded to medication."

POTENTIAL RISKS AND DISCOMFORTS

- Fifth bullet. If possible the Committee would like this information to include a common denominator with respect to patients who have had seizures while receiving rTMS treatment.
- Seventh bullet. The next to the last sentence could possibly be reworded to read, "Among people who have worn ear protection there has been no report of hearing loss."

EMERGENCY CARE AND COMPENSATION FOR INJURY

- The committee suggested that this section be split into two sections with the following language:

EMERGENCY CARE AND TREATMENT FOR RESEARCH-RELATED INJURY

Your participation in this research study is done at your own risk. Should you be injured as a direct result of your participation in this research study, the VA will provide you with free medical care, including emergency treatment, for those injuries. Should you believe that taking part in this research has injured you, you should contact the study investigator [insert name and contact number of PI] immediately. In case of an emergency in which you are unable to reach [insert name of PI], please call 911 or go to the nearest emergency room.

COMPENSATION FOR RESEARCH-RELATED INJURY

[Insert name of Institution] will not pay you compensation for research-related injury or other related costs such as lost wages, disability, or discomfort. You do not lose any of your legal rights to seek payment by signing this form.

- The material in the second paragraph which talks about suicidal thoughts should be placed in another area of the informed consent. The Committee thought an appropriate place would be directly before the SCREENING PHASE, but after the DESCRIPTION OF RESEARCH STUDY.

GENERAL

- There are references to being under the care of a primary psychiatrist used throughout the informed consent. The Committee recommends that this statement be revised to read "primary psychiatrist or mental health provider."

RECOMMENDATION: The Human Rights Committee approved the informed consent with the above suggested changes being made and presented to Human Rights Committee Chairman for final approval. (Total = 8; Vote: For – 8, Opposed – 0, Deferred – 0)



CLINT MCSHERRY, Ph.D.
Chairperson, Human Rights Committee

HUMAN RIGHTS COMMITTEE VOTE

MEETING DATE: 5/15/09

CSP NO. 556

	FOR	AGAINST	ABSTAIN	ABSENT
JOSEPH LIBERTO, M.D.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
CANDACE ROSEN, J.D.	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
LETTIE CARR	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
THOMAS MURTAUGH, Ph.D.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
ADELE M. GILPIN, PH.D., J.D.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
ELI PERENCEVICH, M.D., M.S.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
TONI POLLIN, Ph.D.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
TERESA BERMAN	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
EDWARD HOBSON	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
WILLIAM C. MCSHERRY, Ph.D.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>


Signature of HR Committee Chairperson

**COOPERATIVE STUDIES PROGRAM COORDINATING CENTER
PERRY POINT, MARYLAND
HUMAN RIGHTS COMMITTEE MEETING
Sheraton BWI – Four Points (7032 Elm Street)
March 13, 2009**

A meeting of the Human Rights Committee occurred on March 13, 2009 with the following in attendance:

Clint McSherry, Ph.D.
Lettie Carr, J.D. (left early)
Edward Hobson
Thomas Murtaugh, Ph.D.
Eli Perencevich, M.D.
Teresa Berman, J.D.

Non-Committee members:
Joseph Collins, Sc.D.
Stephen Bingham, Ph.D.
Susan Stinnett

ABSENT:

Ashish Joshi, M.D.
Robert Lavin, M.D.
Toni Pollin, Ph.D.
Adele Gilpin, Ph.D., J.D.

The committee met to review of **CS #556** – “The Effectiveness of rTMS in Depressed VA Patients. This study was submitted to the Central IRB for review and they suggested changes be made to both the protocol and informed consent. The documents presented to this committee reflect these changes being incorporated.

The following materials were provided to the Human Rights Committee:

- Abstract
- Minutes from last HRC (dated 3/20/07)
- Protocol (includes Central IRB changes)
- Informed Consent (includes Central IRB changes)

Dr. Stephen Bingham, Biostatistician for this study, gave a brief overview. This study will evaluate the efficacy, safety, durability of benefits and cost effectiveness of repetitive Transcranial Magnetic Stimulation (rTMS) in the resolution of Treatment-Resistant Major Depression (TRMD). Three hundred and sixty veterans diagnosed with TRMD will be enrolled at 9 VA Medical Centers over a three year period. Patients will be randomized into a double-blind clinical trial to left prefrontal rTMS treatment or to sham (control) rTMS treatment (180 participants each group) for up to 30 treatment sessions (45 minutes of magnetic stimulus over a 6 week period organized in 5 block treatments) with a 24 week post treatment follow-up.

This study was approved by CSSEC for funding and has recently been reviewed by the Central IRB who made considerable recommendations for changes to both the protocol and informed consent. The study will be resubmitted to the Central IRB next month.

One of the major issues facing this study is the device. Ongoing contracting has not yet identified a company who can provide both the device and sham. FDA has approved a device developed by Neuronetics, however the company will not sell us the device unless the VA agrees to change the protocol (i.e., do not allow patients to be on anti-depressant medication).

Dr. Bingham indicated that one of the major recommendations from the Central IRB which has been incorporated into the protocol is the monitoring of suicidality. Subjects will now be assessed for suicidality at the beginning of the study, after every 5th treatment, and during follow-up. Another change is the replacement of the Columbia Neuropsychological Battery test with other neuropsychological testing measures.

Committee Recommendations to Informed Consent

General

1. Informed consent is too long. Also, reading level for this document is too high; needs to be rewritten with this in mind. Simpler language needs to be used.
2. The spelling out of the acronym rTMS only needs to be done once; this would help to shorten the informed consent.
3. Subjects need to be asked if they are receiving psychotherapy and this information needs to be recorded.
4. Subjects need to be told that the device being used has not been approved by the FDA.
5. Subjects need to be informed that there will be a separate genetics informed consent for them to review.
6. Throughout the entire informed consent there are sample questions listed. These should be removed. They are of no benefit to the subjects and could be misleading or introduce bias in responding.

Page 1

1. Introduction: Last sentence. The term “psychiatrist” needs to be changed to “mental health provider” unless it is certain that every subject will have a psychiatrist and not any other prescribing mental health provider.
2. Sham Treatment:
 - a. Second sentence, “This treatment may resemble the active treatment but has no medical value” may need to be reconsidered. The phrase “has no medical value” may suggest that the active treatment is known to have medical value, whereas that remains to be seen, and is the purpose of this study.
 - b. Third sentence. The word “placebo” needs to be explained.
 - c. Fourth sentence. Needs to be revised to read, “The sham treatment will be administered to an **approximately** equal number of participants.”
3. rTMS machine. The word “machine” needs underlining.

Page 2

1. Double Blind Trial: The second sentence, “This is used to prevent the influence of the active or sham treatment.” is unclear. What is being influenced? The results of the study?

2. Background and Purpose

- a. First bullet: Needs to be shortened. Also, the last sentence, "This coil uses repetitive short pulses of magnetic energy to stimulate nerve cells within the portion of your brain below the magnetic coil." needs to be reworded so it is easy for the subject to understand. Also is the phrase "to stimulate nerve cells" correct? Is this actually what's happening? Do we know that nerve cells are being "stimulated" by this device?
- b. Second bullet: First sentence, "There have been many research studies using rTMS, but it is still considered experimental." How many research studies? Be more specific. Also, change the word "but" to "and."
- c. Third bullet: Second sentence should read, "About 52 will come from **each** medical center."

Page 3

1. Sixth Bullet: Last sentence should read, "This sample will be screened for the use of drugs, ~~such as marijuana, heroin or cocaine. It is required to participate.~~" What happens if the urine sample is positive? Subject needs to know that results will be confidential.
2. For Women of Child-Bearing Potential. This section should be combined with the similar title on Page 5. Why are there two separate sections?
3. Active Treatment Phase header: Typographical – the letter "I" should not be underlined.

Page 4

1. Graphic: Last box should also state that there will be up to 30 sessions.

Page 6

1. Description of Study Treatment. Last bullet. The word "attending" should change to "attend."
2. Follow-Up Phase section. Typo – should be period at end of paragraph.

Page 7

1. 1st Bullet: Take out all underlining.
2. Possible Risks or Discomforts. Last paragraph. All the detail provided in this paragraph is unnecessary and confusing. The last sentence should be revised to state that "There is little evidence of risk of seizures using rTMS."

Page 8

1. 5th paragraph. This paragraph is unclear. Appears to only apply to those patients having a safety plan. The word "patients" in the second sentence should be changed to "subjects" in order to remain consistent with wording throughout. How will it be verified that keys have been given to a family member or friend?
2. 6th paragraph. First sentence should read, "Your study investigator will be **monitoring** you during....." to reduce subjects' fear of being "followed."
3. 7th paragraph. Last sentence should read, "You will be informed of any new information **that** is developed.....

Page 9

1. Alternative Procedures. Last sentence. Explain the word “comorbid.” Also, this sentence seems out of place. Perhaps it belongs under “Background and Purpose” section.

Page 10

1. 2nd full paragraph. Is there any other information the subject can receive regarding the study. Perhaps a copy of the manuscript when complete?
2. Use of Research Results section. Last sentence of first paragraph. The word “sponsor” should be changed to “VA.”

Page 11

1. Last full sentence on this page, “This is not because we think the treatment will make you suicidal, but rather because we know that you are depressed and many depressed people think of suicide.” This sentence should be placed earlier in the informed consent, before all the warnings about suicidality. This is a helpful explanation that will likely reduce potential subjects’ concerns as they read all the sections about the risk of suicide.

Page 12

1. Last two sentences on this page, “By signing this form, I voluntarily agree to participate in this study. I will receive a signed copy of this consent form.” These two sentences are redundant. This information is also found in other places in the informed consent.

Page 13

1. The section header, “AGREEMENT TO PARTICIPATE IN THE RESEARCH STUDY,” the word “PARTICIPATE” is spelled incorrectly.

Page 16

1. Question 11, “You will receive the real active treatment throughout the study.” could be confusing to the patient.

RECOMMENDATION: The Human Rights Committee approved the continuation of this study with the recommendation that the suggested changes be made to the informed consent.
(Total = 5; Vote: For – 5; Opposed – 0; Deferred – 0)



W. CLINT MCSHERRY, Ph.D.
Chairman, Human Rights Committee

HUMAN RIGHTS COMMITTEE VOTE

MEETING DATE: 3/13/09

CSP NO. 556

 Kristin Messer
Signature of HR Committee Chairperson

Participant Name: _____ Date: _____

Title of Study: CSP # 556, "The Effectiveness of rTMS in Depressed VA Patients"Principal Investigator: Jerome Yesavage, M.D. Facility: Palo Alto VAMC

INTRODUCTION

You are being invited to take part in a research study that is being funded by the Department of Veterans Affairs. Before you decide to take part, it is important for you to know four things. Why the research is being done. What it will involve. What the potential risks are. What the potential benefits are.

Read the information below closely. Discuss it with family and friends if you wish. Ask study staff about anything that is not clear or if you would like more details. Take your time to decide. If you do decide to take part, your signature on this consent form will show that you received all of the information below. It will also show that you were able to discuss any questions and concerns you had with a member of the study team.

You will be asked to answer questions (Attachment #1) about the information in this consent form to show that you understand it.

You will remain under the care of your primary VA psychiatrist before, during and after participation in this study.

TERMS

There are some terms you may need to know while reading this consent form:

rTMS (repetitive Transcranial Magnetic Stimulation): rTMS uses brief pulses of magnetic energy to stimulate nerve cells in the brain.

TRMD (Treatment Resistant Major Depression): Major Depression is a serious psychiatric illness. Some of the symptoms are feeling sad or blue, hopeless, helpless, and worthless. Other symptoms are problems sleeping, changes in appetite, guilt, and thoughts of death. TRMD is a type of depression where drugs have not worked very well.

Sham Treatment: In sham treatments, the doctor or nurse goes through the motions without actually treating. This will look, feel and sound like the real treatment but will not stimulate the brain. This is like using a placebo. A placebo is a pill that looks like a real pill but does not contain the real drug. The sham treatment will be used by about half the participants.

rTMS machine: An rTMS machine is a device that can deliver a high number of magnetic pulses per second. The magnetic pulses are delivered through coils that are encased in plastic. The machine consists of a computer console, much like a desktop computer, connected to a 'wand'. The wand is collection of wires wrapped in plastic. This wand is not magnetic when

FOR VA CENTRAL IRB USE ONLY

PI/SC Approval Date: 02/08/2016

LSI Approval Date: n/a

LSI Verification Date: n/a

Participant Name: _____ Date: _____

Title of Study: CSP # 556, "The Effectiveness of rTMS in Depressed VA Patients"

Principal Investigator: Jerome Yesavage, M.D. Facility: Palo Alto VAMC

there is no electricity going through it. When the machine sends electricity through the wand, this creates a powerful but temporary magnetic field that travels through skin and bones. During rTMS sessions, you sit in a comfortable chair next to the console, and the wand rests on your head. The wand is used to focus the magnetic pulses on certain parts of the brain.

BACKGROUND AND PURPOSE

- The purpose of this study is to find out if rTMS helps people with depression who have not been helped by medication or who have not been helped enough by medication. A magnetic coil will be placed on your head. This coil uses short pulses of magnetic energy to stimulate the part of your brain below the coil.
- There have been more than 70 research studies using rTMS, and some devices, including one similar to what is used in this study, are approved by the FDA for the treatment of depression. However, the device and treatment protocol as used in this study is still considered experimental. We hope to learn whether or not rTMS helps people who have major depression that has not been helped by drugs. You have been selected as a possible participant because you have depression that does not appear to have been helped by drugs.
- Three hundred and sixty veterans at around 9 VA Medical Centers across the United States will be in this study. About 40 will come from each medical center.
- This study will be conducted and sponsored by the Department of Veterans Affairs.

DURATION OF THE RESEARCH

The entire study will last about 3.5 years. You will be in the study about 39 weeks.

STUDY PROCEDURES

If you decide to take part in this study, this is what will happen. This study has 3 phases: screening (2-4 weeks), intervention (4-11 weeks), and follow-up (24 weeks).

1. SCREENING PHASE

If you agree to be in this study, you will complete a number of tests to make sure that you are healthy enough. You will read and sign this informed consent form before you begin the screening phase. The screening phase will take 7 to 8 hours to complete. It may be done in

FOR VA CENTRAL IRB USE ONLY

PI/SC Approval Date: 02/08/2016

LSI Approval Date: n/a

LSI Verification Date: n/a

Participant Name: _____ Date: _____

Title of Study: CSP # 556, "The Effectiveness of rTMS in Depressed VA Patients"

Principal Investigator: Jerome Yesavage, M.D. Facility: Palo Alto VAMC

one day or over several days. The screening phase will last between 2 and 4 weeks after signing the informed consent form.

During the screening phase and before you are given any rTMS treatments, the following will happen:

- You will be given a physical examination. A clinician will assess your medical history, and will ask questions about your mental health, your income and living situation, your mood, your current depressive symptoms and any feelings or thoughts of suicide.
- Study staff will review with you any drugs (prescriptions, "natural food products" and "over the counter") that you are taking or have taken in the past. During the study, you will not be able to take any drugs known to greatly increase the risk of seizures. Your primary VA psychiatrist will adjust your drugs as needed.
- You will complete several self-assessments about your mood (including thoughts of suicide), your health, your use of alcohol and other substances, and any possible traumatic experiences you may have had.
- You will work with study staff and your treatment team to complete a suicide safety plan prior to enrolling in the study. This is required of all participants.
- A blood sample will be taken to check how various systems in your body, like your liver and kidneys, are working. The total amount of blood in the sample will equal about 4 tablespoons.
- If you have a liver function test that is abnormal, you may need to return for additional tests.
- You will be asked to provide a urine sample. This sample will be screened for the use of drugs. Your urine screen results will not be disclosed to anyone outside this study but positive results may require that you be excluded from this study. If you are able to stop using these drugs, you may be re-screened later.
- You will have an alcohol test to measure your blood alcohol level. This will be for the screening of alcohol use. Your results will not be disclosed to anyone outside this study but positive results may require that you be excluded from this study. If you are able to limit your alcohol consumption, you may be re-screened later.
- You will be provided with the results of these blood, urine, and alcohol tests, if you request them.
- You will be tested with an rTMS coil in order to find the settings that will be used for your treatments. This is called a "motor threshold" and is the amount of magnetic power required to make your right thumb move by stimulating your brain. We will attach pads to your right thumb and hand with tape and non-permanent sticky glue. The pads will be

FOR VA CENTRAL IRB USE ONLY

PI/SC Approval Date: 02/08/2016

LSI Approval Date: n/a

LSI Verification Date: n/a

Participant Name: _____ Date: _____

Title of Study: CSP # 556, "The Effectiveness of rTMS in Depressed VA Patients"Principal Investigator: Jerome Yesavage, M.D. Facility: Palo Alto VAMC

connected to a machine which measures the movement in your hand. We will use this machine, called an electromyograph or EMG, to find your motor threshold.

2. INTERVENTION PHASE

If you agree and are eligible to participate in this research study, you will be enrolled in the intervention phase of the study. This phase will last up to 11 weeks. You will come to the clinic for 20 to 30 sessions to receive your rTMS treatments. Each session will last around one hour. 25 minutes will consist of the actual rTMS treatment. There will normally be five daily sessions per week, Monday through Friday. After every fifth treatment, you will meet with study staff to complete study assessments that will last up to an additional hour. After the 20th session, you will be evaluated to determine if there has been any improvement in your depression. This will determine if any future sessions are needed. If you need additional sessions, you will receive either five or ten additional sessions. Your final session will require around 4 hours.

During the intervention phase, the following will happen:

- You will be randomized to either active "real rTMS" treatment or to sham treatment. In active treatment "real rTMS", brief pulses of magnetic energy are used to stimulate nerve cells in your brain. In sham treatment, the same machine is used but the nerve cells are not stimulated. Randomization is a process that is similar to flipping a coin where one side of the coin is active and the other side is sham. It is also similar to drawing a piece of paper out of a hat where some pieces say active and others say sham. There is a 50:50 chance of being randomized to either treatment group.
- All patients, regardless of whether they are getting active or sham TMS, will have mild electrical pads placed on the skin just underneath the TMS coil. During the TMS, there will be a slight electrical current passing through these pads, which will produce a mild tingling sensation. The purpose of this tingling is to make it hard to tell whether you are getting the active or sham TMS.
- Neither you nor your study doctor will know which treatment you are getting until the study is over. This type of study is called a double blind trial and this study type is being used so that your treatment and evaluation won't be affected by someone knowing whether or not you are getting active "real rTMS" or sham treatment. The study machine will know which treatment you are getting so that you will receive the same treatment at each visit. If your study doctor needs to know which treatment you are getting, he or she will be able to get that information.

FOR VA CENTRAL IRB USE ONLY

PI/SC Approval Date: 02/08/2016

LSI Approval Date: n/a

LSI Verification Date: n/a

Participant Name: _____ Date: _____

Title of Study: CSP # 556, "The Effectiveness of rTMS in Depressed VA Patients"Principal Investigator: Jerome Yesavage, M.D. Facility: Palo Alto VAMC

- Before the first treatment, we will ask you whether you believe you will receive the active "real rTMS" or the sham (inactive) treatment. After the first treatment, we will ask you whether you believe you received the active "real rTMS" or the sham treatment.
- You will be retested to find your motor threshold on the first day of each of the 5-session blocks. You will be tested with an active coil to find the settings that will be used for you.
- You will be asked about any other drugs that you are taking and about side effects that may have occurred since your last visit. These may or may not be related to the study treatment. You will also be asked about the amount of alcohol or other substances you have consumed since your last visit. These questions will be asked at every session.
- You will be asked to provide a urine sample several times randomly during this phase. This sample will be screened for the use of drugs. Your urine screen results may be disclosed to your primary mental health provider if we think that you are using in a risky manner. You may also not be allowed to receive your rTMS treatment.
- You will have an alcohol test to determine your blood alcohol level several times randomly during this phase. This will be for the screening of alcohol use. Your results may be disclosed to your primary mental health provider if we think that you are using alcohol in a risky manner. You may also not be allowed to receive your rTMS treatment.
- You will be asked about your physical and mental health, your use of alcohol and other drugs, your mood, your current depressive symptoms and any thoughts or feelings of suicide.
- You will complete several self-assessments about how you are feeling after every 5th session.

The following is a description of the study procedure:

- You will be awake and alert throughout the treatment session.
- You will be seated in a chair. You will be provided with ear protection. Your head will be placed in a holder so that it is correctly positioned. You may close your eyes during treatment but not fall asleep.

FOR VA CENTRAL IRB USE ONLY

PI/SC Approval Date: 02/08/2016

LSI Approval Date: n/a

LSI Verification Date: n/a

Participant Name: _____ Date: _____

Title of Study: CSP # 556, "The Effectiveness of rTMS in Depressed VA Patients"Principal Investigator: Jerome Yesavage, M.D. Facility: Palo Alto VAMC

- A metal coil in a plastic case will be held against the scalp on the left side of your head. You will hear a clicking noise as a few magnetic pulses are produced. The administrator will use the coil to find the area in your brain that causes your right thumb to move. This is called the Motor Threshold (MT).
- Participants normally notice only a loud clicking noise, and tingling sensation on the scalp. The coil may feel warm or hot against your head.
- Depending on the treatment group that you have been assigned to, you will receive either active "real rTMS" or sham (inactive) treatments.
- You may drive yourself to and from treatment sessions and attend to your normal daily tasks.

3. FOLLOW-UP PHASE

After the intervention phase of the study, you will enter a 24-week follow-up phase. If your depression has significantly improved during the intervention phase, you will receive 6 additional treatment sessions during the first three weeks (3 during the first week, 2 during the second, and 1 during the third) of the follow-up phase. During the follow-up phase, you will meet with study staff to complete study assessments. The amount of time required to complete each monthly visit (testing and evaluation) should be around 1 hour. The final follow-up visit will take about 4 to 5 hours. If you are unable to come in for a face to face follow-up visit, telephone visits may be arranged.

During the 24- week follow-up phase, the following will happen:

- Study staff will ask you about the following:
 - Any drugs that you are taking and side effects that may have occurred since your last visit.
 - Your physical and mental health, your mood and your current depressive symptoms.
 - Any thoughts or feelings of suicide.
- You will complete several self-assessments about your mood, your health, and any possible traumatic experiences you may have had.

FOR VA CENTRAL IRB USE ONLY

PI/SC Approval Date: 02/08/2016

LSI Approval Date: n/a

LSI Verification Date: n/a

Participant Name: _____ Date: _____

Title of Study: CSP # 556, "The Effectiveness of rTMS in Depressed VA Patients"Principal Investigator: Jerome Yesavage, M.D. Facility: Palo Alto VAMC

- You will be asked to provide a urine sample several times during this phase. This sample will be screened for the use of drugs. Your urine screen results may be disclosed to your primary mental health provider if we think that you are using drugs in a risky manner.
- You will have an alcohol test to determine your blood alcohol level several times during this phase. This will be for the screening of alcohol use. Your results may be disclosed to your primary mental health provider if we think that you are using alcohol in a risky manner.
- At your final follow-up visit, we will ask you whether you believe you received the active "real rTMS" or the sham treatment.

4. FOR ALL STUDY PHASES

- Sleep is frequently disrupted when people are depressed. We recognize that you may have trouble sleeping. It is important for the treatment team to monitor the amount of sleep you get prior to each treatment session. If study staff believes that you have not gotten adequate sleep, they may cancel or reschedule that session.
- It is important for study staff to be aware of any changes in your medications during your participation in the study. If there are changes to your medications or you take them not as prescribed prior to a treatment session, study staff may choose to cancel or reschedule that session.
- You will interact with members of the entire study team. This includes a psychiatrist or neurologist, a nurse or physician assistant rTMS Operator, and a Study Coordinator. The study takes place at the (insert site name) during normal business hours, Monday through Friday, 8am to 4:30pm. If asked, we will provide a note for your employer that you were receiving medical treatment. We will not compensate for missed work time.
- You will be asked about adverse events whenever you are seen by study staff for treatment, evaluation, and follow-up visits. An adverse event is anything bad that happens with you and may or may not be related to your participation in this study. An independent committee will be told about all adverse events at least once every six months. If they believe that any aspect of this study is unsafe, they will recommend that changes be made to eliminate the safety problem.

FOR VA CENTRAL IRB USE ONLY

PI/SC Approval Date: 02/08/2016

LSI Approval Date: n/a

LSI Verification Date: n/a

Participant Name: _____ Date: _____

Title of Study: CSP # 556, "The Effectiveness of rTMS in Depressed VA Patients"Principal Investigator: Jerome Yesavage, M.D. Facility: Palo Alto VAMC**RESPONSIBILITIES AND EXPECTATIONS OF STUDY PARTICIPANTS**

In order to maximize the possible benefits of the rTMS treatment and to best ensure the safety of study participants, we will now go over the responsibilities and expectations of participation.

- Complete your questionnaires as instructed. You are free to skip any questions that you prefer not to answer.
- Ask questions as you think of them.
- Tell the investigator or research study staff if you think you might be pregnant.
- Tell the investigator or research staff if you change your mind about staying in the study.
- While participating in this research study, do not take part in any other research study without approval from the investigators. This is to protect you from possible injury from things such as extra blood drawing or potential drug interactions. Taking part in other research studies without approval from the investigators may invalidate the results of this research, as well as that of the other studies.
- Keep your study appointments. If it is necessary to miss an appointment, please contact the investigator or study staff to reschedule as soon as you know you will miss the appointment.
- It is important that you not give false, incomplete, or misleading information about your medical history, including past and present drug use, because this could have serious consequences for your well-being.
- The effects of alcohol and substance use while undergoing rTMS are not well known at this time. Alcohol use will be limited to 1 alcoholic beverage, defined as 12 oz. beer, 5 oz. wine, or 1.5 oz. hard liquor, a day. You cannot use illegal substances, such as marijuana, cocaine, and amphetamines, during your participation in the study. If you begin to use substances in a risky manner during your participation in this trial, study staff will notify your primary VA psychiatrist and you may be removed from the study. If you report consuming more than one alcoholic beverage or using substances prior to your treatment session, study staff may choose to cancel or reschedule that session.

FOR VA CENTRAL IRB USE ONLY

PI/SC Approval Date: 02/08/2016

LSI Approval Date: n/a

LSI Verification Date: n/a

Participant Name: _____ Date: _____

Title of Study: CSP # 556, "The Effectiveness of rTMS in Depressed VA Patients"Principal Investigator: Jerome Yesavage, M.D. Facility: Palo Alto VAMC**POSSIBLE RISKS OR DISCOMFORTS**

Any procedure has possible risks and discomforts. The procedures in this study may cause all, some or none of the risks or side effects listed. Rare, unknown, or unforeseeable (unanticipated) risks also may occur. You need to carefully consider the following:

The drawing of blood may cause pain, bleeding, bruising, feeling faint and, on rare occasions, infection at the site of the needle insertion. Precautions will be taken to minimize these risks. The total amount of blood that you will be asked to give during the study is about 4 tablespoons.

If you are taking any drugs that may increase the risk of having a seizure, you will need to be taken off those drugs before you can participate. You and your physician will need to discuss the feasibility of your discontinuing any such medication. Withdrawal from such drugs may cause discomfort or illness.

A few patients receiving rTMS have had seizures. All of the reported seizures resolved promptly on their own and none had any lasting effects or adverse impact on the patients. There is little evidence of risk of seizures using rTMS the way it will be used in this study.

There may be an increased risk of seizures from combining the use of bupropion and rTMS.

In the unlikely event that a seizure does occur, you will be closely monitored and treated for any medical or psychological consequences. Lab tests will be drawn and you will be seen by a neurologist as soon as possible. The rooms where the rTMS studies are performed are fully equipped to safely handle a seizure. After the neurologist has seen you and determined what caused your seizure, you will be given a letter regarding the seizure to share with your primary health care provider. If you have no other medical or neurological problem that caused the seizure, the letter will indicate that the seizure during rTMS does not increase your risk for future seizures.

rTMS treatment can result in mild to moderate headaches in as many as 30 out of 100 of patients. Some people also report discomfort at the site of rTMS stimulation. This occurs in around 15 out of 100 of patients. Headaches and site discomfort usually readily respond to acetaminophen or ibuprofen. Painfulness improves over time or goes away. Often patients fall asleep in the second week while receiving the same treatment that on the first day was reported as very painful.

FOR VA CENTRAL IRB USE ONLY

PI/SC Approval Date: 02/08/2016

LSI Approval Date: n/a

LSI Verification Date: n/a

Participant Name: _____ Date: _____

Title of Study: CSP # 556, "The Effectiveness of rTMS in Depressed VA Patients"

Principal Investigator: Jerome Yesavage, M.D. Facility: Palo Alto VAMC

There is a small risk of dental pain with rTMS, during or immediately after the treatment. If this occurs, let your study doctors and nurses know and they may be able to move the rTMS coil position or provide you with a bite block to reduce this pain or make it not happen.

rTMS treatment may produce movement or tingling of the arm, leg, face or scalp. You may also experience a temporary feeling of numbness in the face.

During treatment the coil may get warm. It may feel about the same as a heating pad on low or medium setting. This may be uncomfortable but should not be painful.

There is a possible risk of hearing loss due to the sounds made by the device. You will wear earplugs and headphones during your rTMS sessions. This should greatly reduce the possibility of hearing loss. If you think your hearing is getting worse during the study, tell the study team right away. After your last study treatment, you may keep the headphones if you choose.

The rTMS operator will monitor you for ear protection, coil placement, and seizure activity during all sessions.

In some people, daily prefrontal rTMS can cause them to have increased energy, no need for sleep, and rapid racing thoughts. This is called mania. If you notice these changes let your primary mental health provider and study team know.

A major risk in treating seriously depressed patients is the risk of suicide. We will work with you and your primary mental health provider in the creation of a written safety plan prior to your participation in the study. One part of the safety plan may be the requirement that all firearms either be removed from your residence or be placed under lock and key, including trigger locks, with guns and ammunition locked separately and the keys given to another family member or friend.

You will frequently be asked about "suicidal thoughts" during the study. This is not because we think the treatment will make you suicidal, but rather because we know that you are depressed and many depressed people think of suicide. Please give honest and open answers to such questions and we will try to help you get over any such feelings. And because this is such an important issue, if you have any suicidal thoughts, it is vital that you seek appropriate care immediately. An actual suicide attempt will result in not being able to continue study treatments and you will immediately enter the 24 weeks (6 month) follow-up phase.

FOR VA CENTRAL IRB USE ONLY

PI/SC Approval Date: 02/08/2016

LSI Approval Date: n/a

LSI Verification Date: n/a

Participant Name: _____ Date: _____

Title of Study: CSP # 556, "The Effectiveness of rTMS in Depressed VA Patients"

Principal Investigator: Jerome Yesavage, M.D. Facility: Palo Alto VAMC

Your study investigator will be monitoring you during your participation to see if you are experiencing any side effects. It is important that you report promptly any side effect to study staff. If you feel, or your study investigator feels, that the side effects are not well tolerated, treatment may be stopped altogether and you may be withdrawn from the study.

The possibility of long-term risks is unknown. In previous studies, animal and human brains have shown no evidence of any kind of damage from rTMS. As with any experimental treatment, there may be unforeseen risks associated with this device. You will be informed of any new information that is developed during the study that might affect your willingness to continue your participation.

You will also be evaluated for current and previous medical and psychiatric diagnoses. You will be asked to report your use of alcohol and other substances (marijuana, cocaine, heroin, etc). You will also be asked to complete questionnaires that ask about your life satisfaction, quality of life, work, suicide ideation and other aspects of your life, as well as an interview about symptoms of depression. These questionnaires take around 5-30 minutes each to complete (total time, around 8 hours). The type, frequency, and intensity of your major depression symptoms will be evaluated during a 2 hour interview. The total time required for completing questionnaires, assessments, and interviews is around 5-10 hours and will be done over several visits. These questions may bring on uncomfortable thoughts, feelings, and lead to recalling troubling memories. In some cases the subject of questions and length may cause fatigue, discomfort, and/or boredom. It is important to remember that these questions are to be answered at your own pace. If you feel anything described above let the study coordinator know and he/she can continue the questions another day.

For Women of Child-bearing Potential

For safety reasons, pregnant women will not be allowed to participate in this study. This is because the effects of rTMS on an unborn child are not known. There may be unforeseeable (unanticipated) risks to the participant (or to the unborn child) if the participant is pregnant or becomes pregnant during the study.

You will have a urine pregnancy test within 7 days prior to your starting study treatment. Thereafter, you will have a urine pregnancy test every four weeks through the end of the study to be sure that you are not pregnant.

You must agree to use a medically acceptable form of birth control while participating in the study. Acceptable forms of birth control are:

- Complete abstinence (not having sexual intercourse with anyone)

FOR VA CENTRAL IRB USE ONLY

PI/SC Approval Date: 02/08/2016

LSI Approval Date: n/a

LSI Verification Date: n/a

Participant Name: _____ Date: _____

Title of Study: CSP # 556, "The Effectiveness of rTMS in Depressed VA Patients"Principal Investigator: Jerome Yesavage, M.D. Facility: Palo Alto VAMC

- An oral contraceptive (birth control pills)
- Norplant
- Depo-Provera
- A condom with spermicide
- A cervical cap with spermicide
- A diaphragm with spermicide
- An intrauterine device
- Surgical sterilization (having your tubes tied)

If you become pregnant during the intervention phase of the study, you will not be able to continue the study treatments and you will immediately enter the 24 week (6 visits) follow-up phase. You will also be referred to a Women's Health Clinic. If you become pregnant during the follow-up phase of the study, you will continue to come in for all remaining follow-up phase visits and will complete all assessments as you normally would.

If you become pregnant at any time during the study, you will be asked to sign a release of information form for study staff to access medical records to obtain information regarding the outcome of your pregnancy. No pediatric records will be reviewed.

There is no likely effect on sperm count or the motility of sperm or other reproductive risks associated with fathering a child, although this has not been formally tested in humans. Likewise, there are no known risks on sperm and ova (eggs).

Risks of the usual care you receive are not risks of the research. They are not included in this consent form. You should talk with your health care providers about risks of usual care.

POTENTIAL BENEFITS

We can't promise that you will get any benefits from taking part in this research study. However, possible benefits may include relief from depression and improvement in quality of life. The information that is obtained during this study may be scientifically useful and may lead to greater knowledge about the treatment of depression.

FOR VA CENTRAL IRB USE ONLY

PI/SC Approval Date: 02/08/2016

LSI Approval Date: n/a

LSI Verification Date: n/a

Participant Name: _____ Date: _____

Title of Study: CSP # 556, "The Effectiveness of rTMS in Depressed VA Patients"

Principal Investigator: Jerome Yesavage, M.D. Facility: Palo Alto VAMC

The medical testing done in this study could reveal a medical condition that you might not have previously been aware of and for which you may need treatment. Study staff will refer you for additional treatment if such problems are identified but the study will not pay for the treatment of any such identified problems.

ALTERNATIVE PROCEDURES

You may choose not to participate in this study. If this is your decision, there are other choices including the standard treatments provided by the local clinic. Your study investigator or a study clinician will discuss any alternatives with you before you agree to participate in this study.

Alternative treatments include talk therapy, antidepressant drugs, rTMS treatment outside of the study, and electroconvulsive therapy (ECT). ECT is a medical treatment for severe mental illness in which a small, carefully controlled amount of electricity is introduced into the brain to cause a seizure. It is also known as "electrotherapy" or "shock therapy". You may also discuss these options with your doctor.

CONFIDENTIALITY

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov> as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

The information collected for this study will be kept confidential. We will include information about your study participation in your medical record. We will not share your study records or identify you except as described in this informed consent document. There are times when we might have to show your records to other people. For example, someone from the Office of Human Research Protections, the Government Accountability Office, the Office of the Inspector General, the VA Office of Research Oversight, the VA Central IRB, our local Research and Development Committee, and other study monitors may look at or copy portions of records that identify you.

We have obtained a Certificate of Confidentiality from the Federal Government. This helps protect your privacy by allowing us to refuse to release your name or other information outside of the research study, even by a court order. The Certificate of Confidentiality will not be used to prevent disclosures to local authorities of child or elder abuse and neglect, harm to self or others, or if we become aware that you have an infectious disease that State or Federal Law requires us to report. If we learn of such a situation, we are mandated to act appropriately, which may include revealing your identity as a research participant to authorities. The

FOR VA CENTRAL IRB USE ONLY

PI/SC Approval Date: 02/08/2016

LSI Approval Date: n/a

LSI Verification Date: n/a

Participant Name: _____ Date: _____

Title of Study: CSP # 556, "The Effectiveness of rTMS in Depressed VA Patients"Principal Investigator: Jerome Yesavage, M.D. Facility: Palo Alto VAMC

Certificate does not prevent you or a member of your family from releasing data about yourself or your involvement in this study.

During this research study we will use personal and health information for the scientific goals of the study. The information collected for this study will be kept confidential except where disclosure is required by law. For example, if you appear to want to do harm to yourself (suicide) or to others, we will report this information to the appropriate authorities and assist you in obtaining care. We may also contact your primary mental health provider regarding clinically significant status changes. All local, state and federal regulations will be followed when releasing study data. Any reports or publications resulting from this study will not include any information that could identify you.

We will use your SSN to access VA databases to extract information about your use of VA health care services outside of the trial, including those provided by non-VA providers that the VA pays for, and the costs of these services. This includes records on all of the medicines that you receive from the VA. Your SSN will be matched to the scrambled SSN that the VA uses as a patient identifier in these datasets. Your actual SSN will only be used to obtain the scrambled SSN; the real and scrambled SSNs will never be in the same data file and the real SSN will be in an encrypted file except for when we use it to link to the scrambled SSN.

Your social security number and name will be kept separate from all of your study data. In signing this informed consent you authorize the use of your social security number and last name for administrative access to the databases described above. You may not participate in this study if you are not willing to give us your social security number.

Data collected during the study will be stored in a way that does not identify you by name. All data forms and reports will be coded. Research and clinical records will be stored in a locked cabinet. Only selected study researchers will have access to this information. They are bound by rules of confidentiality not to reveal identifying information to others. All data collected for this study will be sent electronically via a secure fax and/or online server to the VA Cooperative Studies Program Coordinating Center (CSPCC), Perry Point, Maryland and will be kept in a secure database. The CSPCC will be responsible for the processing and analyses of all research data. The Chairman's Office (located at VAMC Palo Alto, CA), the Cooperative Studies Program Clinical Research Pharmacy Coordinating Center in Albuquerque, NM and members of the Executive Committee and the Data Monitoring Committee, as well as monitoring bodies associated with the study will review research data. Study records will be kept for the length of time required by law after the study is completed.

FOR VA CENTRAL IRB USE ONLY

PI/SC Approval Date: 02/08/2016

LSI Approval Date: n/a

LSI Verification Date: n/a

Participant Name: _____ Date: _____

Title of Study: CSP # 556, "The Effectiveness of rTMS in Depressed VA Patients"

Principal Investigator: Jerome Yesavage, M.D. Facility: Palo Alto VAMC

Authorized personnel from the VA will see your medical records and the consent form that you signed. Other federal agencies such as the Food and Drug Administration (FDA) and other Federal agencies; e.g., the Office for Human Research Protection (OHRP) and the Government Accountability Office (GAO), the Office of the Inspector General, the VA Office of Research Oversight, the VA Central IRB, our local Research and Development Committee, and other study monitors may review your records to make sure that they meet federal, state or local regulations. Because of the need to allow access to your medical records by these agencies, absolute confidentiality cannot be guaranteed but every effort will be made to keep information about you both private and confidential.

You will not be able to have access to the research data that has been collected about you during the study. However, after the study is completed, which is after last participant has completed their follow-up, you will be notified which treatment you received during the study.

By signing this informed consent form, you are giving us permission to use the information collected about your health only until the end of the study. You have the right, at any time, to take back your permission to use your personal health information for research purposes. However, if your information has already been sent to the Perry Point Cooperative Studies Program Coordinating Center or has been combined with other participants' information (such as when numbers are averaged) it will continue to be used. No further information about you will be collected. When your information is combined with other participants' information in the study, your personal information cannot be identified.

If you have any questions about withdrawing your permission, you may contact [insert name] at [insert phone number]. To withdraw your permission for the use of your personal health information, you must contact Dr. [insert name of PI] in writing at [insert address]. If you withdraw permission or do not give your permission, you will still receive all the medical care and benefits for which you are otherwise eligible but you will be unable to continue in this research study.

COSTS TO PARTICIPANTS AND PAYMENT

Costs to Participants

You, your insurance company or any other third party payer will not be billed for any study-related treatments, blood or urine tests or other procedures that are part of this study and not part of your routine treatment. If you receive treatment that is part of your usual care, you may be billed as you usually are.

FOR VA CENTRAL IRB USE ONLY

PI/SC Approval Date: 02/08/2016

LSI Approval Date: n/a

LSI Verification Date: n/a

Participant Name: _____ Date: _____

Title of Study: CSP # 556, "The Effectiveness of rTMS in Depressed VA Patients"

Principal Investigator: Jerome Yesavage, M.D. Facility: Palo Alto VAMC

For veterans who are required to pay co-payments for medical care and services provided by VA, these co-payment requirements will continue to apply for medical care and services provided by VA that are not part of this study.

Payment Offered for Participation

You will be compensated for your time and inconvenience. You will be responsible for transportation to and from all treatment and follow-up sessions.

You will be paid for your time and inconvenience in each of the three study phases as follows:

- Screening Phase: \$40
- Intervention Phase: \$300
- Follow-up Phase: \$60

If you withdraw or stop early in any of the three phases, you will be paid according to what phase you are in. For example, if you withdraw at any time during the Intervention Phase you would receive payment of \$40 for the screening phase and \$300 for the Intervention Phase, but not \$60 for the follow-up phase. If you complete all three phases you would receive a total of \$400.

MEDICAL TREATMENT AND COMPENSATION FOR INJURY

Every reasonable safety measure will be used to protect your well-being. If you are injured as a result of taking part in this study, the VA will provide necessary medical treatment at no cost to you. Financial compensation is not available for such things as lost wages, disability or discomfort due to an injury.

If you should have a medical concern or get hurt or sick as a result of taking part in this study, call:

DURING THE DAY:

Dr./Mr./Ms. _____ at _____ and

AFTER HOURS:

Dr. /Mr. /Ms. _____ at _____.

Emergency and ongoing medical treatment will be provided as needed.

FOR VA CENTRAL IRB USE ONLY

PI/SC Approval Date: 02/08/2016

LSI Approval Date: n/a

LSI Verification Date: n/a

Participant Name: _____ Date: _____

Title of Study: CSP # 556, "The Effectiveness of rTMS in Depressed VA Patients"

Principal Investigator: Jerome Yesavage, M.D. Facility: Palo Alto VAMC

You do not give up any of your legal rights and you do not release the VA from any liability by signing this form.

In case of an emergency in which you are unable to reach [insert name of PI at (add contact information)], please call 911 or go to the nearest emergency room.

No promises have been given to you since the results and the risks of a research study are not always known in advance. However, every reasonable safety measure will be taken to protect your well-being. You have not released this institution from liability for negligence.

VOLUNTARY PARTICIPATION

Your participation is voluntary. It is up to you to decide whether or not to take part in this study. If you do not wish to be in this study or leave the study early, you will not lose any benefits to which you are otherwise entitled and still receive all usual care that is available to you. Your decision not to take part will not affect the relationship you have with your doctor or other staff and it will not affect the usual care that you receive as a patient.

If you decide to take part you may still withdraw your consent at any time and stop participation without penalty or loss of benefits. You are not waiving any legal claims, rights or remedies because of your participation in this research study. If you leave the study early for any reason, it is important to come in for a final study visit to ensure appropriate follow-up care outside of this research study.

For data already collected prior to your withdrawal, the investigator may continue to review the data already collected for the study but cannot collect further information, except from public records, such as survival data. Specimens already used cannot be withdrawn.

RIGHT OF INVESTIGATOR TO TERMINATE PARTICIPATION

At the discretion of the study team you may be withdrawn from this study.

Possible reasons for withdrawing you from the study include:

- You fail to follow instructions.
- You drink more than one glass of alcohol a day, defined as 12 oz. beer, 5 oz. wine, or 1.5 oz. hard liquor
- You abuse illegal drugs.

FOR VA CENTRAL IRB USE ONLY

PI/SC Approval Date: 02/08/2016

LSI Approval Date: n/a

LSI Verification Date: n/a

Participant Name: _____ Date: _____

Title of Study: CSP # 556, "The Effectiveness of rTMS in Depressed VA Patients"Principal Investigator: Jerome Yesavage, M.D. Facility: Palo Alto VAMC

- You abuse or misuse prescription drugs.
- You become pregnant.
- The investigator decides that continuation could be harmful to you.
- You need treatment not permitted for participation in the study.
- The study is cancelled.
- Other administrative reasons.
- Unanticipated circumstances.

If you leave the study early for any reason, it is important to come in for a final study visit to ensure appropriate follow-up care outside of this research study.

PERSONS TO CONTACT

If you have any questions, complaints, and concerns about the research or related matters, you may contact _____, the participating investigator at _____, _____, the study coordinator at _____, or the Patient Advocate of the [Insert Medical Center name here] at _____.

If you have questions about your rights as a study participant, or you want to make sure this is a valid VA study, you may contact the VA Central Institutional Review Board (IRB). This is the Board that is responsible for overseeing the safety of human participants in this study. You may call the VA Central IRB toll free at 1-877-254-3130 if you have questions, complaints or concerns about the study.

SIGNIFICANT NEW FINDINGS

Sometimes during the course of a research study, new information becomes available about the treatment that is being studied that could change your willingness to continue in the study. If this happens, your research doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw at that time, your research doctor will make arrangements for your medical care to continue. If you decide to continue in the study, you may be asked to sign an updated consent form. Your research doctor could also decide that it may be in your best interests to withdraw you from the study. He/she will explain the reasons and arrange for your medical care to continue.

FOR VA CENTRAL IRB USE ONLY

PI/SC Approval Date: 02/08/2016

LSI Approval Date: n/a

LSI Verification Date: n/a

Participant Name: _____ Date: _____

Title of Study: CSP # 556, "The Effectiveness of rTMS in Depressed VA Patients"Principal Investigator: Jerome Yesavage, M.D. Facility: Palo Alto VAMC**AGREEMENT TO PARTICIPATE IN THE RESEARCH STUDY**

Dr./Mr./Ms. _____ has explained the research study to you. You have been told of the risks or discomforts and possible benefits of the study. You have been told of other choices of treatment available to you. You have been given the chance to ask questions and obtain answers.

You voluntarily consent to participate in this study. You also confirm that you have read this consent, or it has been read to you. You will receive a copy of this consent after you sign it. A copy of this signed consent will also be put in your medical record if applicable.

I agree to participate in this research study as you have explained in this document.

Participant's Name	Participant's Signature	Date
Name of person obtaining authorization and consent	Signature of person obtaining authorization and consent	Date

FOR VA CENTRAL IRB USE ONLY

PI/SC Approval Date: 02/08/2016

LSI Approval Date: n/a

LSI Verification Date: n/a

Participant Name: _____ Date: _____

Title of Study: CSP # 556, "The Effectiveness of rTMS in Depressed VA Patients"Principal Investigator: Jerome Yesavage, M.D. Facility: Palo Alto VAMC**ATTACHMENT 1 - CONSENT FORM QUESTIONS****The Effectiveness of rTMS in Depressed VA Patients**

	TRUE	FALSE
1) Your participation in this research study is voluntary.	<input type="checkbox"/>	<input type="checkbox"/>
2) There are no potential risks or side effects associated with the use of this experimental device in this research study.	<input type="checkbox"/>	<input type="checkbox"/>
3) Your participation in the study may last up to 21 weeks.	<input type="checkbox"/>	<input type="checkbox"/>
4) You will not have to give any blood or urine samples at any time during the course of the study.	<input type="checkbox"/>	<input type="checkbox"/>
5) Your participation in the study will be kept confidential except as required by law.	<input type="checkbox"/>	<input type="checkbox"/>
6) The study staff may end your participation in this study if they feel that to do so would be in your best interest.	<input type="checkbox"/>	<input type="checkbox"/>
7) You will be compensated during this trial for completing all required tests and study assessments.	<input type="checkbox"/>	<input type="checkbox"/>
8) A woman who becomes pregnant during the intervention phase of the study may continue to receive rTMS treatments and will not be terminated from the study.	<input type="checkbox"/>	<input type="checkbox"/>
9) You do not have to inform the study staff of any new medicines that you take during the study.	<input type="checkbox"/>	<input type="checkbox"/>
10) You will receive active "real rTMS" treatment.	<input type="checkbox"/>	<input type="checkbox"/>
11) After your final follow-up visit, you will not receive further rTMS treatment as a part of the study.	<input type="checkbox"/>	<input type="checkbox"/>

The correct answers to the questions above have been discussed with me.

Participant's Signature

Date

FOR VA CENTRAL IRB USE ONLY

PI/SC Approval Date: 02/08/2016

LSI Approval Date: n/a

LSI Verification Date: n/a

HIPAA Authorization
Palo Alto VA Medical Center
Research and Development Service

**Written Permission for Release of Protected Health Information for
Research Purposes**

Title of Study: The Effectiveness of Repetitive Transcranial Magnetic Stimulation (rTMS) in Depressed VA Patients

You have been asked to be part of a research study called The Effectiveness of Repetitive Transcranial Magnetic Stimulation (rTMS) in Depressed VA Patients.

Dr. Jerome Yesavage and members of his research team are in charge of this study at this VA. We hope to learn whether rTMS is effective for treatment-resistant major depression. As part of this study, we will be collecting and sharing information about you with others.

We understand that information about you obtained in connection with your health care is private. **The Palo Alto VA Medical Center** has rules to protect information about you. In our research, we use and share information about people and their health. The law lets us use and share health information for research if you agree to let us do this. Federal and state laws protect health information. If you let us use and share information about you, we will protect it as required by law. This form explains how we will use and share your health information. It lists who can see and use your information. It explains what we will do to keep your information private.

If you sign this form, it means you are letting us use and share this information for research.

Who will share, receive, and/or use the information?

In addition to Dr. Jerome Yesavage and his research staff, the following individuals will or may have access to your identifiable medical record information related to your participation in this research study:

Subjects Name: _____, _____
Last First

Version October 2012 _____

Authorized representatives of the Veterans Affairs Central Institutional Review Board (IRB) and the local IRB and Research and Development Committee where you receive VA care may review your identifiable medical record information for the purpose of monitoring the appropriate conduct of this research study.

Authorized representatives of the Veterans Affairs Cooperative Studies Program and their Coordinating Center at Perry Point, MD will review and/or obtain your identifiable medical record information for the purpose of monitoring the accuracy and completeness of the research data and for performing required scientific analyses of the research data.

Authorized representatives of the Veterans hospital or other affiliated health care providers you are receiving care from may have access to your identifiable medical record information.

The following individuals, for purposes of monitoring and oversight of this research activity may include:

- Any agency of the federal, state, or local government that regulates this research. This includes the Food and Drug Administration (FDA) and the Department of Health and Human Services (DHHS).
- Office for Human Research Protection (OHRP)
- Government Accountability Office
- The Office of the Inspector General

In unusual cases, the investigators may be required to release your identifiable research information (which may include your identifiable medical record information) in response to an order from a court of law. If the investigators learn that you or someone with whom you are involved is in serious danger or potential harm, they will need to inform, as required by state law, the appropriate agencies.

Who else can use and share this information?

Anyone listed above may use consultants or other associates with whom they have a formal business relationship, such as through a contract, to help them understand, analyze, and conduct this study. They may use and share information about you to

Subjects Name: _____, _____
Last _____ First _____

Version October 2012 _____

do this research with these consultants or other associates. If you have questions about who they are, you can ask us.

What personal health information will be shared and used?

- Medical information, reports and questionnaire data from study-related visits such as neuropsychological and PTSD data, and substance abuse disclosure.
- Medical information, including demographics, from VA data systems.
- Information about use and cost of all VA-provided health care (obtained from centralized VA data systems called electronic abstracts utilizing SSN).
- Information about use and costs of all non-VA healthcare covered by Medicare (obtained from centralized Medicare databases).

We will use and share your information only as described in this form. People outside **the Palo Alto VA Medical Center** and the Perry Point VA Cooperative Studies Program Coordinating Center who receive your information may not be covered by this promise. Once information is shared outside the VA, it may not be protected in the same manner and may be subject to re-disclosure by the recipient. We try to make sure that everyone who needs to see your information keeps it confidential – but we cannot guarantee this.

By signing this document, you will authorize the Veterans Health Administration (VHA) to permit **Dr. Jerome Yesavage** and members of his/her research team to **use and share** the protected health information (PHI) described above.

Your Rights

You can refuse to sign this form.

If you do not sign this form:

- You will not be able to take part in this research.
- This will not change or affect your health care outside of this study.
- This will not change or affect your VA benefits or health care benefits.

How Long Will My Permission Last?

Subjects Name: _____, _____
Last _____, First _____

Version October 2012 _____

This permission will expire when this research study is completed, unless you revoke it in writing first.

Can I Withdraw My Permission?

- You can revoke or cancel your permission at any time. To do so, you must write a letter to Dr. Jerome Yesavage and address to: Department of Veterans Affairs, 3801 Miranda Avenue, Palo Alto, CA 94304. You can ask a member of the research team to give you a form to cancel your permission.
- Your request will be valid when Dr Yesavage receives your request.
- We will stop collecting information about you.
- You cannot withdraw information that we had before you told us to stop. We may already have used or shared it. Or we may need it to complete the research.
- Staff may follow-up with you if there is a medical reason to do so.

Participant Authorization:

- **I have read this form.**
- **I have been given the chance to ask questions.**
- **My questions have been answered.**
- **If I have more questions, I am to call <insert name and contact information>**
- **I agree to the release of my protected health information as described in this form.**
- **I will receive a copy of this authorization form after I sign it.**

Participant's Signature

Date

Subjects Name: _____, _____
Last _____, First _____

Version October 2012 _____

Revocation of Authorization for Release of Protected Health Information For Research Purposes

Title of Study: The Effectiveness of Repetitive Transcranial Magnetic Stimulation (rTMS) in Depressed VA Patients

TO: Dr. Jerome Yesavage

I revoke my previous authorization for you to use or disclose my protected health information (PHI) as part of your study.

I understand that the research team may continue to use and disclose PHI about me that has already been collected if such continued use is necessary to protect the integrity of this research study. However, they will use and disclose PHI only for the reasons discussed in the Informed Consent Form (ICF) I signed when I joined the study.

I understand the revoking this authorization may mean that my participation in the study will also end. It will not affect my rights as a VHA patient, including health care I may need when I am no longer in the study.

Signed:

Participant Signature

Date

Subjects Name: _____, _____
Last First

Version October 2012 _____

APPENDIX B

Study Budget

APPENDIX C

CURRICULA VITAE

Jerome A. Yesavage, M.D.
Principal Proponent

Kousick Biswas, PhD
Study Biostatistician



NAME

Yesavage, Jerome A.

POSITION TITLE

ACOS, Mental Health

EDUCATION / TRAINING

(Begin with Baccalaureate or other initial professional education, such as nursing, and include post-doctoral training. Do not include Honorary Degree.)

NAME, LOCATION OF INSTITUTION	DEGREE (if applicable)	YEAR AWARDED	FIELD OF STUDY
Yale University, New Haven, Connecticut Stanford University, Stanford, California	BA MD	1971 1974	Philosophy Medicine

NOTE: The Biographical Sketch may not exceed four pages. Items A and B (together) may not exceed two of the four-pages.

A. Positions and Honors

(List in chronological order previous positions, concluding with your present position. List any honors, professional memberships or present membership on any Federal Government public advisory committee.)

Positions and Employment:

1978-1996	Director, Psychiatric Intensive Care Unit, VA Medical Center, Palo Alto, California
1979-1985	Assistant Professor of Psychiatry, Stanford University, Stanford, California
1980-present	Associate Director, Gero-Psychiatric Rehabilitation Unit, VA Medical Center, Palo Alto, CA
1985-1990	Member, Life Course (Aging) Review Board, NIMH
1985-1991	Associate Professor of Psychiatry, Stanford University, Stanford, California
1991-present	Professor of Psychiatry, Stanford University, Stanford, California
1996-2001	Director, Psychiatric Inpatient Units, VA Palo Alto Health Care System, Palo Alto, California
1998-present	Director, Department of Veterans Affairs Sierra-Pacific Mental Illness, Research, Education, and Clinical Center (MIRECC)
2001-2002	Acting Associate Chief of Staff for Mental Health, VA Palo Alto Health Care System, Palo Alto, CA
2002-present	Associate Chief of Staff for Mental Health, VA Palo Alto Health Care System, Palo Alto, CA

Other Experience and Professional Memberships:

1985-1989	Member, Life Course (Aging) peer review section for NIMH Aging proposals
1998-present	Stanford University School of Medicine, Department of Psychiatry, Executive Committee
1979-present	Gerontological Society of America
1982-present	International Psychogeriatric Association
1982-present	Family Survival Project, Scientific Advisory Council
2000-present	EthicAd.org National Advisory Board

Honors:

1971	Graduated magna cum laude with Class Prize in Philosophy, Yale University
1974	Class Prize in Psychiatry, Stanford University, Stanford, California
1976	Falk Fellow, American Psychiatric Association
1978	American Gerontology Traveling Fellowship
1989-1992	Chair, Council on Aging, American Psychiatric Association
1993	Weinberg Award for Excellence in Geriatric Psychiatry, American Psychiatric Association
1993	Advisory Panel on Alzheimer's Disease, United States Congress

B. Selected peer-reviewed publications (in chronological order)

(Do not include publications submitted or in preparation)

Brooks JO, Hoblyn JC, Kraemer HC, Yesavage JA: Factors associated with psychiatric hospitalization of dementia patients with comorbid bipolar disorder. *Journal of Geriatric Psychiatry and Neurology* 19: 72-77, 2006.

Chuu JY, Taylor JL, Tinklenberg J, Noda A, Yesavage JA, Murphy GM: The brain-derived neurotropic factor Val66Met polymorphism and rate of decline in Alzheimer's disease. *Journal of Alzheimer's Disease* 9: 43-49, 2006.

Hoblyn J, Noda A, Yesavage JA, Brooks JO, Sheikh J, Lee T, Tinklenberg J, Schneider B, O'Hara R, Leslie DL, Rosenheck RA, Kraemer HC: Factors in choosing atypical antipsychotics: Toward understanding the bases of physician's prescribing decisions. *Journal of Psychiatric Research* 40: 160-166, 2006.

Kraemer HC, Mintz J, Noda A, Tinklenberg J, Yesavage JA.: Caution regarding the use of pilot studies to guide power calculations for study proposals. *Arch Gen Psychiatry* 63: 484-9, 2006.

Neylan TC, Lenoci M, Samuelson KW, Metzler TJ, Henn-Haase C, Hierholzer RW, Lindley SE, Otte C, Schoenfeld FB, Yesavage JA, Marmar CR: No improvement of posttraumatic stress disorder symptoms with guanfacine treatment. *Am J Psychiatry* 163: 2186-8, 2006.

Noda A, Kraemer HC, Taylor JL, Schneider B, Ashford JW, Yesavage JA: Strategies to reduce site differences in multi-site studies of rapid cognitive decline among Alzheimer's patients. *American Journal of Geriatric Psychiatry* 14: 931-938, 2006.

Ota KS, Friedman L, Ashford JW, Hernandez B, Penner A, Stepp AM, Raam R, Yesavage JA: The Cost-Time Index: A new method for measuring the efficiencies of recruitment resources in clinical trials. *Contem Clin Trials* 27: 494-7, 2006.

Steffens DC, Otey E, Alexopoulos GS, Butters MA, Cuthbert B, Ganguli M, Geda Y, Hendrie HC, Krishnan RR, Kumar A, Lopez OL, Lyketsos CG, Mast BT, Morris JC, Norton MC, Peavy GM, Petersen RC, Reynolds CF, Salloway S, Welsh-Bohmer KA, Yesavage JA: Perspectives on depression, mild cognitive impairment, and cognitive decline. *Archives of General Psychiatry* 63: 130-138, 2006.

Yesavage JA, Sheikh JS, Noda A, Murphy G, O'Hara R, Hierholzer R, Battista M, Ashford JW, Schnieder B, Hoblyn J, Kraemer HC, Tinklenberg JR: Spatial test of the effects of agricultural pesticide "blow on" effect on prevalence of Parkinson's disease. *Journal of Geriatric Psychiatry and Neurology* 19: 32-35, 2006.

Aulakh JS, Hawkins JW, Athwal HS, Sheikh JI, Yesavage J, Tinklenberg JR: Tolerability and effectiveness of lamotrigine in complex elderly patients. *J Geriatr Psychiatry Neurol* 18 (1):8-11, 2005

Wisor J, Edgar D, Yesavage J, Ryan H, McCormick C, Lapustea N, Murphy GM: Sleep and circadian abnormalities in a transgenic mouse model of Alzheimer's disease: A role for cholinergic transmission. *Neuroscience* 131:375-385, 2005

Benson K, Friedman L, Noda A, Wicks D, Wakabayashi E, Yesavage J: The measurement of sleep by actigraphy: direct comparison of 2 commercially available actigraphs in a nonclinical population. *Sleep* 27(5):986-9, 2004

Newkirk LA, Kim JM, Thompson JM, Tinklenberg JR, Yesavage JA, Taylor JL: Validation of a 26-point telephone version of the Mini-Mental State Examination. *J Geriatr Psychiatry Neurol* 17(2):81-7, 2004

Rosen C, Chow H, Finney H, Greenbaum M, Moos R, Sheikh J, Yesavage J: VA practice patterns and practice guidelines for treating posttraumatic stress disorder. *Traumatic Stress* 17(3):213-222, 2004

Yesavage J, Sheikh J, Noda A, Murphy G, O'Hara R, Hierholzer R, Battista M, Ashford W, Kraemer H, Tinklenberg J: Use of a VA pharmacy database to screen for areas at high risk for disease: Parkinson's Disease and exposure to pesticides. *J Geriatr Psychiatry Neurol* 17 (1):36-38, 2004

Yesavage JA, Friedman L, Kraemer H, Tinklenberg JR, Salehi A, Noda A, Taylor JL, O'Hara R, Murphy G: Sleep/wake disruption in Alzheimer's disease: APOE status and longitudinal course. *J Geriatr Psychiatry Neurol* 17(1):20-4, 2004

Brooks JO, 3rd, Friedman L, Yesavage JA: Use of an external mnemonic to augment the efficacy of an internal mnemonic in older adults. *Int Psychogeriatr* 15(1):59-67, 2003

Mumenthaler MS, Yesavage JA, Taylor JL, O'Hara R, Friedman L, Lee H, Kraemer HC: Psychoactive drugs and pilot performance: a comparison of nicotine, donepezil, and alcohol effects. *Neuropsychopharmacology* 2003; 28:1366-73

Fountoulakis KN, O'Hara R, Iacovides A, Camilleri CP, Kaprinis S, Kaprinis G, Yesavage J: Unipolar late-onset depression: A comprehensive review. *Annals of General Hospital Psychiatry* 2003; 2(1):11

Rosen AC, Prull MW, Gabrieli JD, Stoub T, O'Hara R, Friedman L, Yesavage JA, deToledo-Morrell L: Differential associations between entorhinal and hippocampal volumes and memory performance in older adults. *Behav Neurosci* 2003; 117(6):1150-60

Yesavage J, Hoblyn J, Sheikh J, Tinklenberg J, Noda A, O'Hara R, Fenn C, Mumenthaler M, Friedman L, Kraemer H: Age and disease severity predict choice of atypical neuroleptic: a signal detection approach to physicians' prescribing decisions. *Journal of Psychiatric Research* 2003; 37(6):535-8

Yesavage JA, Friedman L, Ancoli-Israel S, Bliwise D, Singer C, Vitiello MV, Monjan AA, Lebowitz B: Development of diagnostic criteria for defining sleep disturbance in Alzheimer's disease. *Journal of Geriatric Psychiatry and Neurology* 2003; 16(3):131-9

Coman E, Moses JA, Jr., Kraemer HC, Friedman LF, Benton AL, Yesavage JA: Interactive influences on BVRT performance level: Geriatric considerations. *Archives of Clinical Neuropsychology* 2002; 17:595-610

Ford JM, Askari N, Gabrieli JD, Mathalon DH, Tinklenberg J, Menon V, Yesavage J: Event-related brain potential evidence of spared knowledge in Alzheimer's disease. *Psychology and Aging* 2002; 16(1):161-76.

O'Hara R, Tinklenberg J, Thompson J, Fenn C, Taylor J, Ross L, Yesavage J, Kraemer H: Which Alzheimer patients are at risk for rapid cognitive decline? *Journal of Geriatric Psychiatry and Neurology* 2002; 15:1-6

O'Hara R, Yesavage JA: The Geriatric Depression Scale: It's development and recent application, in *Principles and Practice of Geriatric Psychiatry*. Ed Copeland J, Abou-Saleh M, Balzer D. Sussex, Wiley & Sons, 2002

Rosen A, Prull M, O'Hara R, Race E, Desmond J, Glover G, Yesavage J, Gabrieli J: Variable effects of aging on frontal lobe contributions to memory. *Neuroreport* 2002; 13(18):2425-2428

Rosen AC, Bokde AL, Pearl A, Yesavage JA: Ethical, and practical issues in applying functional imaging to the clinical management of Alzheimer's disease. *Brain and Cognition* 2002; 50(3):498-519

Rosen C, Chow H, Greenbaum M, Finney J, Moos R, Sheikh J, Yesavage J: How well are clinicians following dementia practice guidelines? *Alzheimer's Disease and Associated Disorders* 2002; 16:15-23

Taylor JL, Kraemer HC, Noda A, Friedman L, Zarcone V, Tinklenberg JR, Yesavage JA: On disentangling states versus traits: Demonstration of a new technique using the Alzheimer's Disease Assessment Scale. *Alzheimer's Disease and Associated Disorders* 2002; 16(4):254-60

Taylor JL, Mumenthaler MS, Kraemer HC, Noda A, O'Hara RM, Yesavage JA: Longitudinal study of older small-aircraft pilots: Changes in CogScreen-AE performance, in *Proceedings of the 11th International Symposium on Aviation Psychology*. Edited by Jensen RS. Columbus, Ohio, Ohio State University, 2002

Yesavage J, Mumenthaler M, Taylor J, Friedman L, O'Hara R, Sheikh J, Tinklenberg J, Whitehouse PJ: Donepezil and flight simulator performance: Effects on retention of complex skills. *Neurology* 59(1):123-5, 2002

Yesavage JA, O'Hara R, Kraemer H, Noda A, Taylor JL, Ferris S, Gely-Nargeot MC, Rosen A, Friedman L, Sheikh J, Derouesne C: Modeling the prevalence and incidence of Alzheimer's disease and mild cognitive impairment. *J Psychiatr Res* 36(5):281-6, 2002

Yesavage JA, Taylor JL, Kraemer HC, Noda A, Friedman L, Tinklenberg JR: Sleep/wake cycle disturbance in Alzheimer's disease: How much is due to an inherent trait? *International Psychogeriatrics* 14(1):73-81, 2002

Mumenthaler MS, O'Hara R, Taylor JL, Friedman L, Yesavage JA: Influence of the menstrual cycle on flight simulator performance after alcohol ingestion. *Journal of Studies on Alcohol* 62(4):422-433, 2001

C. Research Support

List selected ongoing or completed (during the last three years) research projects (federal and non-federal support). Begin with the projects that are most relevant to the research proposed in this application. Briefly indicate the overall goals of the projects and your role (e.g. PI, Co-Investigator, Consultant) in the research project. Do not list award amounts or percent effort in projects.

AG 17824 (PI: Yesavage, Jerome A.) **9/1/2000 - 4/30/2006**
NIA Role: Center Director

Stanford NIA Alzheimer's Disease Core Center

The focus of our Center is the study of aspects of the heterogeneity of AD, including etiology; progression of disease; and pathophysiology of associated behavioral symptoms. This research is closely integrated with major research programs in basic neurosciences and genetics, neuroimaging, and sleep/chronobiology. We foster research efforts that bridge disciplines and increase cross-fertilization of ideas.

(no project number) (PI: Yesavage, Jerome A.) **1/1/2005 - 12/31/2010**
Department of Veterans Affairs Role: Principal Investigator
PTSD, Sleep Apnea, and APOE Genotype: Effects on Cognition

To examine whether sleep-disordered breathing, APOE status, increasing age and their interactions will predict rate of cognitive decline in veterans who have PTSD, a population already at risk for cognitive deficits.

MH 35182 (PI: Yesavage, Jerome A.) **2/1/1984 - 6/30/2006**
NIMH Role: Principal Investigator

Memory and Mental Health in Aging

A study of methods to help elderly persons improve memory, especially for names and faces, lists, and reading. Various training methods, with and without donepezil, will be compared.

AG 12713 (PI: Yesavage, Jerome A.) **9/10/1995 - 6/30/2006**
NIA Role: Principal Investigator

Age-Related Longitudinal Changes in Aviator Performance

Longitudinal study of changes in performance among aviators 50 to 70 to evaluate effects of age on performance over time.

AG 12914-07 (PI: Yesavage, Jerome A.) **9/1/1990 - 1/31/2006**
NIA Role: Principal Investigator

Treatments for Insomnia

A comparison of the efficacy of nonhypnotic treatments for insomnia: a behavioral treatment that using sleep hygiene to improve sleep; and timed exposed to bright light in addition to sleep hygiene principles.

(no project number) (site PI: Yesavage, Jerome A.) **7/1/2002 - 7/31/2005**
HealthCare Technology Systems, Inc. / NIH Role: site Principal Investigator

Assessing Cognition: Interactive Voice Response Systems

Test a computer-automated method, using IVR technology, to obtain data on measuring treatment efficacy in clinical trials.

AG024904 (PI: Weiner, Michael ; site PI Yesavage, Jerome A.)
NIA

9/30/2004 - 9/29/2009
Role: site Principal Investigator

Alzheimer's Disease Neuroimaging Initiative

The goals are to: 1) Develop improved methods for acquiring longitudinal, multi-site MRI and PET data on patients with AD, MCI, and elderly controls. 2) Acquire a data repository describing longitudinal changes in brain structure and metabolism. 3) Determine methods which provide maximum power to determine treatment effects.

98-01 (site PI: Yesavage, Jerome A.)
NIA/Alzheimer's Disease Cooperative Studies

2/1/2002 - 1/31/2006
Role: site Principal Investigator

Healthy Aging and Memory

Development and testing of efficient, cost effective measures designed for use in AD primary prevention trials.

98 HC (site PI: Yesavage, Jerome A.)
NIA/Alzheimer's Disease Cooperative Studies

2/1/2003 - 3/9/2006
Role: site Principal Investigator

High Dose Supplements to Reduce Homocysteine and Slow the Rate of Cognitive Decline in Alzheimer's Disease (VITAL)

To determine is reducing the blood level of homocysteine affects the progression of Alzheimer's Disease.

98AX (site PI: Yesavage, Jerome A.)
NIA/Alzheimer's Disease Cooperative Studies

6/1/05 – 6/30/06
Role: site Principal Investigator

Evaluation of the Safety, Tolerability, and Impact on Biomarkers of Antioxidant Treatment of Mild to Moderate Alzheimer's Disease

The goal of this trial is to assess the effect on biomarkers related to oxidative damage two antioxidant treatments in patients with mild to moderate AD.

98 VP (site PI: Yesavage, Jerome A.)
NIA/Alzheimer's Disease Cooperative Studies

7/1/03 – 6/30/06
Role: site Principal Investigator

Valproate in Dementia (VALID)

This is a multi-site, randomized, placebo-controlled clinical trial looking at the effects of valproate on Alzheimer's Disease.

98-00 (site PI: Yesavage, Jerome A.)
NIA/Alzheimer's Disease Cooperative Studies

12/1/2002 – 12/31/05
Role: site Principal Investigator

Cholesterol-Lowering Agent to Slow the Progression of Alzheimer's Disease (CLASP)

This is a multi-site, randomized, placebo-controlled trial to determine if simvastatin has an effect on the progression of AD.

NAMMD15 (Yesavage) 2/1/2003 – 12/31/2007

Forest Research Institute

Role: Principal Investigator

The Effect of Memantine on Brain Structure and Chemistry in alzheimer's Disease Patients: A Randomized, Placebo-Controlled, 52-Week Clinical Trial

MRI scans before and after treatment with Memantine will be compared.

AG 16976 (site PI: Yesavage, Jerome A.)

NIA: University of Washington

7/1/2000 - 6/30/2006

Role: site Principal Investigator

NACC Minimum Data Set

This project contributes data from the Stanford AD Core Center to the National Alzheimer Coordinating Center.

AG 18784 (PI: O'Hara, Ruth M.)

NIH

9/30/2001 - 8/31/2006

Role: Investigator

Stress, Cortisol, and Cognitive Decline in Older Adults(PI: O'Hara); part of Stress, the HPA and Health in Aging (PI: Spiegel)

To determine if levels of stress, as measured by cortisol levels, affects cognitive decline in older adults.

AG 21134 (PI: Sheikh, Javaid I.)

NIA

2/1/2004 - 1/31/2009

Role: Investigator

Light Treatment for Sleep/Wake Disturbances in AD

To compare short-term efficacy of 2 treatments for sleep/wake cycle disturbances in community-dwelling AD patients: a) Bright light treatment and b) Dim light treatment. Outcome measures are circadian rhythm parameters and actigraphy.

AG 021632 (PI: Joy Taylor)

8/15/2003 - 7/31/2008

NIA

Role: Investigator

MRI and Decline of Aging Aviator Performance

To determine if one can improve models of age-related decline on a “real world” cognitive task by adding assessments of longitudinal brain volume changes to the model. Half of the sample will possess an Apolipoprotein E (APOE) epsilon 4 allele (e4 carriers), a genetic risk factor for Alzheimer’s disease.

03-75273 (PI: Jared R. Tinklenberg)

07/01/2003 - 06/30/2006

State of California

Role: Investigator

Stanford/VA Alzheimer's Disease Research Center of California (ARCC)

This project is a California State Alzheimer's Disease Research Center of California (ARCC). The funding helps provide for diagnostic services, as well as some caregiver and referral services to Alzheimer's patients and their families; and to collect epidemiologic data on Alzheimer's patients and their caregivers.

D. Time and Effort Statement

Indicate percentage of time spent on research, clinical, teaching/mentoring, and administration. List persons mentored in last 3 years and type of mentoring awards.

Dr. Yesavage's effort is distributed: 67% of his time on his VA appointment and 33% on his Stanford University appointment. His VA appointment is distributed: 10% on Clinical, 25% on Administration, 7% on Teaching, and 25% on Research. His Stanford University appointment is distributed: 23% on Research and 10% on Others.

The following persons have been mentored over the last three years:

2003-2005 M. Bret Schnieder VA MIRECC Fellowship

2003-2002 Eric Wexler VA MIRECC Fellowship

E. Significant Life Events (OPTIONAL)

List any significant life events that have interrupted the PI's research activities for a significant period of time.

Kousick Biswas

P.O. Box 1010, VA Medical Center, Perry Point, MD 21902

Tel: 410-642-2411x5283; Fax: 410-642-1860; email: Kousick.Biswas@va.gov

Updated on 8/26/2009

CURRICULUM VITAE

Current Position:

Deputy Director (Health Science Officer)

Cooperative Studies Program Coordinating Center

VA Maryland Health Care System, Department of Veterans Affairs

VA Maryland Medical Center, Perry Point, MD

(2009 – current)

Other Positions:

Mathematical Statistician, Cooperative Studies Program Coordinating Center, VA Maryland Health Care System, Department of Veterans Affairs, VA Medical Center, Perry Point, MD *(2008 – 2009)*;

Biostatistician, Baltimore Research and Educational Foundation (contracted at Cooperative Studies Program Coordinating Center, VA Maryland Health Care System, Department of Veterans Affairs, VA Medical Center, Perry Point, MD *(2003 – 2008)*);

Adjunct Faculty, Science, Technology, Engineering and Mathematics Division, Harford Community College, Bel Air, MD *(2008 – current)*;

Adjunct Faculty, Department of Mathematics, Cecil College, North East, MD *(2004 – 2008)*;

Occupational Safety & Health Specialist, Spokane Research Lab, NIOSH, Spokane, WA *(2001-2003)*;

Assistant Professor, School of Engineering, University of Idaho, Moscow, ID *(2000-2003)*;

Assistant Professor, School of Engineering, University of Ballarat, Australia *(1997-2000)*;

Post Doctoral Fellow, Southern Illinois University, Carbondale, IL *(1997)*;

Education:

Ph.D., West Virginia University, 1997

M.S., West Virginia University, 1997

B.S., Calcutta University, 1986

Kousick Biswas

P.O. Box 1010, VA Medical Center, Perry Point, MD 21902

Tel: 410-642-2411x5283; Fax: 410-642-1860; email: Kousick.Biswas@va.gov

Major Trials:

VA/CSP#576 trial on "Cost Effectiveness of Augmentation of Antidepressants with Second Generation Antipsychotics in the Treatment of Refractory Depression"

Role: Study Biostatistician

Project Status: In Planning

Funding Agency: VA

VA/NIDA/SYNOSIA trial on "Double-blind, Placebo-Controlled Multi-center trial of Nepicastat for the treatment of cocaine dependence"

Role: Study Biostatistician

Project Status: In planning (Tentative start date - March 2009)

Funding Agency: National Institute on Drug Abuse

VA/NIDA "A Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of Vigabatrin for the Treatment of Cocaine Dependence"

Role: Study Biostatistician

Project Status: In Planning (Tentative start date – Feb/March 2009)

Funding Agency: National Institute on Drug Abuse/Ovation Pharmaceutical Inc.

VA/NIDA "Phase II, Double-blind, Placebo-controlled Trial of Modafinil for the Treatment of Methamphetamine Dependence"

Role: Study Biostatistician

Project Status: Enrolling subjects

Funding Agency: National Institute on Drug Abuse

UMD/CSP "Etiology of Diarrheal Disease in Infants and Young Children in Developing Countries"

Role: Biostatistician and Data Center Team Leader

Project Status: Phase-I: Health Utilization Survey Completed; Phase-II: Full case-control study on-going

Funding Agency: Bill & Melinda Gates Foundation

VA "Glucocorticoid-Induced Osteoporosis and Outcomes in Veterans using VHA"

Role: Biostatistician

Project Status: Resubmission to VA Epidemiological Research, August 2007

Funding Agency: Department of Veterans Affairs

VA/CSP#561 "An Electronic Reminder to prevent and treat Glucocorticoid Osteoporosis"

Role: Study Biostatistician

Project Status: Study Disapproved by CSSMRB, November 2005

Funding Agency: Department of Veterans Affairs

VA/NIDA/USWM#1024 "Phase III, Randomized, Multi-center, Double-blind, Placebo-controlled, Comparison Study of Safety and Efficacy of Lofexidine and Placebo"

Kousick Biswas

P.O. Box 1010, VA Medical Center, Perry Point, MD 21902

Tel: 410-642-2411x5283; Fax: 410-642-1860; email: Kousick.Biswas@va.gov

Role: Study Biostatistician

Project Status: Primary and Secondary Analyses phase

Funding Agency: National Institute on Drug Abuse/US World Med, Inc

UMD/CSP “Maryland Genetics of Interstitial Cystitis Study (MaGIC)”

Role: Group Leader – Data Management/Analysis

Project Status: Recruitment phase

Funding Agency: National Institute of Health

JHU/UMD/CSP “Tinnitus Retraining Therapy Trial”

Role: Study Co-Biostatistician

Project Status: Disapproved by NIDCD 2006

VA/NIDA#1021 trial on “Double-blind, Placebo-Controlled Multi-center trial of Baclofen for the treatment of cocaine dependence”

Role: Study Biostatistician

Project Status: Preparation and Submission of primary and secondary manuscripts.

Funding Agency: National Institute on Drug Abuse

CSP#430 trial on “Reducing the Efficacy-Effectiveness Gap in Bipolar Disorder”

Role: Study Biostatistician

Project Status: Preparation and Submission of secondary manuscripts.

Funding Agency: Department of Veterans Affairs

Professional Services:

- Permanent member (Statistical) of the National Center of PTSD review panel, VA Office of Mental Health Services
- Team Leader, Data Management and Informatics Sub-domain, VA Cooperative Studies Program - 2009
- Permanent member (Statistical) of the CSR&D Data Monitoring Committee for Medical and Surgical Protocols evaluation of the Merit Review submissions – 2008 to 2011
- Ad hoc member (Statistical) of the CSR&D Data Monitoring Committee for Mental Health Protocols evaluation of the Merit Review submissions – 2008 - 2011
- Reviewer for the VA Merit Review – Neurobiology subcommittee – 2008
- Team Leader, “Development and Implementation of An Electronic Clinical Trial Management System” Task Force at CSPCC, Perry Point – 2005 - 2008;
- Team Leader, “Data Capturing Systems” subgroup of the “Information Technology Standardization Workgroup” for the VA Cooperative Studies Program – 2007 - 2008;
- Coordinating Center Representative, “Data Management and Informatics Functional Domain” for the VA Cooperative Services Program;
- Reviewer for the Journal of Immigrant and Minority Health;
- Reviewer for the Journal of Rehabilitation Research and Development;

Kousick Biswas

P.O. Box 1010, VA Medical Center, Perry Point, MD 21902
Tel: 410-642-2411x5283; Fax: 410-642-1860; email: Kousick.Biswas@va.gov

- Session Chair for 'AP-Evaluation & Mining System Optimization Through Artificial Intelligence & Neural Network' at APCOM (Application of Computers in Mineral Industry), February 2002, Phoenix, AZ.

Relevant Publications/Presentations/Abstracts:

Bauer, M, **Biswas, K.**, and Kilbourne, A, *Enhancing Long-Term Guideline Concordance for Bipolar Disorder through Collaborative Care*, American Journal of Psychiatry, 2009 [accepted for publication].

Khan, R., **Biswas, K.**, et al. A Multi-center Baclofen Trial for Abstinence Initiation in Heavy Cocaine Users, Drug and Alcohol Dependence, Volume 103, Issues 1-2, July 2009

Kotloff, K., **Biswas, K.**, Blackwelder, W., Nasrin, D., Farag, T., Levine, M, and Horney, R., *The Health Utilization and Attitude Survey in Developing Countries in Asia – Some Analysis*, In preparation (2009)

Kotloff, K., **Biswas, K.**, Blackwelder, W., Nasrin, D., Farag, T., Levine, M, and Horney, R., *The Health Utilization and Attitude Survey in Developing Countries in Africa – Some Analysis*, In preparation (2009)

Walker, D., Rheingans, R., **Biswas, K.**, Kotloff, K, Nasrin, D., and Farag, T, *The Economic Burden of Childhood Diarrhoea in Developing Countries in Asia*, In preparation (2009).

Walker, D., Rheingans, R., **Biswas, K.**, Kotloff, K, Nasrin, D., and Farag, T, *The Economic Burden of Childhood Diarrhoea in Developing Countries in Africa*, In preparation (2009).

Bauer, M, **Biswas, K.**, and Kilbourne, A, *Improving Long-Term Quality of Care for Serious Mental Illness through Collaborative Care Models*, HSR&D National Meeting, Baltimore, MD, February 11-13, 2009

Pirraglia, P., **Biswas, K.**, Kilbourne, A. M., Fenn, H., and Bauer, M., *A prospective study of the impact of comorbid medical disease on bipolar disorder outcomes*, accepted for publication, Journal of Affective Disorder, (In Press) 2008 [EPub ahead of print 2008 Oct 17]

Kilbourne, A. M., **Biswas, K.**, Sajatovic, M., Pirraglia, P.A., Williford, W., and Bauer, M.S., *Is The Chronic Care Model Effective for Complex Patients? Analyzing Moderators of Treatment Effect*, Journal of Affective Disorder, (In Press) 2008 [EPub ahead of print 2008 May 24];

Sajatovic, M., **Biswas, K.**, Kilbourne, A. M., Fenn, H., Williford, W., and Bauer, M, *Factors associated with long-term treatment adherence among individuals with bipolar disorder*, Psychiatry Services, 2008 Jul;59(7):753-759

Kousick Biswas

P.O. Box 1010, VA Medical Center, Perry Point, MD 21902

Tel: 410-642-2411x5283; Fax: 410-642-1860; email: Kousick.Biswas@va.gov

Biswas, K. and Jenkins, M., *An Electronic Clinical Trial Management System based on Microsoft Office Groove, DIA's 44th Annual Meeting*, Boston, MA, June 22-26, 2008

Biswas, K., McSherry, F., and Jindal, P., *An Electronic Data Capturing System Using Microsoft Groove Virtual Office, Society of Clinical Trials Annual Meeting*, St. Louis, MO, May 16-18, 2008

Bauer, M.S, Kilbourne, A. M., and **Biswas, K.**, *From Clinic toward Community: Care for Complex, Chronic Cases, HSR&D Annual Meeting*, Baltimore, MD, February 13-15, 2008.

Kilbourne AM, **Biswas K**, Sajatovic M, Pirraglia PA, Williford WO, Bauer MS. *Is the Chronic Care Model Effective for Complex Patients: Analyzing Moderators of Treatment Effect in Bipolar Disorder*, *Journal of Mental Health Policy and Economics*; 10(1):S22, 2007.

Biswas, K., *Groove Based Communication Protocol for GEMS Trial, First Annual Meeting, GEMS* September 5-7, 2007, Mali, Africa.

Nasrin, D, and **Biswas, K.**, *A Preliminary Analysis of Health Utilization Attitude Survey for the GEMS Study, First Annual Meeting, GEMS*, September 5-7, 2007, Mali, Africa.

Biswas, K., McSherry, F., and Jindal, P, *Microsoft® Office® Groove® Based Electronic Clinical Trial Management System, MS-HUG Tech Forum 2007*, August 21-22, 2007, Redmond, WA

Pirraglia, P., **Biswas, K.**, et al, *Conceptualization Of Comorbid Medical Disease: An Exploration in Bipolar Patients, Academy Health 2007: Annual Research Meeting*, June 3 – 5, 2007 Orlando, FL

Pirraglia, P., **Biswas, K.**, et al, *Concept of Comorbid Medical Disease in Bipolar Patients, Annual Meeting of Society for General Internal Medicine*, June 2007

Kilbourne, A. M., **Biswas, K.**, Sajatovic, M., Pirraglia, P.A., Williford, W., and Bauer, M.S., *Is The Chronic Care Model Effective for Complex Patients? Analyzing Moderators of Treatment Effect, 8th Workshop on Costs and Assessment in Psychiatry: Investing in Mental Health Policy and Economics Research*, Venice, Italy, March 9-11, 2007

Bauer, M.S., Kilbourne, A. M., et al, and **Biswas, K.**, *Outcome and Costs in a Randomized Controlled Effectiveness Trial of a Collaborative Chronic Care Model for Bipolar Disorder, 8th Workshop on Costs and Assessment in Psychiatry: Investing in Mental Health Policy and Economics Research*, Venice, Italy, March 9-11, 2007

Kousick Biswas

P.O. Box 1010, VA Medical Center, Perry Point, MD 21902
Tel: 410-642-2411x5283; Fax: 410-642-1860; email: Kousick.Biswas@va.gov

Altshuler, L. Biswas, K., and et al, *Executive Function and Work Outcomes in Bipolar Disorder*, Psychiatry Services, 58: 1441-1447 November 2007

Bauer, M.S., et al, and Biswas, K., *Collaborative Chronic Care for Bipolar Disorder, I: Intervention Development and Implementation in a Randomized Controlled Efficacy Trial*, Psychiatry Services, July 2006

Bauer, M.S., et al, and Biswas, K., *Collaborative Chronic Care for Bipolar Disorder, II: Clinical and Functional Outcome in a 3-Year, 11-Site Randomized Controlled Trial*, Psychiatry Services, July 2006

Horney, A, and Biswas, K., *A SAS Macro for Adaptive Randomization*, 26th Annual Meeting of Society for Clinical Trials, Portland, OR, May 22-25, 2005

Weinstock, M., Biswas, K. and CSP 402 study group, *Association of Eyeglass Use with Periocular Keratinocyte Carcinoma (BCC or SCC) Risk*, Abstract, Journal of Investigative Dermatology, Vol. 122, No.3, March 2004

Biswas, K., and Zipf, K., *Root Causes of Ground Fall Accident Data – Its Importance and Methodology*, Proc. 22nd Int. Conf. On Ground Control, August 2003, Morgantown, WV

Biswas, K., and Jung, S.J., *Application of Statistical Modeling in Analyzing Health and Safety Data for Mineral Industry*, APCOM (Application of Computers in Mineral Industry), 2002, Phoenix, AZ

Jung, S.J., and Biswas, K., *Safety Education Based on Needs of Western Operators: Focus of UI Web Based Outreach Program*, Mining Engineering Journal, December 2001

Other Publications:

Biswas, K., and Ghose, A.K., *Fracture Toughness of Indian Coal and Coal-measure Rocks – Some Investigations*, Journal of Institute of Engineers (India), vol. 72, May 1991

Biswas, K., and Ghose, A.K., *Index Properties and Physico-mechanical Properties of Indian Coal and Coal-measure Rocks Vis-a-Vis Fracture Toughness*, Journal of Mines, Metals and Fuels, Oct. - Nov. 1992

Biswas, K., Behera, P.K., and Ghose, A.K., *Acoustic Emission Signature of Indian Coal-measure Rocks Vis-a-Vis Fracture Toughness*, Indian Journal of Technology, vol. 30, Oct. 1992

Bandopadhyay, S., Biswas K., and Nelson, N. G., *Development of a 2D Axisymmetric Finite Element Model and Evaluation of Support Systems in Arctic Mines*, Transaction of SME/AIME, vol. 296, 1995

Kousick Biswas

P.O. Box 1010, VA Medical Center, Perry Point, MD 21902
Tel: 410-642-2411x5283; Fax: 410-642-1860; email: Kousick.Biswas@va.gov

Biswas, K., Peng, S. S. and Tsang, P., *Current Practice of Pillar Design in US Coal Mines*, Mining Engineering Journal, Dec. 1996

Biswas, K. and Peng, S. S., *Study of Weathering Actions in Coal Pillar and Its Effects on Long Term Stability*, Mining Engineering Journal, Jan. 1999

Skabar, A, Biswas, K., Maeder, A, and Pham, B *Contextual Classification of Multisource Geoscientific Data using a Fuzzy/Genetic Learner*, AIDA (Advanced Intelligent Data Analysis), Rochester, NY 1999

Skabar, A, Biswas, K., Maeder, A, and Pham, B., *Inductive Concept Learning based on Limited Class Information Using Evolutionary Search*, IEEE (Institute of Electrical and Electronics Engineers) Brisbane, Australia 1999

Skabar, A, Biswas, K., Maeder, A, and Pham, B., *Learning a Concept in the Absence of Labeled Counter-Examples*, ICAPRDT'99, 4th Int. Conf. On Advances in Pattern Recognition & Digital Techniques, Calcutta, India, Dec 1999

Biswas, K., Mark, C and Peng, S. S., *An Unique Approach of Time Dependent In-situ Strength Determination for Coal Pillar* SME Annual Meeting, Feb-Mar1999, Denver, CO

Biswas, K., Mark, C and Peng, S. S., *Development of a Time Dependent Pillar Design Equation*, Proceedings of 2nd Int. Workshop for Coal Pillar Mechanics and Design, Vale, CO 1999

Felipe, F. C., Biswas, K., and Thomas, E. G., *Influence of Material Properties and Binders on the Behavior of Paste Backfill*, SME Annual Meeting, Feb-Mar 2000, Salt Lake City, Utah

Jung, S.J., and Biswas, K., *Safety Education Based on Needs of Western Operators: Focus of UI Web Based Outreach Program*, Mining Engineering Journal, December 2001

Biswas, K., and Jung, S.J., *Behavior of Rock under Cyclic Loading – Some Preliminary Study*, Rock Mechanics in National Interest, 38th U.S. Rock Mechanics Symposium Vol1, Washington DC, July 2001

Jung, S.J., Wyatt, J., and Biswas, K., *Analysis of Shear Fracture Toughness for Brittle Materials*, Rock Engineering and Rock Mechanics, 2001

Jung, S.J., and Biswas, K., *Current Status of High Density Paste Fill and its Technology*, Mineral Resources Engineering, June 2002

Kousick Biswas

P.O. Box 1010, VA Medical Center, Perry Point, MD 21902
Tel: 410-642-2411x5283; Fax: 410-642-1860; email: Kousick.Biswas@va.gov

Jung, S.J., **Biswas, K.**, and Lee, H., *Understanding Rock Flow Mechanisms in Ore Pass Using Working Model 2D®*, North American Rock Mechanics Symposium (NARMS), July 2002, Toronto, Canada

Biswas, K., and Jung, S.J., *Application of Statistical Modeling in Analyzing Health and Safety Data for Mineral Industry*, APCOM (Application of Computers in Mineral Industry), March 2002, Phoenix, AZ

Biswas, K., and Jung, S.J., *Residual Strain Energy in Rock – A key to Energy Savings: Some Investigations*, SME Annual Meeting, March 2002, Phoenix, AZ

Biswas, K., Jung, S.J., *Simulation of Rock Fragments Flow in Ore Passes*, APCOM (Application of Computers in Mineral Industry), March 2002, Phoenix, AZ

Jung, S.J., **K. Biswas**, and H. Lee, *Understanding Rock Flow Mechanism in Ore Pass using Working Model 2D*, Mining and Tunneling Innovation and Opportunity, Editor, R. Hammah, University of Toronto, Canada, 2002, pp1283-1287

Iverson, S., SJ Jung, & **Biswas, K.**, 2003, *Ore pass Computer Simulation Based on Existing Design Criteria*, SME Annual Meeting, March 2003

Professional Development:

- The eClinical Trial: using the CDISC Standards as the Foundation Stone
- The CDASH Initiative: Standardized CRFs – An idea whose time has come? [23rd Annual DIA Conference and Exhibition, Washington DC, March 16 – 18, 2008]
- Introduction to Survey Sampling - A short course by Joint Program in Survey Methodology (JPSM), U of Maryland, College Park, MD/U of Michigan, Ann Arbor, MI [Crystal City, Arlington, VA, March 15-16, 2007]
- Introduction to Survey Estimation - A short course by Joint Program in Survey Methodology (JPSM), U of Maryland, College Park, MD/U of Michigan, Ann Arbor, MI [Adelphi, College Park, MD, February 26-27, 2007]
- Treatment of Missing Data by Multiple Imputation and Maximum Likelihood – A Short Course by Professor Paul Allison, University of Pennsylvania [Washington, DC, November 12 – 13, 2004]
- Analysis of Longitudinal Data – A Short Course [Summer Course, University of Florida, Gainesville, March 8-9, 2004]
- Handling Missing Data in Longitudinal Studies [FDA/Industrial Statistical Workshop, Sept. 17-19, 2003 Bethesda, MD]
- Applied Survival Analysis
- Advanced Issues in Clinical Trials
- Correlated Data Analysis

Kousick Biswas

P.O. Box 1010, VA Medical Center, Perry Point, MD 21902

Tel: 410-642-2411x5283; Fax: 410-642-1860; email: Kousick.Biswas@va.gov

[Fifth Annual Epidemiology & Biostatistics Summer Session, June 23-27, 2003
Seattle, WA (Offered by Seattle Epidemiological Research and Information
Center, Dept. of Veteran Affairs and University of Washington at Seattle)]

- Randomized Clinical Trial Course

[VA Cooperative Studies Program, Department of Veterans Affairs, April 6 – 11,
2003, Chicago, IL]

Affiliation:

- Member of Drug Information Association (DIA)
- Member of American Statistical Association
- Member of Society of Clinical Trials

Honor & Award:

- Special Contribution Award, VA Cooperative Services Program, 2008
- Certificate of Appreciation, VA Cooperative Services Program, 2007
- Special Contribution Award, VA Cooperative Services Program, 2007
- Special Contribution Award, VA Cooperative Services Program, 2006
- Best Paper Award, Indian Institute of Engineers, 1992

APPENDIX D

BIOSTATISTICAL AND RESEARCH DATA PROCESSING PROCEDURE (BRDP)

I. INTRODUCTION

This study will evaluate the efficacy, safety, durability of benefit and cost-effectiveness of repetitive Transcranial Magnetic Stimulation (rTMS) in the resolution of Treatment-Resistant Major Depression (TRMD) with emphasis on the unique population served by the VA Healthcare System.

II. STUDY MANAGEMENT AT THE CSPCC

A CSPCC study team has been formed to ensure that the study is conducted both efficiently and professionally and that the study investigators are provided with all of the assistance that they need for the successful completion of the study. This team is composed of a Biostatistician, Project Manager, Statistical Programmer, Database Programmer, and one Computer Assistant. Other core staff at the CSPCC, such as Program Assistants, Travel Clerks, Computer Operators, and Print Machine Operator will provide help as required. The study team assigned to this study is composed of:

• Biostatistician	Dr. Kousick Biswas
• Project Manager	Ms. Heather Buckland
• Statistical Programmer	Ms. Anne Horney
• Database Programmer	Mr. Joseph Tadalan
• Computer Assistant	Ms. Brittany Coker

The Biostatistician is the study team leader and has the overall responsibility for the conduct of the study at the CSPCC. He is the CSPCC's representative to the Study Group and will also serve on the study's Executive Committee. He is responsible for providing the Study Group with statistical and clinical trial advice, for working with other CSPCC team members in the preparation of routine interim reports, and for conducting the final analyses at the end of the study. The Biostatistician has the overall responsibility for the validation of the study database and for implementing quality control procedures to reduce data errors in the study database.

The Project Manager is responsible for the administrative coordination of the study at the CSPCC. She serves as the Biostatistician's Administrative Assistant and works with the CSPCC study team to ensure that all reports, study materials, and meeting arrangement notices are sent to the proper individuals in a timely fashion. She will work closely with the National Study Coordinator in the Chairman's Office to ensure that the study runs smoothly and will be in contact with the Nurse Practitioners and the Study Coordinators at the participating centers at least monthly to discuss any problems that they may be having, including those with the CSPCC. She will also work with the R&D Offices at the participating sites, obtaining initial and continuing reviews by the Central IRB and by local Human Studies Subcommittees/IRBs and local Research and Development Offices. She also works with the Chairman's Office in the preparation of the study budget.

The Statistical Programmer is responsible for the preparation of the tables and analyses for all interim and summary study reports. These include reports for the Study Group, the Executive Committee, the Data and Safety Monitoring Board, and the Human Rights Committee as well as the mid-study report to Cooperative Studies Scientific Evaluation Committee (CSSEC). He also prepares the tables and reports for the final analyses. He works with the Biostatistician in the performance of the statistical analysis of the data.

The Database Programmer is responsible for establishing and maintaining the study's database. In addition, he will write a set of computer edits that will thoroughly check the data for errors and missing information. He will prepare monthly reports regarding the quality and quantity of data submitted to the CSPCC.

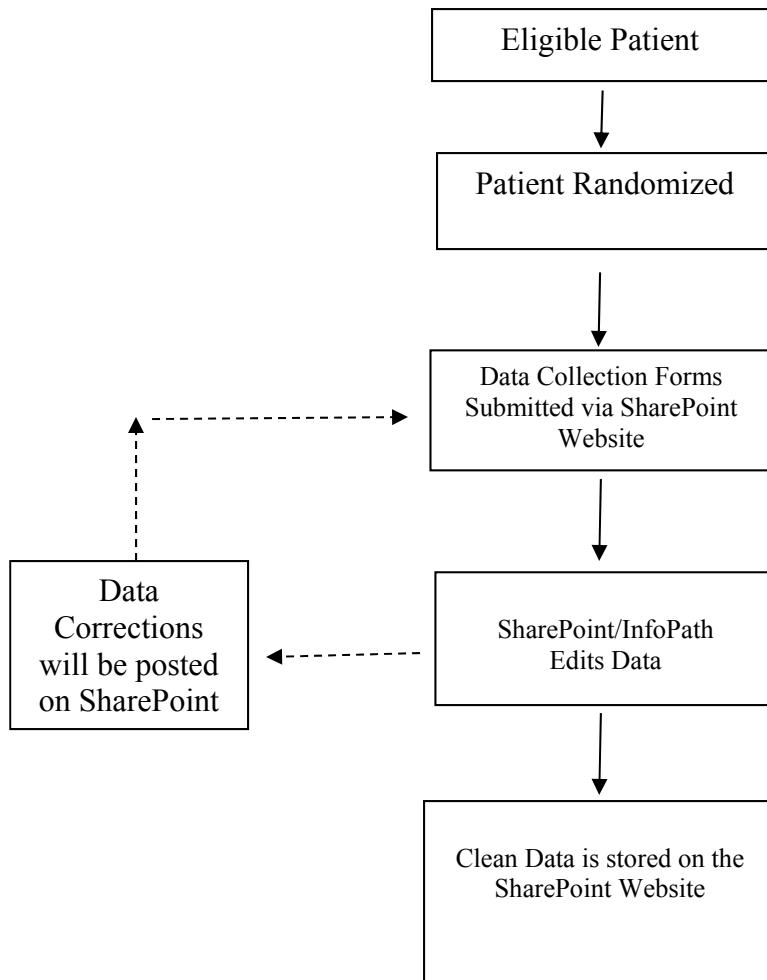
The Computer Assistant is responsible for training the study staff at each site on how to properly manage the data collection process and how to appropriately respond to data edits. All data will be edited. If incomplete or inaccurate data are found, data queries will be generated. The computer assistant will work with each site to resolve these queries.

III. DATA MANAGEMENT

The data flow and management process for the study is given in **Figure 1**. When a participating site has a study participant ready to be randomized, the Site Investigator (SI) or the Study Coordinator (SC) will open the randomization form. If all eligibility checks are passed, randomization software will determine the participant's treatment group assignment. A unique treatment number associated with this treatment group assignment will be provided to the site for this participant and will be used by the treatment software to provide the appropriate (active or sham) treatment for the participant.

Data forms have been developed for collecting study data and samples can be found in **Appendix E** of the protocol. **Table 2 in protocol section VI.G** lists the case report forms and the assessments that will be used in this study and indicates when each will be administered. The SI, the TMS Treater, or the Study Coordinator at each participating site will either record patient data on the study forms or enter data directly into the InfoPath form templates. All data will be submitted using InfoPath and the study's SharePoint website. The final responsibility for the completeness and accuracy of all study data collected at a participating site resides with the SI who will electronically sign all submitted data.

FIGURE 1. Data Flow for CSP #556, “The Effectiveness of rTMS in Depressed VA Patients”



The study database will be continuously updated with new data and changes to previously submitted data. Study and form-specific computer software will be used to edit data for completeness, accuracy, and consistency. Queries will be generated that identify missing, inconsistent, or extremely unusual data on individual forms, as well as, missing or late forms.

In addition, a summary report of all data submitted and problems identified will be generated for each participating site. This report will provide each site with a summary of their progress.

In addition to the SI reviewing the data prior to being submitted and the computerized editing, the Biostatistician will perform a qualitative review and compare a random sample of submitted data from the database with the actual study forms or source documents on a routine basis. The National Study Coordinator in the Chairman's Office will also be reviewing each site's progress to ensure that there are no unforeseen problems with the forms or with a particular patient.

Another mechanism used to monitor the data and the progress of the study will be the preparation of periodic reports to various groups that are responsible for overseeing the conduct of the study. These groups include the Study Group, the Executive Committee, the Data and Safety Monitoring Board, and the CSPCC Human Rights Committee. These groups will receive study progress reports prior to their annual meetings and at least once in between their annual meetings. Thus, on average, these groups will receive a report every six months. The contents of these reports are discussed in the remainder of this appendix.

IV. MONITORING OF STUDY BY STUDY GROUP AND EXECUTIVE COMMITTEE

The Study Group (all of the SIs) and Executive Committee will meet 6 to 9 months after patient recruitment begins and at annual intervals thereafter until the end of the study. Three weeks prior to these meetings and at 6-month intervals between the

meetings, these groups will be provided a report that will allow them to assess study progress. Since both groups are composed of study participants, no outcome data (data that would potentially break the study blind) will be provided in these reports. The information provided will include data on:

- A. Screening, enrollment, and retention
- B. Patient background characteristics at entry
- C. Data quality and protocol adherence.

A. Screening, Enrollment and Retention

The study team at each site will identify patients who might be candidates for the study. After the study has been explained to the patient and the patient signs the informed consent form, the screening process can be initiated. The study team will complete the screening forms. If the patient meets all eligibility criteria, baseline forms will be completed. The patient can then be randomized using the study's randomization software which will assign to the patient a unique treatment number.

The progress of patient accrual will be presented to the monitoring groups in three formats:

1. In the first format, the study progress is presented:
 - by site
 - by the actual number of patients entered into the study (randomized)
 - by the expected number of patients to be entered at the time of the report – high intake rate
 - by the percent of expected that were entered – high intake rate
 - by the expected number of patients to be entered at the time of the report – low intake rate
 - by the percent of expected that were entered – low intake rate

This format, as demonstrated in **Table 1**, will allow the Executive Committee to determine which sites are not recruiting as expected and the SIs to see how their site is doing in comparison with the others.

2. In the second format, as demonstrated in **Table 2**, the study progress is presented by the number of patients entered into the study (randomized) by month. These data will be organized by site. The data will indicate if recruitment is improving or worsening over time at the various sites. Sites where intake is worsening can be detected and the SI can be contacted to identify the reason for the recruitment deficit.
3. In the final format, intake data will be plotted over time for the total number of patients recruited as shown in **Figure 2**. Both high and low expected intake lines are given for comparison purposes assuming constant enrollment rates. The high enrollment rate is 1.5 patients per month per site and the low enrollment rate is 1.1 patients per month per site. The number of patients screened and the number of those that enroll in the study will be presented in **Table 3**. The reasons for the exclusion of screened patients will be presented in **Table 4**.

TABLE 1. Number Of Patients Entered Into CSP #556 And Number Expected

Site	Number Enrolled	Number Expected		Percent of Expected	
		Low Intake	High Intake	Low Intake	High Intake

1					
2					
.					
.					
9					
TOTAL					

TABLE 2. Number Of Patients Entered Each Month Into CSP #556 By Site

Month	Site 1	Site 2	...	Site 9
01/09				
02/09				
.				
.				
TOTAL				

FIGURE 2. Observed Versus Expected Patient Recruitment in CSP #556

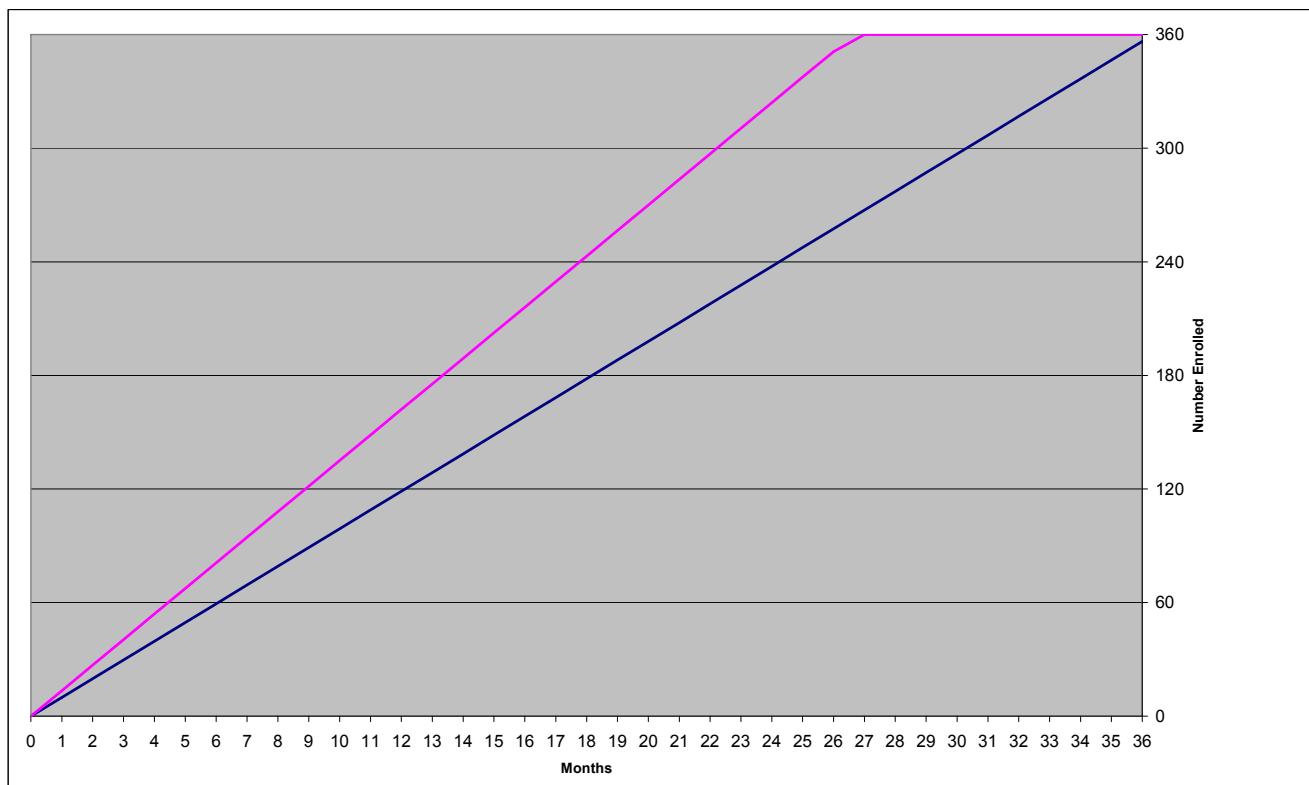


TABLE 3. Cumulative Screening Summary: All Patients by Site

Site	Screened	Rejected	Enrolled	% Rejected
1				
2				
3				
.				
.				
9				
TOTAL				

TABLE 4. Summary of Ineligibility: Reasons for Exclusion, Total and By Site

TOTAL NUMBER SCREENED = _____

Reason	# Excluded	% of Screened
1. < 18 or > 80 years of age		
2. Negative for MDD on SCID		
3. HRSD ₂₄ < 20		
4. Not Moderately Resistant to Antidepressant Treatment		
.		
.		
.		
21. Head Injury with Loss of Consciousness > 15 minutes		
22. Participant in Another Clinical Trial		
23. Prior Exposure to rTMS		
24. Active Current Suicidal Intent or Plan		

B. Background Characteristics at Entry

Background characteristics of the study patients are collected on the Baseline Information Form. Tables summarizing the important background characteristics by site will be prepared and submitted to the Study Group so they will have an idea of the population being studied and comparisons of enrollment among the sites can be made. This information will be presented as means and medians for continuous type variables and as frequency tables for discrete variables. **Table 5** shows how this data will be presented. Other variables that are routinely presented include gender, race, ethnicity, marital status, military history and work history. Analysis of variance and chi-square

techniques will be used to identify any statistically significant differences that may exist between the sites.

TABLE 5. Mean and Median Ages by Site for CSP #556

	Site 1 (N=)			Site 2 (N=)			...			Total (N=)		
Age (years)	mean	s.d.	median	mean	s.d.	median	mean	s.d.	median	mean	s.d.	median
Gender	n	(%)		n	(%)		n	(%)		n	(%)	
Male												
Female												

C. Data Quality and Protocol Adherence

The final type of information that will be provided to the Site Investigators is data that will allow them to assess the quality of the data being submitted and how well their site is adhering to the protocol. These data will be given by site, so sites performing substantially below average can be identified and remedial action taken to improve their performance.

One piece of information that will be routinely provided is the number of forms that are missing according to the patient's assessment schedule. **Table 6** indicates how this information will be displayed.

In addition to the tables for the reports, the computer editing system produces reports that indicate the number of errors that were found on the individual forms. These were discussed previously under **Section III, Data Management**. Edit reports will assist in identifying those sites requiring additional training on forms completion. A monthly report summarizing data submission and problem identification for each site will

be sent to the Study Chairman so that he can monitor how the participating sites are doing.

TABLE 6. Number of Missing Forms in CSP #556

# of Patients		Site				
		1	2	...	9	Total
Form 01	N %					
Form 02	N %					
.	.					
.	.					
.	.					
Form 32	N %					

V. STUDY MONITORING BY DATA AND SAFETY MONITORING BOARD

An independent oversight committee called the Data Monitoring Committee (DMC) will monitor study progress. This committee meets on the same basic schedule as the Study Group and Executive Committee, i.e., they will meet at 6 to 9 months after the start of patient recruitment and yearly thereafter. Initially, they will meet once prior to the study start-up to acquaint themselves with the study and to establish monitoring guidelines. This committee does not usually meet during the last six months of a study.

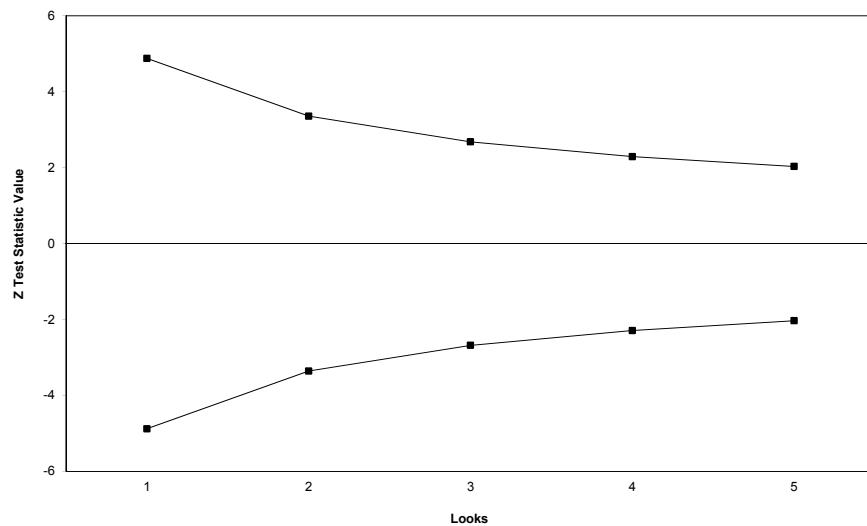
The major responsibility for the DMC members when they meet is to make a recommendation to the Director of the Cooperative Studies Program on whether the study should continue or not. The study could be recommended for termination due to poor recruitment, treatment differences so large that it is possible to reach a final decision, treatment differences so small that continuation would be irresponsible. The

DMC also reviews the participating sites' performance and makes recommendations on them. Their final responsibility is to review all proposed protocol changes and subprotocols and to make recommendations as to their acceptability.

In order for the DMC to carry out its responsibilities, the CSPCC Study Team will provide the committee with a report approximately three weeks prior to their meetings. The report will consist of the tables described previously for the Study Group and Executive Committee reports as well as those presenting outcome analyses. It is the responsibility of the CSPCC Study Team to provide the DMC with whatever information the Board feels that it needs to successfully monitor the study. Thus, additional tables will be added as required. In addition to the reports for the yearly meetings, the DMC will also be provided with reports between meetings at 6-month intervals.

In order for the DMC to make its recommendation for continuation of the study, it will be necessary for them to see the analyses for the primary outcome measure every time that the report is run and it is possible to calculate the primary outcome measure. Periodic monitoring of interim results can significantly affect the probability of making an incorrect decision. A number of formal techniques have been developed for interpreting interim results. At the organizational meeting, the DSMB will select the technique that it wants to use to monitor the study. Suggested techniques are the Haybittle-Peto and Lan-DeMets group sequential boundaries. For the Haybittle-Peto method, a constant z-statistic is used as the monitoring boundary. The Lan-DeMets procedure produces decision boundaries that are quite conservative over the first several looks and then gradually converges to the nominal alpha levels as the final look is approached. **Figure 3** gives an example of the Lan-DeMets boundaries for five looks at an alpha level of 0.05

Figure 3. Lan De - Mets Group Sequential Monitoring Boundaries



The patient characteristics by site that are given to the Investigators will also be considered by treatment group by the DMC. Differences between treatment groups on these patient characteristics may indicate a need to use any significantly different characteristics as covariates for the outcome measures. Formal testing of the differences between treatment groups will be done at the study's conclusion. Analyses of variance techniques will be used to test characteristics that are continuous in nature, while chi-square techniques will be used for the discrete variables.

As with any clinical trial, the safety of the patient will be of utmost concern. Safety will be monitored closely during the course of the study and the adverse event data will be reported in the primary study manuscript. Data will be collected on adverse events throughout the study. The DSMB Report will include data on incidence of adverse events by treatment group. It will also include data on early terminations and treatment dropouts.

Analysis of the primary outcome is discussed in the Statistical Section of the protocol. In addition to the primary outcome, the protocol lists a number of other outcome measures that will be considered. These include:

1. Depression measured by Montgomery-Asberg Depression Rating Scale, (MADRS)
2. Suicide Ideation measured by Beck Scale for Suicide Ideation (BSS)
3. Depression measured by Beck Depression Inventory (BDI)
4. Previous antidepressant medication use measured by Antidepressant Treatment History Form (ATHF)
5. Quality of Life measured by the VR-36
6. Cognitive Function as measured by the Neuropsychological Battery

APPENDIX E

CASE REPORT FORMS (CRFs)

VA COOPERATIVE STUDY #556
The Effectiveness of rTMS in Depressed VA Patients

Site ____ Participant # _____ Alpha Code _____ Date ____/____/____

RETAIN AS SOURCE DOCUMENT; DO NOT DISCARD

FORM 00 - CONTACT INFORMATION

(Complete on all patients who are enrolled in the study. Update as needed. File this form in the patient's study file. Do NOT submit this form to Perry Point CSPCC or Palo Alto Chairman's Office.)

A. PATIENT INFO:

Patient Name _____

Address _____

City _____ State _____ Zip Code _____

B. Patient SSN _____ - _____ - _____

C. Home telephone (____) _____ Work telephone (____) _____

Cell telephone (____) _____

D. Next of Kin:

Name _____

Address _____

City _____ State _____ Zip Code _____

(____) _____ Area Code Home Telephone _____

Relationship to patient _____

E. Friend/ Other family member (not living with patient):

Name _____

Address _____

City _____ State _____ Zip Code _____

(____) _____ Home Telephone _____

Relationship to patient _____

Site ____ Participant # _____ Alpha Code _____ Date ____/____/____

F. Primary psychiatrist

Name _____

City _____ State _____ Zip Code _____

(_____) _____ Telephone _____

Area Code _____

G. Mental health case manager

Name _____

Address _____

City _____ State _____ Zip Code _____

(_____) _____ Telephone _____

Area Code _____

RETAIN AS SOURCE DOCUMENT; DO NOT DISCARD

DO NOT SEND TO CSPCC (SPONSOR)

VA COOPERATIVE STUDY #556
The Effectiveness of rTMS in Depressed VA Patients

Site ____ Participant # _____ Alpha Code _____ Date ____/____/____

Form 01 - SCREENING FORM

COMPLETE AT SCREENING ONLY

Date of Screening: ____/____/____

1. Did patient sign Informed Consent? No Yes

a. If no, using the codes below, circle all reason(s) for not consenting patient:

01 =	Age	15 =	<i>Do not use</i>
02 =	MDD	16 =	Brain Implant
03 =	HRSD24 \geq 20	17 =	Cochlear Implant
04 =	Treatment Resistant	18 =	CNS Disease
05 =	MDD Duration	19 =	Psychosis
06 =	MT	20 =	Bipolar I
07 =	Psychiatrist	21 =	BOMC
08 =	Stable Meds	22 =	Substance Abuse
09 =	Attend Visits	23 =	TBI
10 =	Birth Control	24 =	Clinical Trials
11 =	Informed Consent	25 =	Prior rTMS
12 =	Pregnant	26 =	Suicidal
13 =	Seizure Risks	27 =	Cardiac Disease
14 =	Pacemaker	28 =	Refuses Consent
29 =	Other _____		

VA COOPERATIVE STUDY #556
The Effectiveness of rTMS in Depressed VA Patients

Site ____ Participant # _____ Alpha Code _____ Date ____/____/____ _{MM} _{DD} _{YYYY}

Form 02 – RANDOMIZATION FORM

COMPLETE AT RANDOMIZATION ONLY

1. Please enter this participant's 5-digit participant number _____
2. Please enter this participant's four character Alpha Code _____
3. Was a Safety Plan created for this subject? (*circle one*) No Yes
4. Please provide the date of the most recent HRSD assessment? ____/____/____ _{MM} _{DD} _{YYYY}
Note that the HRSD assessment date cannot exceed 7 days prior to randomization.
5. Please enter this subject's 2-digit HRSD score ____
6. If female, and of child bearing potential, please provide date of most recent pregnancy test
____/____/____ _{MM} _{DD} _{YYYY}
7. Does this subject have a history of substance abuse? (*circle one*) No Yes
8. Has this subject been diagnosed with PTSD? (*circle one*) No Yes
9. Date randomized ____/____/____ _{MM} _{DD} _{YYYY}
10. Randomized treatment number assigned by Perry Point _____

VA COOPERATIVE STUDY #556

The Effectiveness of rTMS in Depressed VA Patients

Site ____ Participant # _____ Alpha Code _____ Date ____ / ____ / ____
MM DD YYYY

Form 03 – BASELINE INFORMATION

COMPLETE AT SCREENING ONLY

A. PARTICIPANT PROFILE

4. Race (Circle one answer for each category)			
American Indian or Alaska Native	No	Yes	Not Collected
Asian	No	Yes	Not Collected
Black or African-American.....	No	Yes	Not Collected
Native Hawaiian or Other Pacific Islander.....	No	Yes	Not Collected
White	No	Yes	Not Collected
Refused/unknown	No	Yes	Not Collected

5. Current Marital status (*Circle one answer that applies*)

1. Single	5. Separated
2. Married	6. Living with partner
3. Widowed	7. Not Collected
4. Divorced	

6. Highest Degree or Certification (*Circle one answer that applies*)

1. None	5. Associate Degree	9. MD, PhD, Law, Dental
2. GED	6. RN Diploma	10. Other (Specify) _____
3. H. S. Diploma	7. Bachelor's Degree	11. Not Collected
4. Voc Tech Diploma	8. Master's Degree	

B. MILITARY HISTORY

7. When did the participant serve? (*Circle one answer for each below*)

a. World War I	No	Yes	Not Collected
b. World War II	No	Yes	Not Collected
c. Korean conflict	No	Yes	Not Collected
d. Vietnam conflict	No	Yes	Not Collected
e. Gulf War	No	Yes	Not Collected
f. Balkans conflict	No	Yes	Not Collected
g. Afghanistan conflict	No	Yes	Not Collected
h. Iraq conflict.....	No	Yes	Not Collected
i. Other war/conflict:	No	Yes	Not Collected
specify _____			
j. Peace time	No	Yes	Not Collected

8. Did the participant serve outside the United States? (*Circle one*) No Yes

9. What was the branch of service? (*Circle one answer for each category*)

a. Army.....	No	Yes	Not Collected
b. Air Force	No	Yes	Not Collected
c. Navy	No	Yes	Not Collected
d. Marines	No	Yes	Not Collected
e. Coast Guard	No	Yes	Not Collected
f. National Guard (active duty)	No	Yes	Not Collected
g. Merchant Marine	No	Yes	Not Collected

C. WORK HISTORY

10. In the past **four weeks**, did the participant work at a job FOR PAY, even for one hour (Includes odd jobs like babysitting, or pick-up work and temporary jobs as well as regular, steady jobs)? (*Circle the correct answer.*) No Yes Not Collected

11. For the job that the participant worked at for the MOST NUMBER OF HOURS in the past four weeks, what specifically was the type of job? (*Circle one answer.*)

1. Regular, steady job for pay	3. Self-employed (work at own business)
2. Temporary or odd job for pay	4. Other (specify) _____

22. Has participant's psychotropic medication been stable for at least 4 weeks prior to randomization?

23. Is participant willing to remain on a stable medication and current regimen during acute treatment?.....

24. Does the participant have a stable place to live that is convenient to reach the VA Medical Center with confirmed transportation available?

25. If female, does the participant agree to use an acceptable method of birth control?
(If male or no childbearing potential, code "2 not screened").....

26. Did the participant sign the informed consent form?

E. EXCLUSION CRITERIA

(0 = No, 1 = Yes, 2 = Not Screened)

27. Is participant pregnant or lactating female (pregnancy test must be completed within 7 days prior to randomization)? *(If male or no childbearing potential, code "2 not screened")*

28. Is the participant unable to be safely withdrawn, at least 2 weeks prior to beginning treatment, from medications that substantially increase the risk of seizures?

29. Does the participant have a cardiac pacemaker?

30. *Question 30 has been removed as per protocol version 4.0 approval (it will not be seen in eDC)*?

31. Does the participant have an implanted device or metal in the brain?

32. Does the participant have a cochlear implant?.....

33. Does the participant have a mass lesion, increased intracranial pressure, cerebral infarct or other active CNS disease, including a seizure disorder?

34. Does the participant have a known current psychosis as determined by DSM-IV or SCID (Axis I, psychotic disorder, schizophrenia) or a history of a non-mood psychotic disorder?

35. Does the participant have a history of known current Bipolar I disorder as determined by the SCID-I or a history of Bipolar I disorder?

Site ____ Participant # _____ Alpha Code _____ Date ____/____/____ MM / DD / YYYY

36. Does the participant have current amnestic disorder, dementia, BOMC > 10, delirium or other cognitive disorder? _____

37. Does the participant have a current substance abuse problem (not including caffeine or nicotine) as determined by positive toxicology screen or by history via SCID, within 3 months, prior to screening? _____

38. Does the participant have elevated risk of seizure due to TBI? _____

39. Is the participant participating in another treatment research trial? _____

40. Has the participant had a prior exposure to rTMS? _____

41. Does the participant have an active current suicidal intent or plan? _____

42. Is the participant unwilling to follow a safety plan? _____

43. Does the participant have unstable Cardiac Disease or recent (<3 months previous) Myocardial Infarction _____

F. Eligible

44. Participant's Eligibility status (*circle one*)

1. Eligible to be Randomized 2. Eligible but declined 3. Ineligible

a. If eligible but declined, please provide reason: _____

IF ANY ANSWERS TO QUESTIONS 15-26 ARE "NO" or ANY QUESTIONS 27-43 ARE "YES" THEN THE PARTICIPANT IS INELIGIBLE.

IF ANSWERS TO QUESTIONS 15-26 ARE "YES" AND ANSWERS TO 27-43 ARE "NO" THE PARTICIPANT IS ELIGIBLE.

VA COOPERATIVE STUDY #556
The Effectiveness of rTMS in Depressed VA Patients

Site ____ Participant # _____ Alpha Code _____ Date ____/____/____ MM / DD / YYYY

Form 04 – MEDICAL HISTORY FORM

COMPLETE AT SCREENING ONLY

<u>Medical Condition</u>	<u>History</u> (Please circle one answer)			<u>If 'Yes' or 'Not Collected' then provide an explanation</u>
1. Allergies, drug, specify	No	Yes	Not Collected	_____
_____	_____	_____	_____	_____
2. Allergies, other, specify	No	Yes	Not Collected	_____
_____	_____	_____	_____	_____
3. HEENT Disorder	No	Yes	Not Collected	_____
_____	_____	_____	_____	_____
4. Cardiovascular Disorder	No	Yes	Not Collected	_____
_____	_____	_____	_____	_____
5. Renal Disorder	No	Yes	Not Collected	_____
_____	_____	_____	_____	_____
6. Hepatic Disorder	No	Yes	Not Collected	_____
_____	_____	_____	_____	_____
7. Pulmonary Disorder	No	Yes	Not Collected	_____
_____	_____	_____	_____	_____
8. Gastrointestinal Disorder	No	Yes	Not Collected	_____
_____	_____	_____	_____	_____
9. Musculoskeletal Disorder	No	Yes	Not Collected	_____
_____	_____	_____	_____	_____
10. Neurological Disorder	No	Yes	Not Collected	_____
_____	_____	_____	_____	_____
11. Psychiatric Disorder	No	Yes	Not Collected	_____
_____	_____	_____	_____	_____

Site ____ Participant # _____ Alpha Code _____ Date MM / DD / YYYY --

<u>Medical Condition</u>	<u>History</u>			<u>If 'Yes' or 'Not Collected' then provide an explanation</u>
12. Dermatologic Disorder	No	Yes	Not Collected	_____
13. Metabolic Disorder	No	Yes	Not Collected	_____
14. Hematologic Disorder	No	Yes	Not Collected	_____
15. Endocrine Disorder	No	Yes	Not Collected	_____
16. Genitourinary Disorder	No	Yes	Not Collected	_____
17. Reproductive System Disorder	No	Yes	Not Collected	_____
18. Infectious Disease Disorder	No	Yes	Not Collected	_____
19. Traumatic Brain Injury	No	Yes	Not Collected	_____
19a. If 'Yes', MRI Results	Positive		Negative	
19b. Date ____ / ____ / ____	19c. Explanation _____			
20. Other, _____	No	Yes	Not Collected	_____

VA COOPERATIVE STUDY #556
The Effectiveness of rTMS in Depressed VA Patients

Site ____ Participant # _____ Alpha Code _____ Date MM / DD / YYYY ____

Form 05 – PHYSICAL EXAMINATION FORM

Circle Visit Below:

Screening

Final Treatment Session

Date of examination: MM / DD / YYYY ____

A. Vital Signs:

1. Height: ____ inches
2. Weight: ____ lbs
3. Temperature (oral): ____ . ____ °F
4. Pulse (sitting): ____ beats/minute
5. Blood pressure (mmHg) (sitting): Systolic ____ / Diastolic ____

B. Physical Examination:

<u>Physical Examination</u>	<u>Results</u> (Please circle one answer)			<u>If 'Abnormal' or 'Not Done' provide explanation</u>
6. General Appearance	Normal	Abnormal	Not Done	_____
7. HEENT	Normal	Abnormal	Not Done	_____
8. Heart	Normal	Abnormal	Not Done	_____
9. Lungs	Normal	Abnormal	Not Done	_____

Site ____

Participant # _____

Alpha Code _____

Date MM / DD / YYYY

<u>Physical Examination</u>		<u>Results</u> (Please circle one answer)			<u>If 'Abnormal' or 'Not Done' provide explanation</u>
10. Abdomen (include liver & spleen)		Normal	Abnormal	Not Done	_____
11. Lymph Nodes		Normal	Abnormal	Not Done	_____
12. Extremities		Normal	Abnormal	Not Done	_____
13. Neurologic		Normal	Abnormal	Not Done	_____
14. Musculoskeletal		Normal	Abnormal	Not Done	_____
15. Skin		Normal	Abnormal	Not Done	_____
16. Other, specify _____		Normal	Abnormal	Not Done	_____
17. Other, specify _____		Normal	Abnormal	Not Done	_____
18. Other, specify _____		Normal	Abnormal	Not Done	_____

VA COOPERATIVE STUDY #556
The Effectiveness of rTMS in Depressed VA Patients

Site ____ Participant # _____ Alpha Code _____ Date ____/____/____

Form 06 – LABORATORY DATA

COMPLETE AT SCREENING ONLY

Date Blood Specimen Collected: ____/____/____

Results (Please circle only one)					If 'Abnormal' or 'Not Done' provide Comment
1. RBC	Normal	Abnormal Clinically Significant	Abnormal Clinically Significant	Not Done	_____
2. WBC	Normal	Abnormal Clinically Significant	Abnormal Clinically Significant	Not Done	_____
3. Hemoglobin	Normal	Abnormal Clinically Significant	Abnormal Clinically Significant	Not Done	_____
4. Hematocrit	Normal	Abnormal Clinically Significant	Abnormal Clinically Significant	Not Done	_____
5. Platelet Count	Normal	Abnormal Clinically Significant	Abnormal Clinically Significant	Not Done	_____
6. Other specify _____	Normal	Abnormal Clinically Significant	Abnormal Clinically Significant	Not Done	_____

B. CHEMISTRY		Results (Please circle only one)			If 'Abnormal' or 'Not Done' provide Comment
7. Sodium	Normal	Abnormal Not Clinically Significant	Abnormal Clinically Significant	Not Done	_____
8. Potassium	Normal	Abnormal Not Clinically Significant	Abnormal Clinically Significant	Not Done	_____
9. Chloride	Normal	Abnormal Not Clinically Significant	Abnormal Clinically Significant	Not Done	_____
10. CO ₂	Normal	Abnormal Not Clinically Significant	Abnormal Clinically Significant	Not Done	_____
11. Glucose	Normal	Abnormal Not Clinically Significant	Abnormal Clinically Significant	Not Done	_____
12. Creatinine	Normal	Abnormal Not Clinically Significant	Abnormal Clinically Significant	Not Done	_____
13. BUN/Urea	Normal	Abnormal Not Clinically Significant	Abnormal Clinically Significant	Not Done	_____
14. Other specify _____	Normal	Abnormal Not Clinically Significant	Abnormal Clinically Significant	Not Done	_____

C. LIVER PANAL		Results (Please circle only one)			If 'Abnormal' or 'Not Done' provide Comment
15. Albumin	Normal	Abnormal Not Clinically Significant	Abnormal Clinically Significant	Not Done	_____
16. Total Bilirubin	Normal	Abnormal Not Clinically Significant	Abnormal Clinically Significant	Not Done	_____
17. Direct Bilirubin	Normal	Abnormal Not Clinically Significant	Abnormal Clinically Significant	Not Done	_____
18. AST	Normal	Abnormal Not Clinically Significant	Abnormal Clinically Significant	Not Done	_____
19. ALT	Normal	Abnormal Not Clinically Significant	Abnormal Clinically Significant	Not Done	_____
20. ALP	Normal	Abnormal Not Clinically Significant	Abnormal Clinically Significant	Not Done	_____
21. Total Protein	Normal	Abnormal Not Clinically Significant	Abnormal Clinically Significant	Not Done	_____
22. Other specify _____	Normal	Abnormal Not Clinically Significant	Abnormal Clinically Significant	Not Done	_____

Site ____ Participant # _____ Alpha Code _____ Date ____/____/____

D. ENDOCRINE		Results (Please circle only one)			If 'Abnormal' or 'Not Done' provide Comment
		Normal	Abnormal Not Clinically Significant	Abnormal Clinically Significant	
23. TSH	Normal	Abnormal Not Clinically Significant	Abnormal Clinically Significant	Not Done	_____
24. Total T3	Normal	Abnormal Not Clinically Significant	Abnormal Clinically Significant	Not Done	_____
25. Total T4	Normal	Abnormal Not Clinically Significant	Abnormal Clinically Significant	Not Done	_____
26. Other specify _____	Normal	Abnormal Not Clinically Significant	Abnormal Clinically Significant	Not Done	_____

VA COOPERATIVE STUDY #556
The Effectiveness of rTMS in Depressed VA Patients

Site ____ Participant # _____ Alpha Code _____ Date ____/____/____

Form 07 - SCID

COMPLETE AT SCREENING ONLY

DX Code	Diagnosis (Module Section)	Lifetime Prevalence			Meets Symptomatic Dx. Crit. past Month	
		Absent	Sub- Threshold	Threshold	Absent	Present
MOOD DISORDERS						
01	Bipolar I Disorder (<i>D.1</i>)	1	2	3	1	3
02	Bipolar II Disorder (<i>D.2</i>)	1	2	3	1	3
03	Other Bipolar Disorder (<i>D.5</i>)	1	2	3	1	3
04	Major Depressive Disorder (<i>D.6</i>)	1	2	3	1	3
05	Dysthymic Disorder (<i>A.41</i>)	1	2	3	1	3
06	Depressive Disorder NOS (<i>D.9</i>)	1		3	1	3
07	Mood Disorder Due to a General Medical Condition (<i>A.44</i>)	1		3	1	3
08	Substance-Induced Mood Disorder (<i>A.46</i>)	1		3	1	3
PSYCHOTIC SYMPTOMS						
09	Primary Psychotic Symptoms (not part of Mood Disorder) (<i>B/C.4</i>)	1	2	3	1	3
SUBSTANCE USE DISORDER (Abuse/Dependence)						
17	Alcohol (<i>E.3/E.6</i>)	1	2	3	1	3
18	Sedative-Hypnotic-Anxiolytic (<i>E.12/E.15</i>)	1	2	3	1	3
19	Cannabis (<i>E.12/E.15</i>)	1	2	3	1	3
20	Stimulants (<i>E.12/E.15</i>)	1	2	3	1	3
21	Opioid (<i>E.12/E.15</i>)	1	2	3	1	3

Site ____ Participant # _____ Alpha Code _____ Date ____/____/____

DX Code	Diagnosis (Module Section)	Lifetime Prevalence			Meets Symptomatic Dx. Crit. past Month	
		Sub- Absent	Threshold	Threshold	Absent	Present

**SUBSTANCE USE DISORDER
(Abuse/Dependence) Continued**

22	Cocaine (E.12/E.15)	1	2	3	1	3
23	Hal./PCP (E.12/E.15)	1	2	3	1	3
24	Poly Drug (E.15)	1	2	3	1	3
25	Other (E.22/E.16)	1	2	3	1	3

ANXIETY DISORDERS

26	Panic Disorder With/Without Agoraphobia (F.3)	1	2	3	1	3
27	Agoraphobia Without History of Panic Disorder (F.9)	1	2	3	1	3
28	Social Phobia (F.14)	1	2	3	1	3
29	Specific Phobia (F.18)	1	2	3	1	3
30	Obsessive Compulsive Disorder (F.23)	1	2	3	1	3
31	Posttraumatic Stress (F.29)	1	2	3	1	3
32	Generalized Anxiety Disorder (F.34)	1	2	3	1	3
33	Anxiety Disorder Due to a General Medical Condition (F.37)	1		3	1	3
34	Substance-Induced Anxiety Disorder (F.39)	1		3	1	3
35	Anxiety Disorder NOS (F.40)	1		3	1	3

SC/TT Signature _____

Date _____

VA COOPERATIVE STUDY #556
The Effectiveness of rTMS in Depressed VA Patients

Site ____ Participant # _____ Alpha Code _____ Date / / _{MM} / _{DD} / _{YYYY} —

Form 08: Antidepressant Treatment History Form (ATHF)

COMPLETE AT SCREENING ONLY

1 Who or what were the sources providing the information for this form? (Circle all that apply)

a. Patient Interview b. Patient Record c. Pharmacy Records d. Family Member Interview
e. Prescribing Physician f. Therapist

2 Were antidepressant medications or other treatments for depression (excluding psychotherapy) taken during past and/or current episodes?

____ No ____ Yes If yes, please list the medications in the table below. If no, form is complete.

Antidepressant Medications Taken During Past and/or Current Episode. Please record the following information for each antidepressant medication taken.

A.	B.	C.	D.	E.	F.	G.	H.	I.	J.	K.
Medication Name Generic name (Please Print)	Blood Level(ng/mL)	Dose(mg/day)	Start Date (mm/dd/yyyy)	Stop Date (mm/dd/yyyy)	Total Number of Weeks in Treatment	Reason Stopped	Outcome	Overall Confidence Rating	Antidepressant Resistance Rating	Adequate Trials
3-1		---	__/__/__	__/__/__			—			
3-2		---	__/__/__	__/__/__			—			
3-3		---	__/__/__	__/__/__			—			
3-4		---	__/__/__	__/__/__			—			
3-5		---	__/__/__	__/__/__			—			
3-6		---	__/__/__	__/__/__			—			
3-7		---	__/__/__	__/__/__			—			
3-8		---	__/__/__	__/__/__			—			
3-9		---	__/__/__	__/__/__			—			
3-10		---	__/__/__	__/__/__			—			

Outcome Abbreviations (H)

- (-1) Worse
- (0) No Change
- (1) Marginally Improved
- (2) Markedly Improved
- (3) Remitted (ineligible)
- (9) No Information

Overall Confidence Rating (I)

- (1) No Confidence
- (2) Low Confidence
- (3) Moderate Confidence
- (4) Strong Confidence
- (5) High Confidence

Antidepressant Resistance Rating (J)

See rating scales (in "ATHF Instruction Guide and Rating Scales") for scoring.

Adequate Trial(K)

- (0) I score OR J score 0-2
- (1) I score AND J score both ≥ 3 AND H ≠ 3

Total scores in K must be ≥ 2 for study eligibility

VA COOPERATIVE STUDY #556
The Effectiveness of rTMS in Depressed VA Patients

Site ____ Participant # _____ Alpha Code _____ Date _____ / _____ / _____

Form 09 – LIFETIME DRINKING HISTORY

COMPLETE AT BASELINE ONLY

	AGE RANGE YOUNGER TO OLDER	FREQUENCY DAYS/MONTH	QUANTITY DRINKS/DAY	TYPE %	STYLE (CIRCLE ONE)	LIFE EVENT OR CHANGES POSITIVE (+) OR NEGATIVE (-)	CONTEXT %	TIME %
1	FROM _____ TO _____		AVERAGE _____	BEER _____	1 Occasional 2 Weekend 3 Binge 4 Frequent	____ 1 Family ____ 2 Work ____ 3 School ____ 4 Medical ____ 5 Residence ____ 6 Legal – Jail ____ 7 Financial ____ 8 Peer Group ____ 9 Drug Use ____ 10 Treatment ____ 11 Death ____ 12 Emotional	Alone _____ With Others _____	Morning _____ Afternoon _____ Evening _____
	MAXIMUM _____		LIQUOR _____ WINE _____					
2	FROM _____ TO _____		AVERAGE _____ MAXIMUM _____	BEER _____ LIQUOR _____ WINE _____	1 Occasional 2 Weekend 3 Binge 4 Frequent	____ 1 Family ____ 2 Work ____ 3 School ____ 4 Medical ____ 5 Residence ____ 6 Legal – Jail ____ 7 Financial ____ 8 Peer Group ____ 9 Drug Use ____ 10 Treatment ____ 11 Death ____ 12 Emotional	Alone _____ With Others _____	Morning _____ Afternoon _____ Evening _____
3	FROM _____ TO _____		AVERAGE _____ MAXIMUM _____	BEER _____ LIQUOR _____ WINE _____	1 Occasional 2 Weekend 3 Binge 4 Frequent	____ 1 Family ____ 2 Work ____ 3 School ____ 4 Medical ____ 5 Residence ____ 6 Legal – Jail ____ 7 Financial ____ 8 Peer Group ____ 9 Drug Use ____ 10 Treatment ____ 11 Death ____ 12 Emotional	Alone _____ With Others _____	Morning _____ Afternoon _____ Evening _____
4	FROM _____ TO _____		AVERAGE _____ MAXIMUM _____	BEER _____ LIQUOR _____ WINE _____	1 Occasional 2 Weekend 3 Binge 4 Frequent	____ 1 Family ____ 2 Work ____ 3 School ____ 4 Medical ____ 5 Residence ____ 6 Legal – Jail ____ 7 Financial ____ 8 Peer Group ____ 9 Drug Use ____ 10 Treatment ____ 11 Death ____ 12 Emotional	Alone _____ With Others _____	Morning _____ Afternoon _____ Evening _____

1 Drink (approx.) = 12 oz. beer
1.5 oz liquor
5 oz wine
3 oz fortified wine
13.6 g absolute alcohol

Liquor: 1 mickey (12oz) = 8 Drinks
1 bottle (25oz) = 17 Drinks
Wine: 1 bottle (25oz) = 5 Drinks
1 bottle fortified = 8 Drinks

VA COOPERATIVE STUDY #556
The Effectiveness of rTMS in Depressed VA Patients

Site ____ Participant # _____ Alpha Code _____ Date ____/____/____

CRF 10A - Retain as Source Document. Do Not Discard.
Form 10A – CAPS SUMMARY SHEET BASELINE

COMPLETE AT BASELINE ONLY

A. History of traumatic event..... No Yes

B. Re-experiencing Symptoms (past month)	PAST MONTH			LIFETIME		
	Freq	Int	F+ I	Freq	Int	F+ I
1. intrusive recollections						
2. distressing dreams						
3. acting or feeling as if event were recurring						
4. psychological distress at exposure to cues						
5. physiological reactivity on exposure to cues						
B Subtotals						

C. Avoidance and Numbing Symptoms	PAST MONTH			LIFETIME		
	Freq	Int	F+ I	Freq	Int	F+ I
6. avoidance of thoughts or feelings						
7. avoidance of activities, places, or people						
8. inability to recall important aspects of trauma						
9. diminished interest in activities						
10. detachment or estrangement						
11. restricted range of affect						
12. sense of foreshortened future						
C Subtotals						

Site ____ Participant # _____ Alpha Code _____ Date ____/____/____

CRF 10A - Retain as Source Document. Do Not Discard.

D. Hyperarousal Symptoms	PAST MONTH			LIFETIME		
	Freq	Int	F+ I	Freq	Int	F+ I
13. difficulty falling or staying asleep						
14. irritability or outbursts of anger						
15. difficulty concentrating						
16. hypervigilance						
17. exaggerated startle response						
D Subtotals						

Total frequency, Intensity, and Severity (F+I)	PAST MONTH			LIFETIME		
	Freq	Int	F+ I	Freq	Int	F+ I
Sum of subtotals (B+C+D)						

E. Duration of disturbance	CURRENT		LIFETIME	
	NO	YES	NO	YES
18. with delayed onset (\geq 6 months delay)				

19. duration of disturbance at least one month	CURRENT		LIFETIME	
	NO	YES	NO	YES
19. duration of disturbance at least one month				

19. acute (< 3 months) or chronic (\geq 3 months)	CURRENT		LIFETIME	
	Acute	Chronic	Acute	Chronic
19. acute (< 3 months) or chronic (\geq 3 months)				

F. Significant distress or impairment in functioning	PAST MONTH			LIFETIME		
	NO	YES	NO	YES	NO	YES
20. subjective distress						
21. impairment in social functioning						
22. impairment in occupational functioning						

Global ratings	PAST MONTH		LIFETIME	
	NO	YES	NO	YES
23. global validity				
24. global severity				
25. global improvement				

SC Signature _____ Date _____

VA COOPERATIVE STUDY #556
The Effectiveness of rTMS in Depressed VA Patients

Site ____ Participant # _____ Alpha Code _____ Date ____/____/____ MM / DD / YYYY

Form 10B – CAPS SUMMARY SHEET

Circle Visit Below:

END OF ACTIVE TREATMENT

FINAL FOLLOW UP VISIT

A. History of traumatic event..... NO Yes

B. Re-experiencing Symptoms (past month)	PAST MONTH		
	Freq	Int	F+ I
1. intrusive recollections			
2. distressing dreams			
3. acting or feeling as if event were recurring			
4. psychological distress at exposure to cues			
5. physiological reactivity on exposure to cues			
B Subtotals			

C. Avoidance and Numbing Symptoms	PAST MONTH		
	Freq	Int	F+ I
6. avoidance of thoughts or feelings			
7. avoidance of activities, places, or people			
8. inability to recall important aspects of trauma			
9. diminished interest in activities			
10. detachment or estrangement			
11. restricted range of affect			
12. sense of foreshortened future			
C Subtotals			

Site ____ Participant # _____ Alpha Code _____ Date ____/____/____ MM / DD / YYYY

D. Hyperarousal Symptoms	PAST MONTH		
	Freq	Int	F+ I
13. difficulty falling or staying asleep			
14. irritability or outbursts of anger			
15. difficulty concentrating			
16. hypervigilance			
17. exaggerated startle response			
D Subtotals			

Total frequency, Intensity, and Severity (F+I)	PAST MONTH		
	Freq	Int	F+ I
Sum of subtotals (B+C+D)			

E. Duration of disturbance	CURRENT	
	NO	YES
18. with delayed onset (\geq 6 months delay)		

19. duration of disturbance at least one month	CURRENT	
	NO	YES
19. duration of disturbance at least one month		

19. acute (< 3 months) or chronic (\geq 3 months)	CURRENT	
	Acute	Chronic
19. acute (< 3 months) or chronic (\geq 3 months)		

F. Significant distress or impairment in functioning	PAST MONTH	
20. subjective distress		
21. impairment in social functioning		
22. impairment in occupational functioning		

Global ratings	PAST MONTH	
23. global validity		
24. global severity		
25. global improvement		

SC Signature _____ Date _____

VA COOPERATIVE STUDY #556

The Effectiveness of rTMS in Depressed VA Patients

Site ____ Participant # _____ Alpha Code _____ Date ____/____/____ MM DD YYYY

Form 11 – TRAUMA HISTORY QUESTIONNAIRE

COMPLETE AT BASELINE ONLY

The following is a series of questions about serious or traumatic life events. These types of events actually occur with some regularity, although we would like to believe they are rare, and they affect how people feel about, react to, and/or think about things subsequently. The questionnaire is divided into questions covering crime experiences, general disaster and trauma questions, and questions about physical and sexual experiences.

For each event, please indicate (*circle*) whether it happened, and if it did, the number of times and your approximate age when it happened (*give your best guess if you are not sure*). Also note the nature of your relationship to the person involved, and the specific nature of the event, if appropriate.

Crime-Related Events

		<u>If Yes</u>		
		# of times	Approx. Age	
1.	Has anyone ever tried to take something directly from you by using force or the threat of force, such as a stick-up or mugging?	No	Yes	_____
2.	Has anyone ever attempted to rob you or actually robbed you (i.e. stolen your personal belongings)?	No	Yes	_____
3.	Has anyone ever attempted to or succeeded in breaking into your home when you weren't there?	No	Yes	_____
4.	Has anyone ever tried to or succeeded in breaking into your home while you <u>were</u> there?	No	Yes	_____

General Disaster and Trauma

If Yes
of
times **Approx.**
 Age

5. Have you ever had a serious accident at work, in a car or somewhere else? No Yes _____

If yes, please specify: _____

6. Have you ever experienced a natural disaster such as a tornado, hurricane, flood, major earthquake, etc., where you felt you or your loved ones were in danger of death or injury? No Yes _____

If yes, please specify: _____

7. Have you ever experienced a "man-made" disaster such as a train crash, building collapse, bank robbery, fire, etc., where you felt you or your loved ones were in danger of death or injury? No Yes _____

If yes, please specify: _____

8. Have you ever been exposed to dangerous chemicals or radioactivity that might threaten your health? No Yes _____

9. Have you ever been in any other situation in which you were seriously injured? No Yes _____

If yes, please specify: _____

		<u>If Yes</u>	<u># of</u>	<u>Approx.</u>
		<u>times</u>	<u>times</u>	<u>Age</u>
10.	Have you ever been in any other situation in which you feared you <u>might</u> be killed or seriously injured?	No Yes	_____	_____
	<u>If yes</u> , please specify:	_____		
11.	Have you ever seen someone seriously injured or killed?	No Yes	_____	_____
	<u>If yes</u> , please specify who:	_____		
12.	Have you ever seen dead bodies (other than at a funeral) or had to handle dead bodies for any reason?	No Yes	_____	_____
	<u>If yes</u> , please specify:	_____		
13.	Have you ever had a close friend or family member murdered, or killed by a drunk driver?	No Yes	_____	_____
	<u>If yes</u> , please specify relationship (e.g. mother, grandson, etc.):	_____		
14.	Have you ever had a spouse, romantic partner, or child die?	No Yes	_____	_____
	<u>If yes</u> , please specify relationship:	_____		
15.	Have you ever had a serious or life-threatening illness?	No Yes	_____	_____
	<u>If yes</u> , please specify:	_____		

		<u>If Yes</u>	# of	Approx.
		times	Age	
16.	Have you ever received news of a serious injury, life-threatening illness or unexpected death of someone close to you?	No Yes	_____	_____

If yes, please specify: _____

17.	Have you ever had to engage in combat while in military service in an official or unofficial war zone?	No Yes	_____	_____
-----	--	-------------	-------	-------

If yes, please specify: _____

Physical and Sexual Experiences

		<u>If Yes</u>	Was it	Approx.	Approx.
		repeated?	how often	what age(s)	
18.	Has anyone ever made you have intercourse, oral or anal sex against your will?	No Yes	_____	_____	_____

If yes, please indicate nature of relationship with person (e.g. stranger, friend, relative, parent, sibling): _____

19.	Has anyone ever touched private parts of your body, or made you touch theirs, under force or threat?	No Yes	_____	_____	_____
-----	--	-------------	-------	-------	-------

If yes, please indicate nature of relationship with person (e.g. stranger, friend, relative, parent, sibling): _____

Site ____ Participant # _____ Alpha Code _____ Date ____/____/____

		If Yes	Was it repeated?	Approx. how often	Approx. what age(s)
20.	Other than incidents mentioned in Questions 18 and 19, have there been any other situations in which another person tried to force you to have unwanted sexual contact?	No Yes			
21.	Has anyone, including family members or friends, ever attacked you with a gun, knife or some other weapon?	No Yes			
22.	Has anyone, including family members or friends, ever attacked you <u>without</u> a weapon and seriously injured you?	No Yes			
23.	Has anyone in your family ever beaten, "spanked" or pushed you hard enough to cause injury?	No Yes			

Other Events

24.	Have you experienced any other extraordinarily stressful situation or event that is not covered above?	No Yes			
-----	--	--------	--	--	--

If yes, please specify: _____

SC Signature _____ Date _____

VA COOPERATIVE STUDY #556
The Effectiveness of rTMS in Depressed VA Patients

Site ____ Participant # _____ Alpha Code _____ Date ____/____/____

Form 12 – LIFE STRESSOR CHECKLIST REVISED

COMPLETE AT BASELINE ONLY

READ THIS FIRST: Now we are going to ask you some questions about events in your life that are frightening, upsetting, or stressful to most people. Please think back over your **whole life** when you answer these questions. Some of these questions may be about upsetting events you don't usually talk about. Your answers are important, but **you do not have to answer any questions that you do not want to.** Thank you.

1. Have you ever been in a serious disaster (for example, an earthquake, hurricane, large fire, explosion)?	Yes	No			
a. How old were you when this happened? ____					
c. At the time of the event did you believe that you or someone else could be killed or seriously harmed ?	Yes	No			
d. At the time of the event did you experience feelings of intense helplessness, fear, or horror?	Yes	No			
e. How much has this affected your life in the past year?	1 Not at all	2	3 Some	4	5 Extremely
2. Have you ever seen a serious accident (for example, a bad car wreck or an on-the-job accident)?	Yes	No			
a. How old were you when this happened? ____					
c. At the time of the event did you believe that you or someone else could be killed or seriously harmed ?	Yes	No			
d. At the time of the event did you experience feelings of intense helplessness, fear, or horror?	Yes	No			
e. How much has this affected your life in the past year?	1 Not at all	2	3 Some	4	5 Extremely
3. Have you ever had a very serious accident or accident-related injury (for example, a bad car wreck or an on-the-job accident)?	Yes	No			
a. How old were you when this happened? ____					
c. At the time of the event did you believe that you or someone else could be killed or seriously harmed ?	Yes	No			
d. At the time of the event did you experience feelings of intense helplessness, fear, or horror?	Yes	No			
e. How much has this affected your life in the past year?	1 Not at all	2	3 Some	4	5 Extremely

4. Was a close family member ever sent to jail?		Yes	No			
a. How old were you when this happened? ____	b. When it ended? ____					
c. At the time of the event did you believe that you or someone else could be killed or seriously harmed ?		Yes	No			
d. At the time of the event did you experience feelings of intense helplessness, fear, or horror?		Yes	No			
e. How much has this affected your life in the past year?		1 Not at all	2	3 Some	4	5 Extremely
5. Have you ever been sent to jail?		Yes	No			
a. How old were you when this happened? ____	b. When it ended? ____					
c. At the time of the event did you believe that you or someone else could be killed or seriously harmed ?		Yes	No			
d. At the time of the event did you experience feelings of intense helplessness, fear, or horror?		Yes	No			
e. How much has this affected your life in the past year?		1 Not at all	2	3 Some	4	5 Extremely
6. Were you ever put in foster care or put up for adoption?		Yes	No			
a. How old were you when this happened? ____	b. When it ended? ____					
c. At the time of the event did you believe that you or someone else could be killed or seriously harmed ?		Yes	No			
d. At the time of the event did you experience feelings of intense helplessness, fear, or horror?		Yes	No			
e. How much has this affected your life in the past year?		1 Not at all	2	3 Some	4	5 Extremely
7. Did your parents ever separate or divorce while you were living with them?		Yes	No			
a. How old were you when this happened? ____	b. When it ended? ____					
c. At the time of the event did you believe that you or someone else could be killed or seriously harmed ?		Yes	No			
d. At the time of the event did you experience feelings of intense helplessness, fear, or horror?		Yes	No			
e. How much has this affected your life in the past year?		1 Not at all	2	3 Some	4	5 Extremely

8. Have you ever been separated or divorced?	Yes	No			
a. How old were you when this happened? ____	b. When it ended? ____				
c. At the time of the event did you believe that you or someone else could be killed or seriously harmed ?	Yes	No			
d. At the time of the event did you experience feelings of intense helplessness, fear, or horror?	Yes	No			
e. How much has this affected your life in the past year?	1 Not at all	2	3 Some	4	5 Extremely
9. Have you ever had serious money problems (for example, not enough money for food or place to live)?	Yes	No			
a. How old were you when this happened? ____	b. When it ended? ____				
c. At the time of the event did you believe that you or someone else could be killed or seriously harmed ?	Yes	No			
d. At the time of the event did you experience feelings of intense helplessness, fear, or horror?	Yes	No			
e. How much has this affected your life in the past year?	1 Not at all	2	3 Some	4	5 Extremely
10. Have you ever had a very serious physical or mental illness (for example, cancer, heart attack, serious operation, felt like killing yourself, hospitalized because of nerve problems)?	Yes	No			
a. How old were you when this happened? ____	b. When it ended? ____				
c. At the time of the event did you believe that you or someone else could be killed or seriously harmed ?	Yes	No			
d. At the time of the event did you experience feelings of intense helplessness, fear, or horror?	Yes	No			
e. How much has this affected your life in the past year?	1 Not at all	2	3 Some	4	5 Extremely
11. Have you ever been emotionally abused or neglected (for example, being frequently shamed, embarrassed, ignored, or repeatedly told that you were "no good")?	Yes	No			
a. How old were you when this happened? ____	b. When it ended? ____				
c. At the time of the event did you believe that you or someone else could be killed or seriously harmed ?	Yes	No			
d. At the time of the event did you experience feelings of intense helplessness, fear, or horror?	Yes	No			
e. How much has this affected your life in the past year?	1 Not at all	2	3 Some	4	5 Extremely

12. Have you ever been physically neglected (for example, not fed, not properly clothed, or left to take care of yourself when you were too young or ill)?					Yes	No	
a. How old were you when this happened? ____	b. When it ended? ____						
c. At the time of the event did you believe that you or someone else could be killed or seriously harmed ?						Yes	No
d. At the time of the event did you experience feelings of intense helplessness, fear, or horror?						Yes	No
e. How much has this affected your life in the past year?	1 Not at all	2	3 Some	4	5 Extremely		
13. WOMEN ONLY: Have you ever had an abortion or miscarriage (lost your baby)?					Yes	No	
a. How old were you when this happened? ____							
c. At the time of the event did you believe that you or someone else could be killed or seriously harmed ?						Yes	No
d. At the time of the event did you experience feelings of intense helplessness, fear, or horror?						Yes	No
e. How much has this affected your life in the past year?	1 Not at all	2	3 Some	4	5 Extremely		
14. Have you ever been separated from your child against your will (for example, the loss of custody or visitation or kidnapping)?					Yes	No	
a. How old were you when this happened? ____	b. When it ended? ____						
c. At the time of the event did you believe that you or someone else could be killed or seriously harmed ?						Yes	No
d. At the time of the event did you experience feelings of intense helplessness, fear, or horror?						Yes	No
e. How much has this affected your life in the past year?	1 Not at all	2	3 Some	4	5 Extremely		
15. Has a baby or child of yours ever had a severe physical or mental handicap (for example, mentally retarded, birth defects, can't hear, see, walk)?					Yes	No	
a. How old were you when this happened? ____	b. When it ended? ____						
c. At the time of the event did you believe that you or someone else could be killed or seriously harmed ?						Yes	No
d. At the time of the event did you experience feelings of intense helplessness, fear, or horror?						Yes	No
e. How much has this affected your life in the past year?	1 Not at all	2	3 Some	4	5 Extremely		

16. Have you ever been responsible for taking care of someone close to you (not your child) who had a severe physical or mental handicap (for example, cancer, stroke, AIDS, nerve problems, can't hear, see, walk)?	Yes	No			
a. How old were you when this happened? ____	b. When it ended? ____				
c. At the time of the event did you believe that you or someone else could be killed or seriously harmed ?	Yes	No			
d. At the time of the event did you experience feelings of intense helplessness, fear, or horror?	Yes	No			
e. How much has this affected your life in the past year?	1 Not at all	2	3 Some	4	5 Extremely
17. Has someone close to you died suddenly or unexpectedly (for example, sudden heart attack, murder or suicide)?	Yes	No			
a. How old were you when this happened? ____	b. When it ended? ____				
c. At the time of the event did you believe that you or someone else could be killed or seriously harmed ?	Yes	No			
d. At the time of the event did you experience feelings of intense helplessness, fear, or horror?	Yes	No			
e. How much has this affected your life in the past year?	1 Not at all	2	3 Some	4	5 Extremely
18. Has someone close to you died (do NOT include those who died suddenly or unexpectedly)?	Yes	No			
a. How old were you when this happened? ____					
c. At the time of the event did you believe that you or someone else could be killed or seriously harmed ?	Yes	No			
d. At the time of the event did you experience feelings of intense helplessness, fear, or horror?	Yes	No			
e. How much has this affected your life in the past year?	1 Not at all	2	3 Some	4	5 Extremely
19. When you were young (before age 16), did you ever see violence between family members (for example, hitting, kicking, slapping, punching)?	Yes	No			
a. How old were you when this happened? ____					
c. At the time of the event did you believe that you or someone else could be killed or seriously harmed ?	Yes	No			
d. At the time of the event did you experience feelings of intense helplessness, fear, or horror?	Yes	No			
e. How much has this affected your life in the past year?	1 Not at all	2	3 Some	4	5 Extremely

VA COOPERATIVE STUDY #556

The Effectiveness of rTMS in Depressed VA Patients

Site ____ Participant # _____ Alpha Code _____ Date _____ / _____ / _____
MM DD YYYY

20. Have you ever seen a robbery, mugging, or attack taking place?	Yes	No			
a. How old were you when this happened? ____					
c. At the time of the event did you believe that you or someone else could be killed or seriously harmed ?	Yes	No			
d. At the time of the event did you experience feelings of intense helplessness, fear, or horror?	Yes	No			
e. How much has this affected your life in the past year?	1 Not at all	2	3 Some	4	5 Extremely
21. Have you ever been robbed, mugged, or physically attacked (not sexually) by someone you did not know?	Yes	No			
a. How old were you when this happened? ____					
c. At the time of the event did you believe that you or someone else could be killed or seriously harmed ?	Yes	No			
d. At the time of the event did you experience feelings of intense helplessness, fear, or horror?	Yes	No			
e. How much has this affected your life in the past year?	1 Not at all	2	3 Some	4	5 Extremely
22. Before age 16, were you ever abused or physically attacked (not sexually) by someone you knew (for example, a parent, boyfriend, or husband, hit, slapped, choked, burned, or beat you up)?	Yes	No			
a. How old were you when this happened? ____	b. When it ended? ____				
c. At the time of the event did you believe that you or someone else could be killed or seriously harmed ?	Yes	No			
d. At the time of the event did you experience feelings of intense helplessness, fear, or horror?	Yes	No			
e. How much has this affected your life in the past year?	1 Not at all	2	3 Some	4	5 Extremely
23. After age 16, were you ever abused or physically attacked (not sexually) by someone you knew (for example, a parent, boyfriend, or husband, hit, slapped, choked, burned, or beat you up)?	Yes	No			
a. How old were you when this happened? ____	b. When it ended? ____				
c. At the time of the event did you believe that you or someone else could be killed or seriously harmed ?	Yes	No			
d. At the time of the event did you experience feelings of intense helplessness, fear, or horror?	Yes	No			
e. How much has this affected your life in the past year?	1 Not at all	2	3 Some	4	5 Extremely

24. Have you ever been bothered or harassed by sexual remarks, jokes, or demands for sexual favors by someone at work or school (for example, a coworker, a boss, a customer, another student, a teacher)?					Yes	No
a. How old were you when this happened? ____		b. When it ended? ____				
c. At the time of the event did you believe that you or someone else could be killed or seriously harmed ?		Yes No				
d. At the time of the event did you experience feelings of intense helplessness, fear, or horror?		Yes No				
e. How much has this affected your life in the past year?		1 Not at all	2	3 Some	4	5 Extremely
25. Before age 16, were you ever touched or made to touch someone else in a sexual way because he/she forced you in some way or threatened to harm you if you didn't?					Yes	No
a. How old were you when this happened? ____		b. When it ended? ____				
c. At the time of the event did you believe that you or someone else could be killed or seriously harmed ?		Yes No				
d. At the time of the event did you experience feelings of intense helplessness, fear, or horror?		Yes No				
e. How much has this affected your life in the past year?		1 Not at all	2	3 Some	4	5 Extremely
26. After age 16, were you ever touched or made to touch someone else in a sexual way because he/she forced you in some way or threatened to harm you if you didn't?					Yes	No
a. How old were you when this happened? ____		b. When it ended? ____				
c. At the time of the event did you believe that you or someone else could be killed or seriously harmed ?		Yes No				
d. At the time of the event did you experience feelings of intense helplessness, fear, or horror?		Yes No				
e. How much has this affected your life in the past year?		1 Not at all	2	3 Some	4	5 Extremely
27. Before age 16, did you ever have sex (oral, anal, genital) when you didn't want to because someone forced you in some way or threatened to hurt you if you didn't?					Yes	No
a. How old were you when this happened? ____		b. When it ended? ____				
c. At the time of the event did you believe that you or someone else could be killed or seriously harmed ?		Yes No				
d. At the time of the event did you experience feelings of intense helplessness, fear, or horror?		Yes No				
e. How much has this affected your life in the past year?		1 Not at all	2	3 Some	4	5 Extremely

28. After age 16, did you ever have sex (oral, anal, genital) when you didn't want to because someone forced you in some way or threatened to hurt you if you didn't?	Yes	No			
a. How old were you when this happened? ____	b. When it ended? ____				
c. At the time of the event did you believe that you or someone else could be killed or seriously harmed ?	Yes	No			
d. At the time of the event did you experience feelings of intense helplessness, fear, or horror?	Yes	No			
e. How much has this affected your life in the past year?	1 Not at all	2	3 Some	4	5 Extremely
29. Are there any events we did not include that you would like to mention? What was the event? _____	Yes	No			
a. How old were you when this happened? ____	b. When it ended? ____				
c. At the time of the event did you believe that you or someone else could be killed or seriously harmed ?	Yes	No			
d. At the time of the event did you experience feelings of intense helplessness, fear, or horror?	Yes	No			
e. How much has this affected your life in the past year?	1 Not at all	2	3 Some	4	5 Extremely
30. Have any of the events mentioned above ever happened to someone close to you so that even though you didn't see it yourself, you were seriously upset by it? What was the event? _____	Yes	No			
a. How old were you when this happened? ____	b. When it ended? ____				
c. At the time of the event did you believe that you or someone else could be killed or seriously harmed ?	Yes	No			
d. At the time of the event did you experience feelings of intense helplessness, fear, or horror?	Yes	No			
e. How much has this affected your life in the past year?	1 Not at all	2	3 Some	4	5 Extremely

SC Signature _____ Date _____

VA COOPERATIVE STUDY #556
The Effectiveness of rTMS in Depressed VA Patients

Site ____ Participant # _____ Alpha Code _____ Date ____ / ____ / ____

**Form 13 – The Six-Item Blessed Orientation-Memory-Concentration
(BOMC) Test**

COMPLETE AT SCREENING ONLY

	Items	Maximum Error	Score	Weight
1	What <i>year</i> is it now?	1	____ x	4 = _____
2	What <i>month</i> is it now?	1	____ x	3 = _____
	Memory phrase	Repeat this phrase after me: John Brown, 42 Market Street, Chicago		
3	About what <i>time</i> is it? (within 1 hour)	1	____ x	3 = _____
4	<i>Count</i> backwards 20 to 1	2	____ x	2 = _____
5	Say the months in reverse order	2	____ x	2 = _____
6	Repeat the memory phrase	5	____ x	2 = _____

SC Signature _____ Date _____

Weighted error scores greater than 10 are consistent with dementia, according to Katzman et al. (1983).

Source: Katzman, R., Brown, T., Fuld, P., Peck, A., Schechter, R., & Schimmel, H. (1983). Validation of a short orientation-memory-concentration test of cognitive impairment. *American Journal of Psychiatry*, 140, 734-739.

Copyright is held by American Psychiatric Association. Permission from test author R. Katzman to VA for VA use.

VA COOPERATIVE STUDY #556
The Effectiveness of rTMS in Depressed VA Patients

Site ____ Participant # _____ Alpha Code _____ Date ____/____/____ MM / DD / YYYY

Form 14 – BIRTH CONTROL/PREGNANCY ASSESSMENT
(Women Only)

**COMPLETE WITHIN 7 DAYS PRIOR TO RANDOMIZATION AND
EVERY 4 WEEKS THEREAFTER, THROUGHOUT THE STUDY**

1. What method of birth control is participant currently using? _____

01 = Complete abstinence (not having sexual intercourse with anyone)

02 = Oral contraceptive (birth control pills)

03 = Norplant

04 = Depo-Provera©

05 = Condom with spermicide

06 = Cervical cap with spermicide

07 = Diaphragm with spermicide

08 = Intrauterine Device

09 = Surgical Sterilization (tubal ligation)

record month/year of procedure / _____

10 = Hysterectomy, record month/year of procedure / _____

11 = Post-menopausal, record date of last menstrual period..... / _____

12 = Other method of birth control, specify _____

2. Was a pregnancy test performed? (0=No, 1=Yes) _____

If Yes:

a. Result of pregnancy test (1 = Positive, 2 = Negative,) _____

b. Date specimen collected Mo ____ Day ____ Yr _____

VA COOPERATIVE STUDY #556

The Effectiveness of rTMS in Depressed VA Patients

Site ____ Participant # _____ Alpha Code _____ Date ____ / ____ / ____
MM DD YYYY

Form 15 - Prior and Concomitant Medications Log

Begin this log on the day the subject signs the informed consent. Record all medications taken by the subject 30 days prior to signing the informed consent through week 24 of Follow-up.

Was medication taken during the time period described above? No Yes

Page #

VA COOPERATIVE STUDY #556
The Effectiveness of rTMS in Depressed VA Patients

Concomitant Medications Codes

Units	Frequency	Dose Form	Route
01 = Capsule/Tablet	1 = Once a day	1 = Tablet	1 = Oral
02 = Drop	2 = Twice daily	2 = Capsule	2 = Topical
03 = International Units	3 = Three times a day	3 = Ointment	3 = Subcutaneous
04 = Micrograms	4 = Four times a day	4 = Aerosol	4 = Transdermal
05 = Milliequivalents	5 = Every other day	5 = Spray	5 = Intraocular
06 = Milligram	6 = Every month	6 = Suspension	6 = Intramuscular
07 = Milliliter	7 = PR (as needed)	7 = Patch	7 = Inhalation
08 = Puff	99 = Other	8 = Gas	8 = Intralesion
09 = Spray/Squirt		9 = Gel	9 = Intraperitoneal
10 = Units (for Insulin)		10 = Cream	10 = Nasal
11 = Tablespoon		11 = Powder	11 = Vaginal
12 = Teaspoon		99 = Other	12 = Rectal
99 = Other			13 = Intravenous
			14 = Sublingual
			99 = Other

VA COOPERATIVE STUDY #556
The Effectiveness of rTMS in Depressed VA Patients

Site ____ Participant # _____ Alpha Code _____ Date ____ / ____ / ____
____ / ____ / ____

FORM 16 –Study Clinic Visit Form

Circle Visit Below:

Acute Treatment Phase Sessions: **5 10 15 20 25 30**

Taper Week: **1 2 3**

Follow-up Phase Weeks: **4 8 12 16 20 24**

1. Did the participant come in for this assessment session? (Circle One) NO YES
a. If 'No', please indicate if the interview was conducted by:
(Circle One) Telephone Mail Both Neither
2. Did the participant drink alcohol since the last assessment session? (Circle One) NO YES
a. If 'Yes', please indicate how many drinks..... _____
3. Did the participant use a non-alcoholic substance in a manner that is restricted by the protocol since the last assessment session? (Circle One) NO YES

ANSWER QUESTION 4 ONLY AFTER ACUTE TREATMENT SESSIONS 20, 25, and 30.

4. Did participant receive a score on the HRSD of ≤ 10 ? (Circle One) NO YES
If 'Yes',
a. Is participant going to Taper? (Circle One) NO YES
i. If 'No', Why? _____
If 'No',
b. If HRSD of >10 is the participant going to continue to additional 5 sessions?
(Circle One) NO YES
i. If 'No', Why? _____
NOTE: If 'No', do not taper and participant will enter Follow-up Phase.

ANSWER QUESTIONS 5-7 IN FOLLOW UP PHASE, STARTING WITH WEEK 4.

5. Did participant experience an Adverse Event? (Circle One) NO YES
If 'Yes', **fill out Adverse Event form pack**
6. Did participant experience a Serious Adverse Event? (Circle One) NO YES
If 'Yes', **fill out Adverse Event form pack**
7. Did participants medications change? (Circle One) NO YES
If 'Yes', **fill Medication form pack**

VA COOPERATIVE STUDY #556
The Effectiveness of rTMS in Depressed VA Patients

Site ____ Participant # _____ Alpha Code _____ Date ____/____/____ MM/ DD/ YYYY

Form 17 – Pure Tone Audiometry

<u>Circle Visit Below:</u>		
Screening	End of Acute Treatment	Final Follow-up Visit

Frequency (Hz)		Lowest Threshold (dB)	
		Left Ear	Right Ear
1	125	_____	_____
3	500	_____	_____
5	1000	_____	_____
6	2000	_____	_____
7	3000	_____	_____
8	4000	_____	_____
9	6000	_____	_____
10	8000	_____	_____

VA COOPERATIVE STUDY #556
The Effectiveness of rTMS in Depressed VA Patients

Site ____ Participant # _____ Alpha Code _____ Date ____ / ____ / ____

Form 18 – rTMS TREATMENT LOG

Circle Visit Below:

Acute Treatment Phase Sessions: 1-5 6-10 11-15 16-20 21-25 26-30

Randomization Treatment Code: _____

Tx Session 01:

1. Date of Treatment Session: ____ / ____ / ____
2. Did participant's medications change from previous session? No Yes **If yes, fill out Medication Form pack**
3. Did the participant have an adverse event since the last session? No Yes **If yes, fill out Adverse Event Form pack** AE Reference # _____
4. Did the participant have a serious adverse event since the last session? No Yes **If yes, fill out Adverse Event Form pack** AE Reference # _____
5. How many hours of sleep did the participant get last night? ____ hours
6. Since your last treatment session have you consumed any of the following:
 - a. Alcohol: No Yes If yes, how many drinks ____ (see drinking chart for conversion)
 - b. Illegal drugs: No Yes If yes, what kind _____ and how much _____
7. Number of Styrofoam layers _____
8. Current Stimulation Intensity (select only one) 3 5 7
9. MT Determination ____ %
10. Power output at treatment delivery ____ %
11. Was the rTMS treatment completed? No Yes
12. If No, specify the primary reason using the codes (see last page for codes) _____
13. rTMS administrator's initials: _____

Tx Session 02:

1. Date of Treatment Session: ____ / ____ / ____
2. Did participant's medications change from previous session? No Yes **If yes, fill out Medication Form pack**
3. Did the participant have an adverse event since the last session? No Yes **If yes, fill out Adverse Event Form pack** AE Reference # _____
4. Did the participant have a serious adverse event since the last session? No Yes **If yes, fill out Adverse Event Form pack** AE Reference # _____
5. How many hours of sleep did the participant get last night? ____ hours
6. Since your last treatment session have you consumed any of the following:
 - a. Alcohol: No Yes If yes, how many drinks ____ (see drinking chart for conversion)
 - b. Illegal drugs: No Yes If yes, what kind _____ and how much _____
7. Number of Styrofoam layers _____
8. Current Stimulation Intensity (select only one) 3 5 7
9. MT Determination ____ %
10. Power output at treatment delivery ____ %
11. Was the rTMS treatment completed? No Yes
12. If No, specify the primary reason using the codes (see last page for codes) _____
13. rTMS administrator's initials: _____

VA COOPERATIVE STUDY #556
The Effectiveness of rTMS in Depressed VA Patients

Site ____ Participant # _____ Alpha Code _____ Date MM / DD / YYYY _____

Tx Session 03:

1. Date of Treatment Session: ____ / ____ / ____
2. Did participant's medications change from previous session? No Yes **If yes, fill out Medication Form pack**
3. Did the participant have an adverse event since the last session? No Yes **If yes, fill out Adverse Event Form pack** AE Reference # _____
4. Did the participant have a serious adverse event since the last session? No Yes **If yes, fill out Adverse Event Form pack** AE Reference # _____
5. How many hours of sleep did the participant get last night? ____ hours
6. Since your last treatment session have you consumed any of the following:
 - a. Alcohol: No Yes If yes, how many drinks ____ (see drinking chart for conversion)
 - b. Illegal drugs: No Yes If yes, what kind _____ and how much _____
7. Number of Styrofoam layers _____
8. Current Stimulation Intensity (select only one) 3 5 7
9. MT Determination ____ %
10. Power output at treatment delivery ____ %
11. Was the rTMS treatment completed? No Yes
12. If No, specify the primary reason using the codes (see last page for codes) _____
13. rTMS administrator's initials: _____

Tx Session 04:

1. Date of Treatment Session: ____ / ____ / ____
2. Did participant's medications change from previous session? No Yes **If yes, fill out Medication Form pack**
3. Did the participant have an adverse event since the last session? No Yes **If yes, fill out Adverse Event Form pack** AE Reference # _____
4. Did the participant have a serious adverse event since the last session? No Yes **If yes, fill out Adverse Event Form pack** AE Reference # _____
5. How many hours of sleep did the participant get last night? ____ hours
6. Since your last treatment session have you consumed any of the following:
 - a. Alcohol: No Yes If yes, how many drinks ____ (see drinking chart for conversion)
 - b. Illegal drugs: No Yes If yes, what kind _____ and how much _____
7. Number of Styrofoam layers _____
8. Current Stimulation Intensity (select only one) 3 5 7
9. MT Determination ____ %
10. Power output at treatment delivery ____ %
11. Was the rTMS treatment completed? No Yes
12. If No, specify the primary reason using the codes (see last page for codes) _____
13. rTMS administrator's initials: _____

VA COOPERATIVE STUDY #556
The Effectiveness of rTMS in Depressed VA Patients

Site ____ Participant # _____ Alpha Code _____ Date _{MM} / _{DD} / _{YYYY} _____

Tx Session 05:

1. Date of Treatment Session: ____ / ____ / ____
2. Did participant's medications change from previous session? No Yes **If yes, fill out Medication Form pack**
3. Did the participant have an adverse event since the last session? No Yes **If yes, fill out Adverse Event Form pack** AE Reference # _____
4. Did the participant have a serious adverse event since the last session? No Yes **If yes, fill out Adverse Event Form pack** AE Reference # _____
5. How many hours of sleep did the participant get last night? ____ hours
6. Since your last treatment session have you consumed any of the following:
 - a. Alcohol: No Yes If yes, how many drinks ____ (see drinking chart for conversion)
 - b. Illegal drugs: No Yes If yes, what kind _____ and how much _____
7. Number of Styrofoam layers _____
8. Current Stimulation Intensity (select only one) 3 5 7
9. MT Determination ____ %
10. Power output at treatment delivery ____ %
11. Was the rTMS treatment completed? No Yes
12. If No, specify the primary reason using the codes (see last page for codes) _____
13. rTMS administrator's initials: _____

CODES:

1 = Equipment malfunction	4 = Adverse Device Event/Adverse Event
2 = Participant refused	5 = Unanticipated Adverse Device Event/Serious Adverse Event
3 = Staff error	6 = Other, specify _____

VA COOPERATIVE STUDY #556
The Effectiveness of rTMS in Depressed VA Patients

Site ____ Participant # _____ Alpha Code _____ Date _____ / _____ / _____ MM DD YYYY

Form 19 – rTMS TAPER LOG

Complete during Follow Up Weeks 1-3

Randomization Treatment Code: _____

WEEK 01 –

Tx Session 01:

1. Date of Treatment Session: ____ / ____ / ____
2. Did participant's medications change from previous session? No Yes **If yes, fill out Medication Form pack**
3. Did the participant have an adverse event since the last session? No Yes **If yes, fill out Adverse Event Form pack** AE Reference # _____
4. Did the participant have a serious adverse event since the last session? No Yes **If yes, fill out Adverse Event Form pack** AE Reference # _____
5. How many hours of sleep did the participant get last night? ____ hours
6. Since your last treatment session have you consumed any of the following:
 - a. Alcohol: No Yes If yes, how many drinks ____ (see drinking chart for conversion)
 - b. Illegal drugs: No Yes If yes, what kind _____ and how much _____
7. Number of Styrofoam layers _____
8. Current Stimulation Intensity (select only one) 3 5 7
9. MT Determination ____ %
10. Power output at treatment delivery ____ %
11. Was the rTMS treatment completed? No Yes
12. If No, specify the primary reason using the codes (see last page for codes) _____
13. rTMS administrator's initials: _____

Tx Session 02:

1. Date of Treatment Session: ____ / ____ / ____
2. Did participant's medications change from previous session? No Yes **If yes, fill out Medication Form pack**
3. Did the participant have an adverse event since the last session? No Yes **If yes, fill out Adverse Event Form pack** AE Reference # _____
4. Did the participant have a serious adverse event since the last session? No Yes **If yes, fill out Adverse Event Form pack** AE Reference # _____
5. How many hours of sleep did the participant get last night? ____ hours
6. Since your last treatment session have you consumed any of the following:
 - a. Alcohol: No Yes If yes, how many drinks ____ (see drinking chart for conversion)
 - b. Illegal drugs: No Yes If yes, what kind _____ and how much _____
7. Number of Styrofoam layers _____
8. Current Stimulation Intensity (select only one) 3 5 7
9. MT Determination ____ %
10. Power output at treatment delivery ____ %
11. Was the rTMS treatment completed? No Yes
12. If No, specify the primary reason using the codes (see last page for codes) _____
13. rTMS administrator's initials: _____

Tx Session 03:

1. Date of Treatment Session: ____ / ____ / ____
2. Did participant's medications change from previous session? No Yes **If yes, fill out Medication Form pack**
3. Did the participant have an adverse event since the last session? No Yes **If yes, fill out Adverse Event Form pack** AE Reference # _____
4. Did the participant have a serious adverse event since the last session? No Yes **If yes, fill out Adverse Event Form pack** AE Reference # _____
5. How many hours of sleep did the participant get last night? ____ hours
6. Since your last treatment session have you consumed any of the following:
 - a. Alcohol: No Yes If yes, how many drinks ____ (see drinking chart for conversion)
 - b. Illegal drugs: No Yes If yes, what kind _____ and how much _____
7. Number of Styrofoam layers _____
8. Current Stimulation Intensity (select only one) 3 5 7
9. MT Determination ____ %
10. Power output at treatment delivery ____ %
11. Was the rTMS treatment completed? No Yes
12. If No, specify the primary reason using the codes (see last page for codes) _____
13. rTMS administrator's initials: _____

WEEK 02 –

Tx Session 01:

1. Date of Treatment Session: ____ / ____ / ____
2. Did participant's medications change from previous session? No Yes **If yes, fill out Medication Form pack**
3. Did the participant have an adverse event since the last session? No Yes **If yes, fill out Adverse Event Form pack** AE Reference # _____
4. Did the participant have a serious adverse event since the last session? No Yes **If yes, fill out Adverse Event Form pack** AE Reference # _____
5. How many hours of sleep did the participant get last night? ____ hours
6. Since your last treatment session have you consumed any of the following:
 - a. Alcohol: No Yes If yes, how many drinks ____ (see drinking chart for conversion)
 - b. Illegal drugs: No Yes If yes, what kind _____ and how much _____
7. Number of Styrofoam layers _____
8. Current Stimulation Intensity (select only one) 3 5 7
9. MT Determination ____ %
10. Power output at treatment delivery ____ %
11. Was the rTMS treatment completed? No Yes
12. If No, specify the primary reason using the codes (see last page for codes) _____
13. rTMS administrator's initials: _____

Tx Session 02:

1. Date of Treatment Session: ____ / ____ / ____
2. Did participant's medications change from previous session? No Yes **If yes, fill out Medication Form pack**
3. Did the participant have an adverse event since the last session? No Yes **If yes, fill out Adverse Event Form pack** AE Reference # _____
4. Did the participant have a serious adverse event since the last session? No Yes **If yes, fill out Adverse Event Form pack** AE Reference # _____
5. How many hours of sleep did the participant get last night? ____ hours
6. Since your last treatment session have you consumed any of the following:
 - a. Alcohol: No Yes If yes, how many drinks ____ (see drinking chart for conversion)
 - b. Illegal drugs: No Yes If yes, what kind _____ and how much _____
7. Number of Styrofoam layers _____
8. Current Stimulation Intensity (select only one) 3 5 7
9. MT Determination ____ %
10. Power output at treatment delivery ____ %
11. Was the rTMS treatment completed? No Yes
12. If No, specify the primary reason using the codes (see last page for codes) _____
13. rTMS administrator's initials: _____

WEEK 03 –

Tx Session 01:

1. Date of Treatment Session: ____ / ____ / ____
2. Did participant's medications change from previous session? No Yes **If yes, fill out Medication Form pack**
3. Did the participant have an adverse event since the last session? No Yes **If yes, fill out Adverse Event Form pack** AE Reference # _____
4. Did the participant have a serious adverse event since the last session? No Yes **If yes, fill out Adverse Event Form pack** AE Reference # _____
5. How many hours of sleep did the participant get last night? ____ hours
6. Since your last treatment session have you consumed any of the following:
 - a. Alcohol: No Yes If yes, how many drinks ____ (see drinking chart for conversion)
 - b. Illegal drugs: No Yes If yes, what kind _____ and how much _____
7. Number of Styrofoam layers _____
8. Current Stimulation Intensity (select only one) 3 5 7
9. MT Determination ____ %
10. Power output at treatment delivery ____ %
11. Was the rTMS treatment completed? No Yes
12. If No, specify the primary reason using the codes (see last page for codes) _____
13. rTMS administrator's initials: _____

CODES:

1 = Equipment malfunction	4 = Adverse Device Event/Adverse Event
2 = Participant refused	5 = Unanticipated Adverse Device Event/Serious Adverse Event
3 = Staff error	6 = Other, specify _____

VA COOPERATIVE STUDY #556
The Effectiveness of rTMS in Depressed VA Patients

Site ____ Participant # _____ Alpha Code _____ Date ___/___/___- MM / DD / YYYY

Form 20 – HRSD and MADRS

Circle Visit Below:

Screening

Acute Treatment Phase Sessions: 5 10 15 20 25 30

Follow-up Phase Weeks: 4 8 12 16 20 24

Interviewer's Initials:	_____		
Start Time:	_____ (24 hour clock)		
MANUAL SCORING INSTRUCTIONS: Write the score of the item in the box for the 24 HRSD items. Take the sum of these values and write it in the Total HRSD Score box at the end of the form.			
Introductory Questions: "I'd like to ask you some questions about the past week. Since last (DAY OF THE WEEK), how have you been feeling? Have you noticed any change in how you have been feeling during the past week compared to before?"			
Interview Guide	HRSD Scoring Criteria	MADRS Scoring Criteria	
SLEEP (Early and Middle Insomnia)			
<i>"Let's talk about your sleep. During the past week, what were your usual hours of going to sleep and waking up? How many hours of sleep at night would be best for you?" If patient had a significant period of euthymia in past 5 years: "How many hours of sleep did you get when you were not depressed and feeling well?"</i>			
<i>"Have you had any trouble this week falling asleep at the beginning of the night?"</i> After you have gone to bed, how long has it been taking you to fall asleep? How many nights this week have you had trouble falling asleep?	H4. INSOMNIA – EARLY <input type="checkbox"/> (0) Less than or equal to 1/2 hr to fall asleep <i>(always add a point for use of a hypnotic at bedtime)</i> <input type="checkbox"/> (1) Greater than 1/2 hr at least 2 days and less than 5 nights in the past week <input type="checkbox"/> (2) Greater than 1/2 hr 5 or more nights in the past week		<input type="checkbox"/>

Interview Guide	HRSD Scoring Criteria	MADRS Scoring Criteria
<p>Middle insomnia typically covers the period between 12 and 3 AM, depending on sleep onset. Rule of thumb is to add 2 hr to sleep onset time and take a 3 hr interval. (Add a point if a hypnotic is taken on awakening during the night).</p> <p><i>“During the past week, have there been some nights where your sleep was restless or disturbed?”</i></p> <p>How many nights have you had that trouble? During the past week, have you been waking up in the middle of the night?</p> <p>IF YES: Did you get out of bed? Was it to go to the bathroom? How long did it take you to fall back asleep? How many nights this past week did you wake up and get out of bed (other than to go to the bathroom)?</p>	<p>H5. INSOMNIA – MIDDLE</p> <p><input type="checkbox"/> (0) Once asleep, stays asleep and is not restless</p> <p><input type="checkbox"/> (1) patient is restless during the night or awakens without getting out of bed (2 or more nights per week)</p> <p><input type="checkbox"/> (2) Patient is awake for any noticeable period of time (5 or more nights). Patient reports getting out of bed for any reason other than to void (2 or more nights)</p>	
<p>SLEEP (Late Insomnia, Hypersomnia, and Reduced Sleep)</p> <p>Many times information on this item is elicited by questions about middle insomnia. As with hypersomnia, ratings of late insomnia are in comparisons to a standard of the total hours of sleep the patient should have. If this is unclear from the initial questioning in the insomnia section (“How many hours of sleep at night would be best for you?”), assume 7-8 hrs as normal sleep duration.</p> <p><i>“This past week, what time have you been waking up in the morning and staying up?”</i></p> <p>Are you waking up at the time you want to or are you waking up earlier than you want?</p> <p>IF WAKING UP EARLY: How many mornings this week have you awakened early?</p> <p>When you got up early, could you fall back to sleep again or were you awake for the day?</p> <p>This past week, did you feel you got enough sleep or were you tired when you woke up?</p>	<p>H6. INSOMNIA – LATE</p> <p><input type="checkbox"/> (0) Sleeps through to morning (7-8 hr since sleep onset or length of preferred sleep)</p> <p><input type="checkbox"/> (1) Awakens towards morning (4-6 AM), but falls back to sleep (2 or more nights)</p> <p><input type="checkbox"/> (2) Awakens towards morning (4-6 AM) and stays awake (2 or more nights)</p>	

Interview Guide	HRSD Scoring Criteria	MADRS Scoring Criteria
<p>Like the insomnia items, rating of hypersomnia are in comparison to some standard of the total number of hours of sleep the patient should have. If this is unclear or doubtful from the initial questioning in the insomnia section ("How many hours of sleep at night would be best for you?"), assume 7-8 hrs as normal sleep duration.</p> <p><i>"During the past week, how many total hours of sleep did you get each day?"</i></p> <p>During the past week, how many hours each day did you spend sleeping and napping?</p>	<p>H26. Hypersomnia</p> <p><input type="checkbox"/> (0) No increase in total sleep length</p> <p><input type="checkbox"/> (1) At least 1 hour increase in sleep length at least 2 days per week</p> <p><input type="checkbox"/> (2) At least 2 hour increase in sleep length at least 5 days per week</p> <p><input type="checkbox"/> (3) At least 4 hour increase in sleep length at least 5 days per week</p>	
<p>After the 4 inquiries about sleep, score the associated MADRS item. Additional questions are usually not necessary.</p>		<p>M4. REDUCED SLEEP</p> <p><input type="checkbox"/> (0) Regardless of severity, sleep disturbance manifested at most one night per week</p> <p><input type="checkbox"/> (1)</p> <p><input type="checkbox"/> (2) Early, middle or late insomnia less than 1 hr per night and present at least 2 or more nights per week or light or fitful sleep 2 or more nights per week</p> <p><input type="checkbox"/> (3)</p> <p><input type="checkbox"/> (4) Awake for at least 2 hours total for 2 or more nights per week</p> <p><input type="checkbox"/> (5)</p> <p><input type="checkbox"/> (6) Unable to sleep so that only 2-3 hours of sleep obtained at least 5 nights per week</p>

Interview Guide	HRSD Scoring Criteria	MADRS Scoring Criteria
<p><i>"This past week have you felt interested in your work, hobbies, and other activities? Did you have to push yourself to get things done or did other people have to encourage you to get things done?"</i></p> <p>LASSITUDE: <i>"Have you had any difficulty in starting activities? Have you been sluggish in starting activities? Do you have to force yourself to complete routine tasks?"</i></p> <p>(Skip for inpatients) <i>"Have you completed your household responsibilities during the past week?"</i> IF NO: <i>"How so? Or Why?"</i></p> <p>(Skip for inpatients) <i>"Are you working or going to school? This past week, did you miss any time from work (or school)?"</i> IF YES: <i>"How so? Or Why?"</i></p> <p>IF LACK OF INTEREST ACKNOWLEDGED: Was there any activity this past week that you felt interested in completing or did you lack interest in everything?</p> <p>Is there anything that you stopped doing altogether this past week?</p> <p>Do you think that you spent less time than you should on your work, household chores, or recreational activities?</p> <p>IF YES, about how much less time did you spend on these activities each day this past week?</p>	<p>WORK AND ACTIVITIES (Interest and Lassitude)</p> <p>H7. WORK AND ACTIVITIES</p> <p><input type="checkbox"/> (0) No lack of interest or diminished activity. Patient feels interested (motivated), spends more than 3 hrs each day in productive activity (household chores, school, work, hobbies, etc.), and believes can return to usual (full) activities without fatigue or feelings of incapacity (or has returned without fatigue or feelings of incapacity)</p> <p><input type="checkbox"/> (1) Spends more than 3 hrs per day in productive activity (see 0 above), but has thoughts or feelings of incapacity, fatigue or weakness</p> <p><input type="checkbox"/> (2) Has diminished interest in activities or experiences or expresses indecision or listlessness. Feels the need to push oneself to complete activities</p> <p><input type="checkbox"/> (3) Decreased time or productivity in activities and/or spends less than 3 hours per day in productive activity</p> <p><input type="checkbox"/> (4) Does not attend to basic activities of daily living (e.g., grooming, keeping room in order, etc.). No longer engages in household chores and is not working. "Not working" alone is insufficient to merit a "4". Patient should have stopped virtually all productive activity and not attended to basic activities of daily living.</p>	

Site ____ Participant # _____ Alpha Code _____ Date MM / DD / YYYY ____

Interview Guide	HRSD Scoring Criteria	MADRS Scoring Criteria
<p>The focus of this item is on difficulties in starting activities, and not on interest in activities, per se. Individuals who procrastinate may have great difficulty starting activities, but may have considerable interest. Severity on this item increases as greater effort and/or supervision are needed to carry out activities, especially routine matters.</p> <p>During the past week, did you have difficulty starting activities?</p> <p>Did you have to "push yourself" to get things done?</p> <p>Did you feel sluggish or rundown when doing routine chores?</p>		<p>M7. LASSITUDE</p> <p><input type="checkbox"/> (0) Difficulty starting any activity is infrequent (less than 2 days per week). does not report sluggishness.</p> <p><input type="checkbox"/> (1)</p> <p><input type="checkbox"/> (2) Difficulty in starting some activity noted and more than 1 day in the week.</p> <p><input type="checkbox"/> (3)</p> <p><input type="checkbox"/> (4) Carries out routine tasks, but exerts extra attention or effort to stay on task. Has difficulty initiating tasks at least 5 days per week.</p> <p><input type="checkbox"/> (5)</p> <p><input type="checkbox"/> (6) Does not initiate any activity and requires assistance and prodding to complete most tasks.</p>

Interview Guide	HRSD Scoring Criteria	MADRS Scoring Criteria
IMPAIRED CONCENTRATION		
<p>Rate the extent of the impairment in concentration. There are at least 3 types of impairment. The patient may not be able to maintain a focus, losing the drift of conversations, etc. This reflects impaired vigilance and is commonly seen in agitated depression. Alternatively, the patient may be so preoccupied that they cannot shift sets and focus on problems at hand (preoccupation leading to inattention). This is commonly seen in hypochondriacal or delusional patients. Third, the individual may be so distracted by environmental or internal stimuli that they cannot maintain a set (a form of impaired vigilance). This is commonly seen in patients with persistent cognitive impairment, e.g., dementia. Regardless of type, rate this item by weighing both patient self-report and objective evidence during the interview (or the observations of others). Concentration difficulties may be minimized by inattentive, preoccupied individuals, even though they will lose the thread of conversations and have other demonstrable deficits.</p> <p><i>"During the past week have you had difficulty concentrating? Did you have any trouble following conversations, following the plot of a TV program or movie, understanding what you read, or in carrying out any other activities? Did anyone comment that you seemed spacey, distracted, preoccupied, or "out-of-it"? Did you feel this way?"</i></p> <p>IF CONCENTRATION DIFFICULTY ACKNOWLEDGED: How bad was your concentration problem this past week?</p> <p>Did you have to give up any activities because you couldn't focus your thoughts?</p>		<p>M6. CONCENTRATION DIFFICULTIES</p> <p><input type="checkbox"/> (0) Difficulties in concentrating are infrequent and manifested less than 2 days per week, regardless of severity.</p> <p><input type="checkbox"/> (1)</p> <p><input type="checkbox"/> (2) Mild difficulties in concentrating or paying attention 2 or more days per week. Does not interfere with performance, but may involve paying special attention.</p> <p><input type="checkbox"/> (3)</p> <p><input type="checkbox"/> (4) Difficulties in concentrating are frequent and interfere with function. Difficulties are manifest at least 5 days of the week and make reading or following conversations or TV programs difficult.</p> <p><input type="checkbox"/> (5)</p> <p><input type="checkbox"/> (6) Pervasive problems in attention and concentration. Cannot maintain a focus and conversations become tangential (off topic). Individual may repeatedly ask the same questions. Unable to complete tasks involving a modicum of complexity.</p>

Interview Guide	HRSD Scoring Criteria	MADRS Scoring Criteria
SOMATIC SYMPTOMS (Physical symptoms, Weight) Introductory comment: "Now I'm going to ask you some questions about your physical state."		
<p>Symptoms of autonomic over activity are being assessed. Note the specific symptoms and their frequency and severity. Except for rare exceptions discussed in the manual, no attribution is made regarding causation. Rating is based on the most severe and/or frequent symptom.</p> <p><i>"Tell me if you have had any of the following physical symptoms in the past week (READ LIST): dry mouth, gas or wind, indigestion or upset stomach, diarrhea, constipation, cramps, belching or burping, heart palpitations, headache, difficulty breathing, hyperventilation, sighing, excessive need to urinate, excessive sweating".</i></p> <p>ASK FOR EACH PHYSICAL COMPLAINT: How often did you experience this problem? How much has the (state physical symptom) bothered you? Has it interfered with your activities?</p>	<p>H11. ANXIETY – SOMATIC</p> <p><input type="checkbox"/> (0) No symptoms</p> <p><input type="checkbox"/> (1) Occurs 2 or more days per week, always mild</p> <p><input type="checkbox"/> (2) Occurs 5 or more days per week with moderate severity, or less frequently but with high severity</p> <p><input type="checkbox"/> (3) Occurs 5 or more days per week and is severe</p> <p><input type="checkbox"/> (4) Any symptom that is incapacitating on a daily basis (5 or more days per week)</p>	
<p>Requests for or use of medications for G.I. symptoms (antacids, laxatives, etc.) are ignored in scoring. G.I. symptoms (including constipation and cramps) should be rated in item 11 (Anxiety Somatic) and not here. Therefore a score of '2' for this item is obtained only with a moderate to marked loss of appetite. Ignore whether dietary supplement is used to maintain weight.</p> <p><i>"How was your appetite this past week?"</i></p> <p>Has your appetite been poor, excessive, or satisfactory? Have you been skipping meals or have you had to force yourself to eat? Have others had to urge you to eat? IF YES: How often?</p>	<p>H12. SOMATIC SYMPTOMS – Gastrointestinal</p> <p><input type="checkbox"/> (0) Any appetite loss is less than 2 days per week</p> <p><input type="checkbox"/> (1) Mild loss of appetite at least 2 days per week, but eats without encouragement. Has heavy feeling in stomach at least 2 days per week</p> <p><input type="checkbox"/> (2) Moderate to marked loss of appetite at least 5 days per week and/or difficulty eating without encouragement (at least 5 days per week)</p>	
<p>In the past week, have you had a heavy feeling in your stomach? IF YES: How often?</p>		

Interview Guide	HRSD Scoring Criteria	MADRS Scoring Criteria
<p>Increased appetite which reflects a return to euthymia (e.g. prior weight loss) is not scored.</p> <p>Scoring of food cravings should be restricted to carbohydrates (starches or sugars).</p> <p>IF INCREASED APPETITE REPORTED: <i>"In the past week, have you been craving any foods such as chocolate or other sweets or starches, like pasta or potatoes?"</i></p> <p>In the past week, have you been eating more than you should? IF YES: Was this a slight or definite increase? Did this occur every day?</p>	<p>H27. INCREASED APPETITE</p> <p><input type="checkbox"/> (0) No increase in appetite or food intake and no specific food craving</p> <p><input type="checkbox"/> (1) Slight increase in appetite (for at least 2 days) and/or specific food craving</p> <p><input type="checkbox"/> (2) Definite and marked increase in food intake</p>	
<p>MADRS scoring should be based on the questioning described in the previous item.</p>		<p>M5. REDUCED APPETITE</p> <p><input type="checkbox"/> (0) Normal or increased appetite. If reduced appetite, occurs less than 2 days/wk</p> <p><input type="checkbox"/> (1)</p> <p><input type="checkbox"/> (2) Mild loss of appetite 2 or more days per week</p> <p><input type="checkbox"/> (3)</p> <p><input type="checkbox"/> (4) Marked loss of appetite 5 or more days. Food is tasteless at least 5 or more days per week</p> <p><input type="checkbox"/> (5)</p> <p><input type="checkbox"/> (6) Pervasive loss of appetite throughout the week. Eats only with encouragement by others or by forcing oneself</p>

Interview Guide	HRSD Scoring Criteria	MADRS Scoring Criteria
SOMATIC SYMPTOMS (Weight, General somatic, Libido, Anergia)		
<p>This item is scored only for weight loss in the last week and regardless of weight loss during the episode. It is most easily assessed by serial weighing. If the patient is deliberately dieting, always rate '0'. If serial weighing is not available, determine if the patient can provide an estimate of weight change during the past week.</p> <p><i>"Do you think you have lost any weight in the past week?" IF YES: "How much did you lose?"</i></p> <p>IF UNSURE: Do you think your clothes fit more loosely on you?</p> <p>IF WEIGHT LOSS REPORTED: Were you trying to lose weight by dieting?</p>	<p>H16. LOSS OF WEIGHT</p> <p><input type="checkbox"/> (0) Less than one pound weight loss</p> <p><input type="checkbox"/> (1) 1-2 pounds weight loss</p> <p><input type="checkbox"/> (2) Greater than 2 pounds weight loss</p> <p>OR if patient cannot report a specific change, ask if clothing fits differently, etc. If so:</p> <p><input type="checkbox"/> (0) Weight loss unlikely</p> <p><input type="checkbox"/> (1) Weight loss probable and minimal</p> <p><input type="checkbox"/> (2) Weight loss definite and significant</p>	
<p>Note: Headache was scored in HRSD item 11 (Anxiety Somatic). Do not score headache here.</p> <p><i>"How has your energy been this past week? Have you felt tired? How often have you felt tired? Were you so tired that you felt as if you were dragging through the day or had to nap?"</i></p> <p><i>This past week, did you feel heaviness in your limbs, back, or head? Did you have any aches or pains this week?</i></p> <p><i>What about backaches or muscle aches? "</i></p>	<p>H13. SOMATIC SYMPTOMS – GENERAL</p> <p><input type="checkbox"/> (0) Reports no fatigue, loss of energy, or heaviness in limbs, back, or head. No report of backache or muscle aches</p> <p><input type="checkbox"/> (1) Report of a non-specific symptom that occurs at least 2 days per week</p> <p><input type="checkbox"/> (2) Report of a clear-cut symptom (e.g., piercing lower back pain) that occurs at least 2 days per week. Marked loss of energy or fatigue at least 5 days per week</p>	

Interview Guide	HRSD Scoring Criteria	MADRS Scoring Criteria
<p>Scoring of this item will overlap considerably with item 13, Somatic Symptoms General. Which includes assessment of fatigue or tiredness. Scoring Anergia is based only on the frequency and severity of fatigue.</p> <p>IF TIREDNESS OR FATIGUE REPORTED: make inquiries for the anergia item.</p> <p>In the past week, have you felt exhausted much of the time? Did you get tired very easily? How often did this occur?</p> <p>IF HEAVINESS OF LIMBS REPORTED:</p> <p>In the past week, have your arms or legs felt like "lead"? How often did this occur?</p>	<p>H25. Anergia</p> <p><input type="checkbox"/> (0) No evidence of tiring quickly or excessive fatigue during the week (i.e., less than 2 days)</p> <p><input type="checkbox"/> (1) Reports mild fatigue or easily tiring, may occasionally nap, occurs at least 2 days per week.</p> <p><input type="checkbox"/> (2) Reports feeling exhausted much of the time (at least 5 days per week), may nap frequently, tires quickly. Spontaneous report adds confidence in a rating of "2", but is not required.</p>	
SOMATIC SYMPTOMS (Libido, Hypochondriasis)		
<p>This item focuses on loss of libido. Other "genital" symptoms in men or women (e.g., menstruation disturbance in women) are not scored. For patients without a current sexual partner, it is important to inquire about sexual fantasies, masturbation, etc. If no libido during extended period of euthymia prior to episode, score as "0".</p> <p><i>"This past week, how has your interest in sex been? We are not discussing whether you actually had sexual activity, but your interest in sex, your desire for sexual activity."</i></p> <p>IF LACK OF INTEREST REPORTED: Did you lack interest in sex throughout the week?</p>	<p>H14. GENITAL SYMPTOMS</p> <p><input type="checkbox"/> (0) No loss of libido</p> <p><input type="checkbox"/> (1) Mild or moderate loss of libido. Diminished or modest sexual interest or behavior</p> <p><input type="checkbox"/> (2) Severe loss of libido. Virtually no interest or sexual behavior on a daily basis (at least 5 days per week)</p>	<input type="checkbox"/>

Interview Guide	HRSD Scoring Criteria	MADRS Scoring Criteria
<p>In rating this item, health should be defined broadly (i.e., the patient does not have to be concerned about having a specific disease). Concerns beyond those appropriate for actual illnesses are the domain of inquiry. Definite disturbances may be apparent before the interview progresses to this item. If not, inquire about the patient's physical health in domains not already sampled.</p> <p><i>"Do you have problems with your physical health? This past week, how often did you find yourself thinking about your physical health or any physical problems you may have?"</i></p> <p>Did you complain frequently to others about your physical health?</p> <p>This past week, did you ask others for assistance or advice because of your physical problems? If so, how often?</p> <p>IF POSSIBLY DELUSIONAL ASK:</p> <p>Have you seen a physician for any of these problems?</p> <p>Was a diagnosis made?</p>	<p>H15. HYPOCHONDRIASIS</p> <p><input type="checkbox"/> (0) No concern or appropriate concerns about health status</p> <p><input type="checkbox"/> (1) Patient is absorbed or inappropriately worried about health. This may be mild, non-specific, and fleeting (at least 2 days per week)</p> <p><input type="checkbox"/> (2) The excessive concern is a preoccupation, brooding with specific concerns more days than not (at least 5 days per week). Differs from (1) in severity, specificity, and/or persistence</p> <p><input type="checkbox"/> (3) Patient spontaneously and frequently complains of physical problems or frequently asks for medications, evaluations, or health advice</p> <p><input type="checkbox"/> (4) Somatic delusions; e.g., cancer, GI or GU blockage, rotting, etc.)</p>	<p><input type="checkbox"/></p>

Interview Guide	HRSD Scoring Criteria	MADRS Scoring Criteria
<p>PSYCHIC SYMPTOMS (Psychic Anxiety, Tension,)</p> <p>Introductory Comment: "Now I am going to ask you some questions about your feelings about yourself. I would like you to think about the feelings and thoughts you've had about yourself during the past week."</p>		
<p>In scoring this item, determine if patient meets criteria for 1. If so, and patient does not meet criteria of 2, give a score of 1 and go to the next item. If patient meets criteria for both 1 and 2, determine if they meet criteria for 3 (and so on).</p> <p><i>"Have you been feeling especially tense or irritable this past week? IF YES: How often were you feeling this way?"</i></p> <p><i>"This past week, have you been argumentative or impatient?" IF YES: "How often were you feeling this way?"</i></p> <p><i>"This past week, have you been worrying a lot about little things?" IF YES: "What have you been worrying about?"</i></p>	<p>H10. ANXIETY – PSYCHIC</p> <p><input type="checkbox"/> (0) Patient neither reports nor nonverbally conveys excessive anxiety, worry fear, or irritability. Any irritability, tension, anxiety experienced < 2 days per week and only mild in severity</p> <p><input type="checkbox"/> (1) On direct inquiry, patient reports feelings of anxiety, tension, or irritability (i.e., free-floating anxiety) for 2 or more days. These feelings, however mild, are disproportionate or inappropriate relative to the situation</p> <p><input type="checkbox"/> (2) A) Meets criteria for (1) and anxiety is expressed nonverbally in the interview (e.g., apparent in face or speech: furrowed brow, hand-wringing, pacing, fidgeting), OR B) Patient reports feelings of at least moderate anxiety, tension or irritability for 5 or more days or the patient worries excessively about minor or insignificant matters (i.e., parking ticket) for 5 or more days</p> <p><input type="checkbox"/> (3) Patient reports feelings of at least moderate anxiety, tension or irritability for 5 or more days and anxiety is expressed nonverbally in the interview</p> <p><input type="checkbox"/> (4) Fears or anxiety are expressed without questioning (verbally or nonverbally) and are severe for 5 or more days</p>	

Interview Guide	HRSD Scoring Criteria	MADRS Scoring Criteria
<p>This item overlaps considerably in content with the HRSD Psychic Anxiety item. Scores increase from ill-defined feelings of discomfort, edginess, turmoil, and mental tension to panic, dread, or anguish. Higher scores are given as a function of intensity and frequency. Discomfort refers to apprehensive feelings and thoughts and other worries and not to physical complaints.</p> <p>"During the past week, have you felt panicky?"</p> <p>IF YES: How often did you feel this way and how did you cope with these feelings?</p>		<p>M3. INNER TENSION</p> <p><input type="checkbox"/> (0) Inner tension experienced less than 2 days per week and mild in presentation</p> <p><input type="checkbox"/> (1)</p> <p><input type="checkbox"/> (2) Feelings of edginess, inner turmoil, etc. at least two days per week, but dissipate spontaneously. These feelings/thoughts are mild.</p> <p><input type="checkbox"/> (3)</p> <p><input type="checkbox"/> (4) Continuous feelings (≥ 5 days) of inner tension or discomfort. Intermittent panic (> 2 days) requiring isolation or a change in medication status</p> <p><input type="checkbox"/> (5)</p> <p><input type="checkbox"/> (6) Pervasive (≥ 5 days) and unrelenting feelings of dread or anguish. Feelings of panic are overwhelming</p>
PSYCHIC SYMPTOMS (Diurnal Variation, Depersonalization, Paranoia)		
<p>Diurnal variation may pertain to any of the symptoms of depression, not just mood. Morning is defined from awakening until noon; evening is defined from 5PM until midnight.</p> <p>"During the past week, have you regularly felt worse at any particular part of the day? Has it been in the morning, afternoon, or evening?"</p> <p>IF YES: How much worse do you feel at this time? A little or a lot worse?</p> <p>How many days in the last week did this happen?</p>	<p>H18. DIURNAL VARIATION</p> <p><input type="checkbox"/> (0) No difference in perceived symptoms in the morning relative to the evening</p> <p><input type="checkbox"/> (1) A mild to moderate difference noted at least 2 days per week (note whether AM or PM is worse) <input type="checkbox"/> AM <input type="checkbox"/> PM</p> <p><input type="checkbox"/> (2) A marked or severe difference noted at least 5 days per week (note whether AM or PM is worse) <input type="checkbox"/> AM <input type="checkbox"/> PM</p>	<input type="checkbox"/>

Interview Guide	HRSD Scoring Criteria	MADRS Scoring Criteria
<p>Patients with these symptoms typically recognize them; while those without the symptoms may have difficulty understanding the inquiries. Patients who state that they do not feel like themselves or do not understand or believe why the illness is happening to them are not reporting symptoms of depersonalization or derealization. Rather the focus is on feelings of unreality. There should be clear-cut feelings that the surroundings or other people are unreal or that the patient is out of the body.</p> <p><i>“During the past week, have you ever had the feeling that some things are unreal, or that you are living in a dream, or cut off from other people in some strange way? Do you feel real to yourself? Do the things around you look and sound real? Have you had out of the body experiences? Have you felt like you’ve been watching yourself do things?”</i></p> <p>IF YES TO ANY OF THE ABOVE: Tell me about these feelings. How often has it happened? How bad has it been?</p> <p>IF YES: How many days during the past week did you have these feelings?</p> <p>IF YES: Did it interfere with work or home life?</p>	<p>H19. DEPERSONALIZATION/DEREALIZATION</p> <p><input type="checkbox"/> (0) No symptoms</p> <p><input type="checkbox"/> (1) Mild or infrequent (2 days per week)</p> <p><input type="checkbox"/> (2) Frequent (at least 5 days per week) and of moderate severity</p> <p><input type="checkbox"/> (3) Frequent and severe, often experienced as intrusive or disturbing</p> <p><input type="checkbox"/> (4) Frequent, severe, and interferes with daily activities</p>	

Interview Guide	HRSD Scoring Criteria	MADRS Scoring Criteria
<p>The focus is on a feeling or belief of malevolence on the part of others and suspiciousness by the patient.</p> <p>Determine whether others are against or out to harm the patient. If the patient states that others are talking about him/her, this should be discussed in detail. If others restrict their statement to the patient being "bad" or "unworthy", determine what motive is attributed by the patient to those make these comments. If these others are only discussing what the patient believes to be true and deserved, the information impacts on ratings of guilt, worthlessness, etc. If others are believed to be malevolent in their discussions or actions, also rate with respect to paranoia, e.g., they are spreading rumors to damage the patient's reputation.</p> <p><i>"During the past week, have you felt that anyone was trying to give you a hard time or hurt or harm you in any way?"</i></p> <p>Did you feel that people were talking behind your back?</p> <p>Did you feel that people had bad intentions towards you?</p> <p>IF YES TO ANY OF THE ABOVE: Tell me about it. Who and why?</p> <p>Have you felt that you are being singled out or persecuted?</p>	<p>H20. PARANOID SYMPTOMS</p> <p><input type="checkbox"/> (0) No evidence of excessive concern about others' motives or behavior</p> <p><input type="checkbox"/> (1) Some, perhaps fleeting, suspiciousness (at least 2 days per week). For example, excessive concerns about the interview's usage or the motives of others</p> <p><input type="checkbox"/> (2) More persistent or intense suspiciousness (at least two days per week). May have impact on behavior, e.g., avoids contact with others</p> <p><input type="checkbox"/> (3) Relatively fixed idea that others are out to harm or have malevolent intentions (at least 5 days per week)</p> <p><input type="checkbox"/> (4) Paranoid ideation is clearly delusional (regardless of duration), e.g., a paranoid system</p>	

Interview Guide	HRSD Scoring Criteria	MADRS Scoring Criteria
PSYCHIC SYMPTOMS (Obsessions and Compulsions, Rejection, Sensitivity)		
<p>Depressed patients frequently ruminate about mood-congruent themes such as guilty acts, inadequacy, life stressors, etc. Such rumination should be distinguished from obsessions (i.e., ego dystonic), and should not be scored for this item.</p> <p>Obsessive thoughts should be recognized as originating in the patient's mind, but also as being unwanted and alien.</p> <p>They should be associated with anxiety. There should be some struggle against them, i.e., substituting another thought or act (compulsion).</p> <p>Compulsions are repetitive, intentional behaviors, performed in a ritualistic fashion or stereotyped fashion, often designed to neutralize an obsession or other dreaded situation, but the compulsive activity is not realistically connected with the stimulus or is clearly excessive. The patient generally recognizes that the behavior is excessive or unreasonable.</p> <p><i>"During the past week, have there been things you have had to do over and over again, like checking the locks on doors several times or washing your hands?" IF YES: "Please give me an example."</i></p> <p><i>"During the past week, have you had any thoughts that do not make sense to you but that kept running over and over in your mind?" IF YES: "Please give me an example."</i></p> <p>Did you have any disturbing thoughts that you could not stop thinking about? If YES, please give me an example.</p> <p>If YES to any of the above: How often in the past week did you have these (repetitive behaviors or disturbing thoughts)?</p>	<p>H21. OBSESSIVE AND COMPULSIVE SYMPTOMS</p> <p><input type="checkbox"/> (0) No evidence for obsessions or compulsions</p> <p><input type="checkbox"/> (1) Obsessions or compulsions that are mild in severity (e.g., infrequent or of short duration during the day) and occur at least 2 days per week</p> <p><input type="checkbox"/> (2) Obsessions and compulsions that are severe (e.g., occupying hours, interfering with functioning) occurring at least 2 days per week or of moderate severity and occurring 5 or more days per week</p>	<p><input type="checkbox"/></p>

Interview Guide	HRSD Scoring Criteria	MADRS Scoring Criteria
<p><i>"During the past week, have you felt especially concerned about what other people think about you? During the past week, have your feelings been easily hurt?"</i></p> <p>During the past week, have you felt particularly sensitive to rejection by other people?</p> <p>IF YES TO ANY OF THE ABOVE, ASK: How so? How often did you feel this way? Did these feelings get in the way of your socializing with others?</p>	<p>H28. REJECTION SENSITIVITY</p> <p><input type="checkbox"/> (0) No evidence in the past week of excessive sensitivity to or fear of rejection</p> <p><input type="checkbox"/> (1) Mild or fleeting sensitivity to rejection experienced on at least 2 days.</p> <p><input type="checkbox"/> (2) Clear-cut rejection sensitivity that is persistent</p> <p><input type="checkbox"/> (3) Severe and persistent rejection sensitivity that leads to social isolation or other functional consequences.</p>	
PSYCHIC SYMPTOMS (Depressed Mood, Apparent Sadness)		
<p>In rating this item it is important to distinguish between depressed mood and anhedonia. Descriptions of depressed mood should reflect feeling blue, sad, black, tearful, gloomy, dejected, despondent, hopeless, worthless, etc. Descriptions of feeling nothing, empty, hollow, dead, blah, etc., do not qualify as depressed mood.</p> <p><i>"What has your mood been like this past week?"</i></p> <p>DEPENDING ON DESCRIPTION, ASK:</p> <p><i>"Have you been feeling sad, blue, or unhappy? OR has your mood been completely black or gray?"</i></p> <p>How many days this past week did you feel depressed?</p> <p>Have you had any periods in the past week when your mood lightened, when you felt better?</p> <p>Have you been crying? IF YES: How often have you cried this past week?</p>	<p>H1. DEPRESSED MOOD</p> <p><input type="checkbox"/> (0) Absent: Feels at most mildly sad and for less than two days per week.</p> <p><input type="checkbox"/> (1) Depressed feelings elicited only on questioning and feels depressed at least two days per week.</p> <p><input type="checkbox"/> (2) Depressed mood elicited on questioning is of at least moderate severity and present 5 or more days per week</p> <p>OR, Patient spontaneously reports depressed mood that is of at least moderate severity two or more days per week.</p> <p><input type="checkbox"/> (3) Depressed mood is communicated nonverbally in the interview and/or depressed mood of at least moderate severity is experienced daily. Patient is tearful in interview.</p> <p><input type="checkbox"/> (4) Patient interview is dominated by reports of depression which is experienced daily.</p>	

Site ____ Participant # _____ Alpha Code _____ Date MM / DD / YYYY _____

Interview Guide	HRSD Scoring Criteria	MADRS Scoring Criteria
<p>This item is scored solely on the patient's appearance during the interview and not on their report of mood state. Thus, facial expression, posture, quality and quantity of speech are all considered when inferring mood state. Included in the scoring is the extent to which apparent sadness or despondency fails to lift with positive events ("inability to brighten up"). To score this aspect, determine whether emotional expression brightens when discussing positive topics, pleasurable activities, or jokes.</p>		<p>M1. APPARENT SADNESS</p> <p><input type="checkbox"/> (0) No appearance of sadness.</p> <p><input type="checkbox"/> (1)</p> <p><input type="checkbox"/> (2) Some physical expressions of sadness, but not pervasive, and dissipates spontaneously or in response to "good news" (e.g., jokes, gifts).</p> <p><input type="checkbox"/> (3)</p> <p><input type="checkbox"/> (4) Expressions of sadness dominant during the interview, and are at least partially resistant to lifting.</p> <p><input type="checkbox"/> (5)</p> <p><input type="checkbox"/> (6) Pervasive expressions of sadness such that the patient appears despondent and unresponsive</p>

Interview Guide	HRSD Scoring Criteria	MADRS Scoring Criteria
PSYCHIC SYMPTOMS (Emotional Blunting)		
<p>This item assesses 3 dimensions of abnormal subjective experience: (I) reduced interest in surroundings and activities (disinterest); (II) reduced ability to react with "adequate emotion to circumstances or people" (emotional reactivity); (III) reduced capacity for pleasure (anhedonia).</p> <p>Earlier discussion for "Work and Activities" and "Lassitude" may provide the needed information for scoring interest in surroundings.</p> <p><i>"During this past week was there a change in your interest in your surroundings, world events, hobbies, friends, or anything else? Is your interest at its usual level?"</i></p> <p>Compared to usual, has your emotional reactions to things and people around you been blunted this past week? Do you feel you are more or less reactive than usual?</p> <p>Tell me about your ability to experience pleasure? This past week could you experience the same degree of pleasure in activities and people that you had in the past? If not, how has this capacity changed?</p>		<p>M8. INABILITY TO FEEL</p> <p><input type="checkbox"/> (0) Typical degree of interest in surroundings and other people; no diminishment in emotional reactivity; preserved or enhanced capacity to experience pleasure in all realms. Any diminishment in these areas experienced less than 2 days in the week</p> <p><input type="checkbox"/> (1)</p> <p><input type="checkbox"/> (2) Reduced interest, emotional reactivity, or capacity for pleasure. Any of these reductions is mild and none are pervasive (i.e., less than 5 days per week)</p> <p><input type="checkbox"/> (3)</p> <p><input type="checkbox"/> (4) Loss of interest, reduced reactivity, or anhedonia are pervasive and of at least moderate intensity. Any one of the three qualify for a rating at this level</p> <p><input type="checkbox"/> (5)</p> <p><input type="checkbox"/> (6) Pervasive and severe deficits in any one of the three: profound lack of interest; emotional flatness (total lack of reactivity); complete anhedonia. Any marked deficit for 5 or more days per week</p>

Interview Guide	HRSD Scoring Criteria	MADRS Scoring Criteria
PSYCHIC SYMPTOMS (Helplessness, Hopelessness)		
<p>It is sometimes difficult for patients to distinguish between "helplessness" and "hopelessness". The helplessness item focuses on 2 domains: The need for urging or assistance in carrying out activities of daily life and the subjective feeling of needing assistance or help in carrying out activities. During the interview, patients report being "overwhelmed" by their obligations and "no longer able to cope" can be taken as statements of helplessness (either spontaneous or elicited). It is often useful to follow-up these reports with direct inquiries, such as, "Do you feel you need assistance to accomplish these things?"</p> <p><i>"During the past week, did you feel you had trouble coping with routine activities?</i></p> <p><i>Were there times when you felt overwhelmed and unable to complete your activities or responsibilities?</i></p> <p>Were these feelings so bad that you would say you felt helpless?</p> <p>Did other people have to encourage or urge you to tend to your work (school) or household responsibilities?</p> <p>During the past week, did you feel that you were giving up trying to cope with life?</p> <p>During the past week, did you need the physical help of others to complete simple activities like grooming, dressing, or eating?</p>	<p>H22. HELPLESSNESS</p> <p><input type="checkbox"/> (0) No evidence of subjective or objective helplessness</p> <p><input type="checkbox"/> (1) Patient reports inability or feelings of inability to accomplish usual tasks only on inquiry, or the patient reports the need or desire for the assistance of others to accomplish usual tasks (personal hygiene, school work, household chores, or job-related duties)</p> <p><input type="checkbox"/> (2) Patient spontaneously volunteers feelings of being overwhelmed or unable to cope with usual tasks</p> <p>OR,</p> <p>on inquiry, patient reports at least moderate feelings of helplessness (overwhelmed, unable to cope, need for help) that are manifest at least 5 days per week</p> <p><input type="checkbox"/> (3) Patient requires the urging or guidance of others to complete usual tasks (personal hygiene, school work, household chores, or job-related duties)</p> <p><input type="checkbox"/> (4) Patient requires the physical assistance of others for elementary tasks of daily living (personal hygiene, eating, dressing, grooming)</p>	<p><input type="checkbox"/></p>

Site ____ Participant # _____ Alpha Code _____ Date MM / DD / YYYY _____

Interview Guide	HRSD Scoring Criteria	MADRS Scoring Criteria
<p>This item focuses on pessimistic feelings or despair about the future, and specifically the probability of getting well or staying well</p> <p><i>“During the past week, were you optimistic or pessimistic about your future?”</i></p> <p>Did you doubt that things would improve for you? IF YES:</p> <p>When people tell you that you will be well (or stay well), do you feel reassured?</p> <p>If your doctor told you he/she was optimistic about your prospects would you feel reassured?</p> <p>IF NO: Do you have a feeling of despair or discouragement about the future that simply will not go away?</p>	<p>H23. HOPELESSNESS</p> <p><input type="checkbox"/> (0) No feelings of pessimism</p> <p><input type="checkbox"/> (1) Patient is more optimistic than pessimistic about getting or staying well, but has doubts (at least 2 days per week)</p> <p><input type="checkbox"/> (2) Persistent pessimism or hopelessness (at least 5 days per week), but states that can be reassured by others</p> <p><input type="checkbox"/> (3) Reports discouragements, despair, and/or pessimism which is persistent (at least 5 days per week) and cannot be relieved by reassurance</p> <p><input type="checkbox"/> (4) Interview is dominated by frequent, repetitive and spontaneous statements of despair and hopelessness which cannot be dispelled</p>	

Interview Guide	HRSD Scoring Criteria	MADRS Scoring Criteria
PSYCHIC SYMPTOMS (Worthlessness, Pessimism, Reported Sadness, Insight)		
<p>Scoring of this item is based on three dimensions. Any delusion of worthlessness merits a rating of "4" regardless of whether spontaneously reported or elicited on inquiry. Spontaneous reports of self-esteem deficits merit a rating of "2" or "3" depending on severity/persistence. Non-delusional feelings of inferiority only manifested on direct inquiry merit a rating of "1" or "2", depending on severity/persistence.</p> <p><i>"During the past week, have you felt that you are as good as other people whom you know and respect?"</i></p> <p>Have you felt that others are better than you?</p> <p>IF YES TO EITHER, ASK:</p> <p>During this past week, did you feel that you are "no good" or "inferior"? Would you say that you had feelings of being "worthless"?</p> <p>IF YES TO EITHER, ASK:</p> <p>How often did you feel this way during the past week?</p> <p>Do you feel that you are worth nothing at all, either to yourself or others?</p>	<p>H24. WORTHLESSNESS</p> <p><input type="checkbox"/> (0) No loss of self-esteem or feelings of inferiority</p> <p><input type="checkbox"/> (1) Poor self-esteem or feelings of inferiority only reported on direct inquiry</p> <p><input type="checkbox"/> (2) Spontaneous report of diminished self-esteem or inadequacy, at least some of the time (≥ 2 days per week), OR, Feelings of inferiority or loss of self-esteem that are persistent and severe but only manifest on direct inquiry</p> <p><input type="checkbox"/> (3) Spontaneous reports of more severe and persistent loss of self-esteem and feelings of inferiority. Notions of worthlessness should be pervasive, i.e., patient believes that there is nothing worthwhile about them</p> <p><input type="checkbox"/> (4) Delusion of worthlessness (or other self-deprecating delusion) regardless of spontaneous or elicited report</p>	

Site ____ Participant # _____ Alpha Code _____ Date MM / DD / YYYY _____

Interview Guide	HRSD Scoring Criteria	MADRS Scoring Criteria
<p>The MADRS Pessimistic thoughts item combines ideation about negative projections for the future (hopelessness) with negative thoughts about the self (worthlessness). Score this item based upon the most flagrant or severe symptoms. Information obtained with the HRSD guilt, suicide, paranoid, hopelessness, and worthlessness items need to be considered. A patient with delusions of self-reproach but optimistic about the future would still receive a score of '6'.</p> <p>Additional questions are not usually unnecessary. Note the scoring conventions.</p>		<p>M9. PESSIMISTIC THOUGHTS</p> <p><input type="checkbox"/> (0) Not pessimistic about the future two or more days per week; no feelings of inferiority, guilt, or failure two or more days per week.</p> <p><input type="checkbox"/> (1)</p> <p><input type="checkbox"/> (2) Occasional pessimistic thoughts about the future or feelings of inferiority or self-reproach 2 days per week</p> <p><input type="checkbox"/> (3)</p> <p><input type="checkbox"/> (4) Persistent pessimism and/or feeling of inferiority, guilt, or failure the majority of days in the week</p> <p><input type="checkbox"/> (5)</p> <p><input type="checkbox"/> (6) Pervasive negativism of delusional proportions. Psychotic thinking pertains to self (e.g., guilt) and/ or prospects for the future</p>

Site ____ Participant # _____ Alpha Code _____ Date MM / DD / YYYY ____

Interview Guide	HRSD Scoring Criteria	MADRS Scoring Criteria
PSYCHIC SYMPTOMS (Guilt, Suicidality)		
<p>For ratings of '2-3' feelings, thoughts, rumination, or beliefs should be present at least 2 days during the week. Any relevant hallucination merits a rating of '4'.</p> <p><i>"This past week, have you been particularly self-critical?</i></p> <p><i>Did you feel that you have done things wrong?</i></p> <p><i>Have you felt like you have let other people down or let yourself down in some way?"</i></p> <p>IF YES TO ANY OF THE ABOVE: <i>"Please give me examples of these critical thoughts."</i></p> <p>During the past week, have you felt guilty about anything you've done or not done? What about things that happened a long time ago?</p> <p>IF YES: What sort of things did you feel guilty about?</p> <p>Have you thought that you've brought this depression on yourself in some way?</p> <p>IF YES: How so?</p> <p>Have you felt that you are being punished in some way? IF YES: How so?</p>	<p>H2. FEELINGS OF GUILT</p> <p><input type="checkbox"/> (0) No feelings or ideas of guilt</p> <p><input type="checkbox"/> (1) Regardless of intensity, feelings of self-reproach or the belief of being a disappointment to others</p> <p><input type="checkbox"/> (2) Explicit ideas of being guilty or rumination about past mistakes or sins</p> <p><input type="checkbox"/> (3) Believes the depression is a punishment, even if due to religious conviction, or has delusions of guilt, regardless of type</p> <p><input type="checkbox"/> (4) Auditory or visual hallucinations of an accusatory or denunciatory nature.</p>	<p><input type="checkbox"/></p>

Site ____ Participant # _____ Alpha Code _____ Date MM / DD / YYYY _____

Interview Guide	HRSD Scoring Criteria	MADRS Scoring Criteria
<p><i>"During the past week, did you have thoughts that life is not worth living?</i></p> <p><i>During this week, did you wish that you were dead? Did you have thoughts in which you imagined yourself dead?</i></p> <p><i>During the past week, did you have thoughts of hurting or killing yourself?"</i></p> <p>IF YES: What did you think about? Do you have a plan for hurting or killing yourself?</p> <p>During this past week, did you do anything to hurt yourself?</p>	<p>H3. SUICIDE</p> <p><input type="checkbox"/> (0) Believes life worth living and denies more than occasional thoughts of death</p> <p><input type="checkbox"/> (1) Feels life is not worth living, but has not contemplated or wished death during the past week.</p> <p><input type="checkbox"/> (2) Persistent wish to die and/or more than occasional thoughts about death to self (e.g., has thought about death but would not do it because of family or religious concerns)</p> <p><input type="checkbox"/> (3) Clear-cut suicidal ideation or gesture (e.g., definite plan, small cuts, starts suicide attempt but does not follow through, practices suicidal plan, purchases items for plan)</p> <p><input type="checkbox"/> (4) Any serious attempt, whether planned or impulsive</p>	

Site ____ Participant # _____ Alpha Code _____ Date MM / DD / YYYY _____

Interview Guide	HRSD Scoring Criteria	MADRS Scoring Criteria
		<p>M10. SUICIDAL THOUGHTS</p> <p><input type="checkbox"/> (0) Generally feels that life is worth living. At most has passing thoughts of death at most one day per week.</p> <p><input type="checkbox"/> (1)</p> <p><input type="checkbox"/> (2) Is tired of living and has thought or wishes for death ≥ 2 days per week. However, has no plan or intent for suicide</p> <p><input type="checkbox"/> (3)</p> <p><input type="checkbox"/> (4) Has a persistent belief that life is not worth living and would rather be dead. May believe that suicide is a potential outcome. These thoughts and feelings occur at least 5 days per week. However, has no specific plan</p> <p><input type="checkbox"/> (5)</p> <p><input type="checkbox"/> (6) Has an explicit plan and may be actively preparing for suicide attempt. Desire to commit suicide is persistent and the belief that life is not worth living is unwavering.</p>

Site ____ Participant # _____ Alpha Code _____ Date MM / DD / YYYY _____

Interview Guide	HRSD Scoring Criteria PSYCHIC SYMPTOMS (Reported Sadness, Insight)	MADRS Scoring Criteria
<p>Item is scored in relation to patient report of depressed mood, regardless of congruence with physical expression. Depressed mood includes feeling low, despondent, helpless, and hopeless. Thus, this item combines elements of the mood, helplessness, and hopelessness items of HRSD. The scoring on the 0-6 scale should reflect a judgment about the intensity of feelings, their frequency and duration (pervasiveness) and imperviousness to influence by positive events (reassurance, expressions of support, etc.). Intense and pervasive feelings of any type (sadness or hopelessness) merit a score of '6'.</p> <p>After inquiring about mood, hopelessness and helplessness, determine whether these feelings are lessened by significant others, positive events, etc.</p> <p><i>"Are these (sad, hopeless, helpless) feelings constant or do you feel better at times?</i></p> <p><i>When you feel better is that due to the support you get from others?</i></p> <p><i>...or due to good things that happen to you at the time?</i></p> <p><i>...or your own efforts to get out of that mood?</i></p>		<p>M2. REPORTED SADNESS</p> <p><input type="checkbox"/> (0) Only occasional feelings of sadness (low, blue), hopelessness, or helplessness that are in keeping with the circumstances</p> <p><input type="checkbox"/> (1)</p> <p><input type="checkbox"/> (2) Sad or low two or more days per week, but intensity mild and/or readily feels better given positive interactions, events, or by own efforts</p> <p><input type="checkbox"/> (3)</p> <p><input type="checkbox"/> (4) Marked sadness or gloominess the majority of days in the week which impacts on activities or others. External circumstances may still influence mood.</p> <p><input type="checkbox"/> (5)</p> <p><input type="checkbox"/> (6) Pervasive and unvarying sadness, misery, or despondency. May have the feeling of being beyond hope or help. Mood is not responsive to environmental events</p>

Interview Guide	HRSD Scoring Criteria	MADRS Scoring Criteria
<p>Before inquiring and scoring this item, the rater should determine whether the patient is sufficiently symptomatic to be said to have an "illness" to be acknowledged and explained. Patients with minimal Symptomatology automatically score '0' on this item (and questions can be skipped).</p> <p>This item can generally be rated without asking specific questions. However, if insight is unclear ask...</p> <p><i>"In your own words, how would you describe or explain why you are (being evaluated or receiving treatment) here?"</i></p> <p>Do you believe you are depressed?</p> <p>IF YES: What is the cause of your depression?</p>	<p>H17. INSIGHT</p> <p><input type="checkbox"/> (0) Acknowledgement of depression or psychological or nervous problem or not ill by interviewer judgment</p> <p><input type="checkbox"/> (1) Acknowledges illness but attributes it to unlikely factors, such as virus, overwork, climate, diet, etc.</p> <p><input type="checkbox"/> (2) Denies being depressed, having a psychological or nervous problem, and is assessed by the rater to be significantly symptomatic (depressed)</p>	
<p>OBSERVED MOTOR SYMPTOMS (Retardation, Agitation)</p> <p>The HRSD items for retardation and agitation should be completed by observation of the patient's behavior during the interview. Subjective experience of being "slowed down" or "agitated" is not considered in scoring these items. While these 2 items are scored only on the basis of observed behavior, it is important to determine that the abnormal motor behavior is not directly attributable to another medical condition (e.g., tremor in Parkinson's disease) or habitual or usual for the patient. Therefore it is important to inquire "I see that you have this 'state the behavior'. What is it due to?"</p>		
	<p>H8. RETARDATION</p> <p><input type="checkbox"/> (0) Expected rate of speech and activity. Response time to questions within normal limits, speech rate appropriate, and no evidence of diminished gesturing or other motor activity</p> <p><input type="checkbox"/> (1) Suggestion of slowing in speech or motor activity</p> <p><input type="checkbox"/> (2) Obvious slowing in motor behavior, response time to questions, and/or speech</p> <p><input type="checkbox"/> (3) Interview is strained because of poverty of speech or slowness of response</p> <p><input type="checkbox"/> (4) Stupor</p>	

Site ____ Participant # _____ Alpha Code _____ Date MM / DD / YYYY

Interview Guide	HRSD Scoring Criteria	MADRS Scoring Criteria
	<p>H9. AGITATION</p> <p><input type="checkbox"/> (0) No evidence of fidgetiness or nervous habits</p> <p><input type="checkbox"/> (1) Fidgetiness</p> <p><input type="checkbox"/> (2) Playing with hands or hair</p> <p><input type="checkbox"/> (3) Moving about, can't sit still.</p> <p><input type="checkbox"/> (4) Repetitive and often continuous excessive motor activity, typically involving hand-wringing, nail biting, rocking, rubbing of legs, pacing, hair-pulling, lip biting, etc.</p>	<input type="checkbox"/>

Total HRSD Score

--	--

SC/Rater Signature _____ Date _____

VA COOPERATIVE STUDY #556
The Effectiveness of rTMS in Depressed VA Patients

Site ____ Participant # _____ Alpha Code _____ Date ____/____/____

Form 21 - Beck Depression Inventory

Circle Visit Below:

Baseline

Acute Treatment Phase Sessions: 5 10 15 20 25 30

Follow-up Phase Weeks: 4 8 12 16 20 24

On this questionnaire are groups of statements. Please read each group of statements carefully. Then pick out the one statement in each group which best describes the way you have been feeling the PAST WEEK, INCLUDING TODAY! Circle the number beside the statement you picked. If several statements in the group seem to apply equally well, circle each one. Be sure to read all the statements in each group before making your choice.

1 0 I do not feel sad.
 1 I feel sad.
 2 I am sad all the time and I can't snap out of it.
 3 I am so sad or unhappy that I can't stand it.

2 0 I am not particularly discouraged about the future.
 1 I feel discouraged about the future.
 2 I feel I have nothing to look forward to.
 3 I feel that the future is hopeless and that things cannot improve.

3 0 I do not feel like a failure.
 1 I feel I have failed more than the average person.
 2 As I look back on my life, all I can see is a lot of failures.
 3 I feel I am a complete failure as a person.

4 0 I get as much satisfaction out of things as I used to.
 1 I don't enjoy things the way I used to.
 2 I don't get real satisfaction out of anything anymore.
 3 I am dissatisfied or bored with everything.

5 0 I don't feel particularly guilty.
1 I feel guilty a good part of the time.
2 I feel quite guilty most of the time.
3 I feel guilty all of the time.

6 0 I don't feel I am being punished.
1 I feel I may be punished.
2 I expect to be punished.
3 I feel I am being punished.

7 0 I don't feel disappointed in myself.
1 I am disappointed in myself.
2 I am disgusted with myself.
3 I hate myself.

8 0 I don't feel I am any worse than anybody else.
1 I am critical of myself for my weaknesses or mistakes.
2 I blame myself all the time for my faults.
3 I blame myself for everything bad that happens.

9 0 I don't have any thoughts of killing myself.
1 I have thoughts of killing myself, but I would not carry them out.
2 I would like to kill myself.
3 I would kill myself if I had the chance.

10 0 I don't cry anymore than usual.
1 I cry more now than I used to.
2 I cry all the time now.
3 I used to be able to cry, but now I can't cry even though I want to.

11 0 I am no more irritated now than I ever am.
1 I get annoyed or irritated more easily than I used to.
2 I feel irritated all the time now.
3 I don't get irritated at all by the things that used to irritate me.

12 0 I have not lost interest in other people.
1 I am less interested in other people than I used to be.
2 I have lost most of my interest in other people.
3 I have lost all of my interest in other people.

13 0 I make decisions about as well as I ever could.
1 I put off making decisions more than I used to.
2 I have greater difficulty in making decisions than before.
3 I can't make decisions at all anymore.

14 0 I don't feel I look any worse than I used to.
1 I am worried that I am looking old or unattractive.
2 I feel that there are permanent changes in my appearance that make me look unattractive.
3 I believe that I look ugly.

15 0 I can work about as well as before.
1 It takes an extra effort to get started at doing something.
2 I have to push myself very hard to do anything.
3 I can't do any work at all.

16 0 I can sleep as well as usual.
1 I don't sleep as well as I used to.
2 I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
3 I wake up several hours earlier than I used to and cannot get back to sleep.

17 0 I don't get more tired than usual.
1 I get tired more easily than I used to.
2 I get tired from doing almost anything.
3 I am too tired to do anything.

18 0 My appetite is no worse than usual.
1 My appetite is not as good as it used to be.
2 My appetite is much worse now.
3 I have no appetite at all anymore.

19 0 I haven't lost much weight, if any lately.
1 I have lost more than 5 pounds.
2 I have lost more than 10 pounds.
3 I have lost more than 15 pounds.

I am purposely trying to lose weight by eating less.

Yes No

20 0 I am no more worried about my health than usual.
1 I am worried about physical problems such as aches and pains; or upset stomach; or constipation.
2 I am very worried about physical problems, and it's hard to think of much else.
3 I am so worried about my physical problems that I cannot think about anything else.

21 0 I have not noticed any recent change in my interest in sex.
1 I am less interested in sex than I used to be.
2 I am much less interested in sex now.
3 I have lost interest in sex completely.

SC Signature _____ Date _____

VA COOPERATIVE STUDY #556
The Effectiveness of rTMS in Depressed VA Patients

Site ____ Participant # _____ Alpha Code _____ Date __ / __ / ____

**Form 22 – Quick Inventory of Depressive Symptomatology (Clinician-Rated)
(QIDS-C)**

Circle Visit Below:

Baseline

Acute Treatment Phase: 5 10 15 20 25 30

Follow-up Phase: 4 8 12 16 20 24

Please circle one response to each item that best describes the participant for the last 7 days.

1. Sleep Onset Insomnia:
 - 0 Never Takes longer than 30 minutes to fall asleep.
 - 1 Takes at least 30 minutes to fall asleep, less than half the time.
 - 2 Takes at least 30 minutes to fall asleep, more than half the time.
 - 3 Takes more than 60 minutes to fall asleep, more than half the time.
2. Mid-Nocturnal Insomnia:
 - 0 Does not wake up at night.
 - 1 Restless, light sleep with few awakenings.
 - 2 Wakes up at least once a night, but goes back to sleep to sleep easily.
 - 3 Awakens more than once a night and stays awake for 20 minutes or more, more than half the time.
3. Early Morning Insomnia:
 - 0 Less than half the time, awakens no more than 30 minutes before necessary.
 - 1 More than half the time, awakens more than 30 minutes before need be.
 - 2 Awakens at least one hour before need be, more than half the time.
 - 3 Awakens at least two hours before need be, more than half the time.
4. Hypersomnia:
 - 0 Sleeps no longer than 7-8 hours/night, without naps.
 - 1 Sleeps no longer than 10 hours in a 24 hour period (include naps).
 - 2 Sleeps no longer than 12 hours in a 24 hour period (include naps).
 - 3 Sleeps longer than 12 hours in a 24 hour period (include naps).
5. Mood (Sad):
 - 0 Does not feel sad.
 - 1 Feels sad less than half the time.
 - 2 Feels sad more than half the time.
 - 3 Feels intensely sad virtually all the time.
6. Appetite (Decreased):
 - 0 No change from usual appetite.
 - 1 Eats somewhat less often and/or lesser amounts than usual.
 - 2 Eats much less than usual and only with personal effort.
 - 3 Eats rarely within a 24-hour period, and only with extreme personal effort or with persuasion by others.
7. Appetite (Increased):
 - 0 No change from usual appetite.
 - 1 More frequently feels a need to eat than usual.
 - 2 Regularly eats more often and/or greater amounts than usual.
 - 3 Feels driven to overeat at and between meals.
8. Weight (Decrease) Within The Last Two Weeks:
 - 0 Has experienced no weight change.
 - 1 Feels as if some slight weight loss occurred.
 - 2 Has lost 2 pounds or more.
 - 3 Has lost 5 pounds or more.
9. Weight (Increase) Within The Last Two Weeks:
 - 0 Has experienced no weight change.
 - 1 Feels as if some slight weight gain has occurred.
 - 2 Has gained 2 pounds or more.
 - 3 Has gained 5 pounds or more.
10. Concentration/Decision Making:
 - 0 No change in usual capacity to concentrate and decide.
 - 1 Occasionally feels indecisive or notes that attention often wanders.
 - 2 Most of the time struggles to focus attention or make decisions.
 - 3 Cannot concentrate well enough to read or cannot make even minor decisions.

11. Outlook (Self):

- 0 Sees self as equally worthwhile and deserving as others.
- 1 Is more self-blaming than usual.
- 2 Largely believes that he/she causes problems for others.
- 3 Ruminates over major and minor defects in self.

12. Suicidal Ideation:

- 0 Does not think of suicide or death.
- 1 Feels life is empty or is not worth living.
- 2 Thinks of suicide/death several times a week for several minutes.
- 3 Thinks of suicide/death several times a day in depth, or has made specific plans, or attempted suicide.

13. Involvement:

- 0 No change from usual level of interest in other people and activities.
- 1 Notices a reduction in former interests/activities.
- 2 Finds only one or two former interests remain.
- 3 Has virtually no interest in formerly pursued activities.

14. Energy/Fatigability:

- 0 No change in usual level of energy.
- 1 Tires more easily than usual.
- 2 Makes significant personal effort to initiate or maintain usual daily activities.
- 3 Unable to carry out most of usual daily activities due to lack of energy.

15. Psychomotor Slowing:

- 0 Normal speed of thinking, gesturing, and speaking.
- 1 Patient notes slowed thinking, and voice modulation is reduced.
- 2 Takes several seconds to respond to most questions; reports slowed thinking.
- 3 Is largely unresponsive to most questions without strong encouragement.

16. Psychomotor Agitation:

- 0 No increased speed or disorganization in thinking or gesturing.
- 1 Fidgets, wrings hands and shifts positions often.
- 2 Describes impulse to move about and displays motor restlessness.
- 3 Unable to stay seated. Paces about with or without permission.

SC Signature _____ Date _____

Site ____ Participant # _____ Alpha Code _____ Date ____/____/_____

MM DD YYYY

Form 23 - COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Circle Visit Below:
Screening/Baseline

Baseline/Screening Version

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended for use by trained clinicians. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidality depends on clinical judgment.

Definitions of behavioral suicidal events in this scale are based on those used in **The Columbia Suicide History Form**, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.] Standardized Evaluation in Clinical Practice, pp. 103 -130, 2003.)

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@childpsych.columbia.edu

SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes," ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.		
Past 6 Months		
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. Have you wished you were dead or wished you could go to sleep and not wake up?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
If yes, describe:		
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g. "I've thought about killing myself") without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. Have you actually had any thoughts of killing yourself?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
If yes, describe:		
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, "I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it....and I would never go through with it". Have you been thinking about how you might do this?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
If yes, describe:		
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to "I have the thoughts but I definitely will not do anything about them". Have you had these thoughts and had some intention of acting on them?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
If yes, describe:		
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
If yes, describe:		
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). For prior to study entry, ask about time he/she was feeling the most suicidal.		
<u>Past 6 Months - Most Severe Ideation:</u>		
Type # (1-5)	Description of Ideation	Most Severe
Frequency How many times have you had these thoughts? (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day		
Duration When you have the thoughts how long do they last? (1) Fleeting - few seconds or minutes (4) 4-8 hours/most of day (2) Less than 1 hour/some of the time (5) More than 8 hours/persistent or continuous (3) 1-4 hours/a lot of time		
Controllability Could /can you stop thinking about killing yourself or wanting to die if you want to? (1) Easily able to control thoughts (4) Can control thoughts with a lot of difficulty (2) Can control thoughts with little difficulty (5) Unable to control thoughts (3) Can control thoughts with some difficulty (0) Does not attempt to control thoughts		
Deterrents Are there things - anyone or anything (e.g. family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide? (1) Deterrents definitely stopped you from attempting suicide (4) Deterrents most likely did not stop you (2) Deterrents probably stopped you (5) Deterrents definitely did not stop you (3) Uncertain that deterrents stopped you (0) Does not apply		
Reasons for Ideation What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both? (1) Completely to get attention, revenge or a reaction from others. (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling). (2) Mostly to get attention, revenge or a reaction from others. (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling). (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain. (0) Does not apply		

SUICIDAL BEHAVIOR (Check all that apply, so long as these are separate events; must ask about all types)		Past 6 Months	
<p>Actual Attempt: A potentially self-injurious act committed with atleast some wish to die, as a result of act. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is any intent/desire to die associated with the act, then it can be considered an actual suicide attempt. There does not have to be any injury or harm, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident or no other intent but suicide can be inferred (e.g. gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred.</p> <p>Have you made a suicide attempt? Have you done anything to harm yourself? Have you done anything dangerous where you could have died? What did you do? Did you _____ as a way to end your life? Did you want to die (even a little) when you _____? Were you trying to end your life when you _____? Or Did you think it was possible you could have died from _____? Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)? (Self-Injurious Behavior without suicidal intent) If yes, describe:</p>		<p>Yes <input type="checkbox"/> No <input type="checkbox"/></p> <p>Total # of Attempts _____</p> <p>Yes <input type="checkbox"/> No <input type="checkbox"/></p>	
<p>Has subject engaged in Non-Suicidal Self-Injurious Behavior?</p> <p>Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act (if not for that, actual attempt would have occurred). Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything? If yes, describe:</p>		<p>Yes <input type="checkbox"/> No <input type="checkbox"/></p> <p>Total # of interrupted _____</p>	
<p>Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything? If yes, describe:</p>		<p>Yes <input type="checkbox"/> No <input type="checkbox"/></p> <p>Total # of aborted _____</p>	
<p>Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g. buying pills, purchasing a gun) or preparing for one's death by suicide (e.g. giving things away, writing a suicide note). Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)? If yes, describe:</p>		<p>Yes <input type="checkbox"/> No <input type="checkbox"/></p>	
<p>Suicidal Behavior: Suicidal behavior was present during the assessment period?</p>		<p>Yes <input type="checkbox"/> No <input type="checkbox"/></p>	
<p>Answer for Actual Attempts Only Within Past 6 Months</p>		<p>Most Recent Attempt Date:</p>	<p>Most Lethal Attempt Date:</p>
<p>Actual Lethality/Medical Damage:</p> <ol style="list-style-type: none"> 0. No physical damage or very minor physical damage (e.g. surface scratches). 1. Minor physical damage (e.g. lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g. conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; medical hospitalization and likely intensive care required (e.g. comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; medical hospitalization with intensive care required (e.g. comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death 		<p>Enter Code</p>	<p>Enter Code</p>
<p>Potential Lethality: Only Answer if Actual Lethality = 0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over).</p> <p>0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care</p>		<p>Enter Code</p>	<p>Enter Code</p>

SC Signature _____ Date _____

VA COOPERATIVE STUDY #556
The Effectiveness of rTMS in Depressed VA Patients

Site ____ Participant # _____ Alpha Code _____ Date _____ / _____ / _____
MM DD YYYY

Form 24 - COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Circle Visit Below:

Acute Treatment Phase Sessions:	5	10	15	20	25	30
Taper Week:	1	2	3			
Follow-up Phase Weeks:	4	8	12	16	20	24

Since Last Visit

Version 7/19/08

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended for use by trained clinicians. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidality depends on clinical judgment.

Definitions of behavioral suicidal events in this scale are based on those used in The Columbia Suicide History Form, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.] Standardized Evaluation in Clinical Practice, pp. 103 -130, 2003.)

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries contact posnerk@childpsych.columbia.edu

SUICIDAL IDEATION Site ____ Participant # _____ Alpha Code _____ Date ____/____/____		Since Last Visit																																																								
<p>Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes," ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.</p>																																																										
<p>1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. <i>Have you wished you were dead or wished you could go to sleep and not wake up?</i></p> <p>If yes, describe:</p>		Yes <input type="checkbox"/> No <input type="checkbox"/>																																																								
<p>2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g. "I've thought about killing myself") without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. <i>Have you actually had any thoughts of killing yourself?</i></p> <p>If yes, describe:</p>		Yes <input type="checkbox"/> No <input type="checkbox"/>																																																								
<p>3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, "I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it....and I would never go through with it". <i>Have you been thinking about how you might do this?</i></p> <p>If yes, describe:</p>		Yes <input type="checkbox"/> No <input type="checkbox"/>																																																								
<p>4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having <u>some intent to act on such thoughts</u>, as opposed to "I have the thoughts but I definitely will not do anything about them". <i>Have you had these thoughts and had some intention of acting on them?</i></p> <p>If yes, describe:</p>		Yes <input type="checkbox"/> No <input type="checkbox"/>																																																								
<p>5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. <i>Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?</i></p> <p>If yes, describe:</p>		Yes <input type="checkbox"/> No <input type="checkbox"/>																																																								
INTENSITY OF IDEATION																																																										
<p>The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe).</p> <p>Most Severe Ideation: _____</p> <table border="1"> <thead> <tr> <th>Type # (1-5)</th> <th>Description of Ideation</th> <th>Most Severe</th> </tr> </thead> <tbody> <tr> <td colspan="3">Frequency</td> </tr> <tr> <td colspan="3"> <p>How many times have you had these thoughts?</p> <p>(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day</p> </td> </tr> <tr> <td colspan="3">Duration</td> </tr> <tr> <td colspan="3"> <p>When you have the thoughts, how long do they last?</p> <table border="0"> <tr> <td>(1) Fleeting - few seconds or minutes</td> <td>(4) 4-8 hours/most of day</td> </tr> <tr> <td>(2) Less than 1 hour/some of the time</td> <td>(5) More than 8 hours/persistent or continuous</td> </tr> <tr> <td>(3) 1-4 hours/a lot of time</td> <td></td> </tr> </table> </td> </tr> <tr> <td colspan="3">Controllability</td> </tr> <tr> <td colspan="3"> <p>Could/can you stop thinking about killing yourself or wanting to die if you want to?</p> <table border="0"> <tr> <td>(1) Easily able to control thoughts</td> <td>(4) Can control thoughts with a lot of difficulty</td> </tr> <tr> <td>(2) Can control thoughts with little difficulty</td> <td>(5) Unable to control thoughts</td> </tr> <tr> <td>(3) Can control thoughts with some difficulty</td> <td>(0) Does not attempt to control thoughts</td> </tr> </table> </td> </tr> <tr> <td colspan="3">Deterrents</td> </tr> <tr> <td colspan="3"> <p>Are there things - anyone or anything (e.g. family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?</p> <table border="0"> <tr> <td>(1) Deterrents definitely stopped you from attempting suicide</td> <td>(4) Deterrents most likely did not stop you</td> </tr> <tr> <td>(2) Deterrents probably stopped you</td> <td>(5) Deterrents definitely did not stop you</td> </tr> <tr> <td>(3) Uncertain that deterrents stopped you</td> <td>(0) Does not apply; wish to die only</td> </tr> </table> </td> </tr> <tr> <td colspan="3">Reasons for Ideation</td> </tr> <tr> <td colspan="3"> <p>What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?</p> <table border="0"> <tr> <td>(1) Completely to get attention, revenge or a reaction from others.</td> <td>(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling).</td> </tr> <tr> <td>(2) Mostly to get attention, revenge or a reaction from others.</td> <td>(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling).</td> </tr> <tr> <td>(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain.</td> <td></td> </tr> </table> </td> </tr> </tbody> </table>		Type # (1-5)	Description of Ideation	Most Severe	Frequency			<p>How many times have you had these thoughts?</p> <p>(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day</p>			Duration			<p>When you have the thoughts, how long do they last?</p> <table border="0"> <tr> <td>(1) Fleeting - few seconds or minutes</td> <td>(4) 4-8 hours/most of day</td> </tr> <tr> <td>(2) Less than 1 hour/some of the time</td> <td>(5) More than 8 hours/persistent or continuous</td> </tr> <tr> <td>(3) 1-4 hours/a lot of time</td> <td></td> </tr> </table>			(1) Fleeting - few seconds or minutes	(4) 4-8 hours/most of day	(2) Less than 1 hour/some of the time	(5) More than 8 hours/persistent or continuous	(3) 1-4 hours/a lot of time		Controllability			<p>Could/can you stop thinking about killing yourself or wanting to die if you want to?</p> <table border="0"> <tr> <td>(1) Easily able to control thoughts</td> <td>(4) Can control thoughts with a lot of difficulty</td> </tr> <tr> <td>(2) Can control thoughts with little difficulty</td> <td>(5) Unable to control thoughts</td> </tr> <tr> <td>(3) Can control thoughts with some difficulty</td> <td>(0) Does not attempt to control thoughts</td> </tr> </table>			(1) Easily able to control thoughts	(4) Can control thoughts with a lot of difficulty	(2) Can control thoughts with little difficulty	(5) Unable to control thoughts	(3) Can control thoughts with some difficulty	(0) Does not attempt to control thoughts	Deterrents			<p>Are there things - anyone or anything (e.g. family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?</p> <table border="0"> <tr> <td>(1) Deterrents definitely stopped you from attempting suicide</td> <td>(4) Deterrents most likely did not stop you</td> </tr> <tr> <td>(2) Deterrents probably stopped you</td> <td>(5) Deterrents definitely did not stop you</td> </tr> <tr> <td>(3) Uncertain that deterrents stopped you</td> <td>(0) Does not apply; wish to die only</td> </tr> </table>			(1) Deterrents definitely stopped you from attempting suicide	(4) Deterrents most likely did not stop you	(2) Deterrents probably stopped you	(5) Deterrents definitely did not stop you	(3) Uncertain that deterrents stopped you	(0) Does not apply; wish to die only	Reasons for Ideation			<p>What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?</p> <table border="0"> <tr> <td>(1) Completely to get attention, revenge or a reaction from others.</td> <td>(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling).</td> </tr> <tr> <td>(2) Mostly to get attention, revenge or a reaction from others.</td> <td>(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling).</td> </tr> <tr> <td>(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain.</td> <td></td> </tr> </table>			(1) Completely to get attention, revenge or a reaction from others.	(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling).	(2) Mostly to get attention, revenge or a reaction from others.	(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling).	(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain.	
Type # (1-5)	Description of Ideation	Most Severe																																																								
Frequency																																																										
<p>How many times have you had these thoughts?</p> <p>(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day</p>																																																										
Duration																																																										
<p>When you have the thoughts, how long do they last?</p> <table border="0"> <tr> <td>(1) Fleeting - few seconds or minutes</td> <td>(4) 4-8 hours/most of day</td> </tr> <tr> <td>(2) Less than 1 hour/some of the time</td> <td>(5) More than 8 hours/persistent or continuous</td> </tr> <tr> <td>(3) 1-4 hours/a lot of time</td> <td></td> </tr> </table>			(1) Fleeting - few seconds or minutes	(4) 4-8 hours/most of day	(2) Less than 1 hour/some of the time	(5) More than 8 hours/persistent or continuous	(3) 1-4 hours/a lot of time																																																			
(1) Fleeting - few seconds or minutes	(4) 4-8 hours/most of day																																																									
(2) Less than 1 hour/some of the time	(5) More than 8 hours/persistent or continuous																																																									
(3) 1-4 hours/a lot of time																																																										
Controllability																																																										
<p>Could/can you stop thinking about killing yourself or wanting to die if you want to?</p> <table border="0"> <tr> <td>(1) Easily able to control thoughts</td> <td>(4) Can control thoughts with a lot of difficulty</td> </tr> <tr> <td>(2) Can control thoughts with little difficulty</td> <td>(5) Unable to control thoughts</td> </tr> <tr> <td>(3) Can control thoughts with some difficulty</td> <td>(0) Does not attempt to control thoughts</td> </tr> </table>			(1) Easily able to control thoughts	(4) Can control thoughts with a lot of difficulty	(2) Can control thoughts with little difficulty	(5) Unable to control thoughts	(3) Can control thoughts with some difficulty	(0) Does not attempt to control thoughts																																																		
(1) Easily able to control thoughts	(4) Can control thoughts with a lot of difficulty																																																									
(2) Can control thoughts with little difficulty	(5) Unable to control thoughts																																																									
(3) Can control thoughts with some difficulty	(0) Does not attempt to control thoughts																																																									
Deterrents																																																										
<p>Are there things - anyone or anything (e.g. family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?</p> <table border="0"> <tr> <td>(1) Deterrents definitely stopped you from attempting suicide</td> <td>(4) Deterrents most likely did not stop you</td> </tr> <tr> <td>(2) Deterrents probably stopped you</td> <td>(5) Deterrents definitely did not stop you</td> </tr> <tr> <td>(3) Uncertain that deterrents stopped you</td> <td>(0) Does not apply; wish to die only</td> </tr> </table>			(1) Deterrents definitely stopped you from attempting suicide	(4) Deterrents most likely did not stop you	(2) Deterrents probably stopped you	(5) Deterrents definitely did not stop you	(3) Uncertain that deterrents stopped you	(0) Does not apply; wish to die only																																																		
(1) Deterrents definitely stopped you from attempting suicide	(4) Deterrents most likely did not stop you																																																									
(2) Deterrents probably stopped you	(5) Deterrents definitely did not stop you																																																									
(3) Uncertain that deterrents stopped you	(0) Does not apply; wish to die only																																																									
Reasons for Ideation																																																										
<p>What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?</p> <table border="0"> <tr> <td>(1) Completely to get attention, revenge or a reaction from others.</td> <td>(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling).</td> </tr> <tr> <td>(2) Mostly to get attention, revenge or a reaction from others.</td> <td>(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling).</td> </tr> <tr> <td>(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain.</td> <td></td> </tr> </table>			(1) Completely to get attention, revenge or a reaction from others.	(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling).	(2) Mostly to get attention, revenge or a reaction from others.	(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling).	(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain.																																																			
(1) Completely to get attention, revenge or a reaction from others.	(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling).																																																									
(2) Mostly to get attention, revenge or a reaction from others.	(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling).																																																									
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain.																																																										

SUICIDAL BEHAVIOR Site ____ Participant # ____ Alpha Code ____ Date ____ / ____ / ____ <i>(Check all that apply, so long as these are separate events; must ask about all types)</i>					Since Last Visit
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, as a result of act. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is any intent/desire to die associated with the act, then it can be considered an actual suicide attempt. There does not have to be any injury or harm , just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g. gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. Have you made a suicide attempt? Have you done anything to harm yourself? Have you done anything dangerous where you could have died? What did you do? Did you _____ as a way to end your life? Did you want to die (even a little) when you _____? Were you trying to end your life when you _____? Or did you think it was possible you could have died from _____? Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)? (Self-Injurious Behavior without suicidal intent) If yes, describe: _____					Yes <input type="checkbox"/> No <input type="checkbox"/> Total # of Attempts _____
					Yes <input type="checkbox"/> No <input type="checkbox"/> Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior? Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act (if not for that, actual attempt would have occurred). Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything? If yes, describe: _____					Yes <input type="checkbox"/> No <input type="checkbox"/> Total # of interrupted _____
					Yes <input type="checkbox"/> No <input type="checkbox"/> Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything? If yes, describe: _____					Yes <input type="checkbox"/> No <input type="checkbox"/> Total # of aborted _____
					Yes <input type="checkbox"/> No <input type="checkbox"/> Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g. buying pills, purchasing a gun) or preparing for one's death by suicide (e.g. giving things away, writing a suicide note). Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)? If yes, describe: _____					Yes <input type="checkbox"/> No <input type="checkbox"/> Total # of aborted _____
					Yes <input type="checkbox"/> No <input type="checkbox"/> Total # of aborted _____
Suicidal Behavior: Suicidal behavior was present during the assessment period?					Yes <input type="checkbox"/> No <input type="checkbox"/> Completed Suicide: Answer for Actual Attempts Only
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g. surface scratches). 1. Minor physical damage (e.g. lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g. conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; medical hospitalization and likely intensive care required (e.g. comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; medical hospitalization with intensive care required (e.g. comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death					Enter Code _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over).					Enter Code _____
0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care					 _____

SC Signature _____ Date _____

VA COOPERATIVE STUDY #556
The Effectiveness of rTMS in Depressed VA Patients

Site ____ Participant # _____ Alpha Code _____ Date ____ / ____ / ____

Form 25- Beck Scale for Suicide Ideation

Circle Visit Below:

Screening

Acute Treatment Phase Sessions: 5 10 15 20 25 30

Taper Week: 1 2 3

Follow-up Phase Weeks: 4 8 12 16 20 24

Part
1

1 0	I have a moderate to strong wish to live.	4 0	I have no desire to kill myself.
1	I have a weak wish to live.	1	I have a weak desire to kill myself.
2	I have no wish to live.	2	I have a moderate to strong desire to kill myself.
2 0	I have no wish to die.	5 0	I would try to save my life if I found myself in a life-threatening situation.
1	I have a weak wish to die.	1	I would take a chance on life or death if I found myself in a life-threatening situation.
2	I have a moderate to strong wish to die.	2	I would not take the steps necessary to avoid death if I found myself in a life-threatening situation.
3 0	My reasons for living outweigh my reasons for dying.		
1	My reasons for living or dying are about equal.		
2	My reasons for dying outweigh my reasons for living.		

Part
2

<p>6 0 I have brief periods of thinking about killing myself which pass quickly.</p> <p>1 I have periods of thinking about killing myself which last for moderate amounts of time.</p> <p>2 I have long periods of thinking about killing myself.</p>	<p>9 0 I can keep myself from committing suicide.</p> <p>1 I am unsure that I can keep myself from committing suicide.</p> <p>2 I cannot keep myself from committing suicide.</p>
<p>7 0 I rarely or only occasionally think about killing myself.</p> <p>1 I have frequent thoughts about killing myself.</p> <p>2 I continuously think about killing myself.</p>	<p>10 0 I would not kill myself because of my family, friends, religion, possible injury from an unsuccessful attempt, etc.</p> <p>1 I am somewhat concerned about killing myself because of my family, friends, religion, possible injury from an unsuccessful attempt, etc.</p> <p>2 I am not or only a little concerned about killing myself because of my family, friends, religion, possible injury from an unsuccessful attempt, etc.</p>
<p>8 0 I do not accept the idea of killing myself.</p> <p>1 I neither accept nor reject the idea of killing myself.</p> <p>2 I accept the idea of killing myself.</p>	<p>11 0 My reasons for wanting to commit suicide are primarily aimed at influencing other people, such as getting even with people, making people happier, making people pay attention to me, etc.</p> <p>1 My reasons for wanting to commit suicide are not only aimed at influencing other people, but also represent a way of solving my problems.</p> <p>2 My reasons for wanting to commit suicide are primarily based upon escaping from my problems.</p>

12	0	I have no specific plan about how to kill myself.	16	0	I have made no preparations for committing suicide.
1		I have considered ways of killing myself, but have not worked out the details.	1		I have made some preparations for committing suicide.
2		I have a specific plan for killing myself.	2		I have almost finished or completed my preparations for committing suicide.
13	0	I do not have access to a method or an opportunity to kill myself.	17	0	I have not written a suicide note.
1		The method that I would use for committing suicide takes time, and I really do not have a good opportunity to use this method.	1		I have thought about writing a suicide note or have started to write one, but have not completed it.
2		I have access or anticipate having access to the method that I would choose for killing myself and also have or shall have the opportunity to use it.	2		I have completed a suicide note.
14	0	I do not have the courage or the ability to commit suicide.	18	0	I have made no arrangements for what will happen after I have committed suicide.
1		I am unsure that I have the courage or the ability to commit suicide.	1		I have thought about making some arrangements for what will happen after I have committed suicide.
2		I have the courage and the ability to commit suicide.	2		I have made definite arrangements for what will happen after I have committed suicide.
15	0	I do not expect to make a suicide attempt.	19	0	I have not hidden any desire to kill myself from people.
1		I am unsure that I shall make a suicide attempt.	1		I have held back telling people about wanting to kill myself.
2		I am sure that I shall make a suicide attempt.	2		I have attempted to hide, conceal, or lie about wanting to commit suicide.

20 0 I have never attempted suicide.

1 I have attempted suicide once.

2 I have attempted suicide two or more times

21 0 My wish to die during the last suicide attempt was low.

1 My wish to die during the last suicide attempt was moderate.

2 My wish to die during the last suicide attempt was high.

SC _____ Date _____

VA COOPERATIVE STUDY #556
The Effectiveness of rTMS in Depressed VA Patients

Site ____ Participant # _____ Alpha Code _____ Date ____/____/____

Form 26- Beck Hopelessness Scale

Circle Visit Below:

Screening

Acute Treatment Phase Sessions: **5 10 15 20 25 30**

Taper Week: **1 2 3**

Follow-up Phase Weeks: **4 8 12 16 20 24**

1. I look forward to the future with hope and enthusiasm.	True	False
2. I might as well give up because there is nothing I can do about making things better for myself.	True	False
3. When things are going badly, I am helped by knowing that they cannot stay that way forever.	True	False
4. I can't imagine what my life would be like in ten years.	True	False
5. I have enough time to accomplish the things I want to do.	True	False
6. In the future, I expect to succeed in what concerns me most.	True	False
7. My future seems dark to me.	True	False
8. I happen to be particularly lucky, and I expect to get more of the good things in life than the average person.	True	False
9. I just can't get the breaks, and there's no reason I will in the future.	True	False
10. My past experiences have prepared me well for the future.	True	False

Site ____ Participant # _____ Alpha Code _____ Date ____/____/____ MM / DD / YYYY

11. All I can see ahead of me is unpleasantness rather than pleasantness. True False

12. I don't expect to get what I really want. True False

13. When I look ahead to the future, I expect that I will be happier than I am now. True False

14. Things just won't work out the way I want them to. True False

15. I have great faith in the future. True False

16. I never get what I want, so it's foolish to want anything. True False

17. It's very unlikely that I will get any real satisfaction in the future. True False

18. The future seems vague and uncertain to me. True False

19. I can look forward to more good times than bad times. True False

20. There's no use in really trying to get anything I want because I probably won't get it. True False

SC Signature _____ Date _____

VA COOPERATIVE STUDY #556
The Effectiveness of rTMS in Depressed VA Patients

Site ____ Participant # _____ Alpha Code _____ Date ____ / ____ / ____

Form 27 – Veterans RAND 36 Item Health Survey (VR-36)

Circle Visit Below:

Baseline

End of Active Treatment

Final Follow-up Visit

Instructions: This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

Please answer every question by filling in one circle on each line. If you are unsure about how to answer a question, please give the best answer you can.

1. In general, would you say your health is:

<input type="radio"/>				
EXCELLENT	VERY GOOD	GOOD	FAIR	POOR

2. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	YES, LIMITED A LOT	YES, LIMITED A LITTLE	NO, NOT LIMITED AT ALL
a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
c. Lifting or carrying groceries?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
d. Climbing several flights of stairs?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
e. Climbing one flight of stairs?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
f. Bending, kneeling, or stooping?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
g. Walking more than a mile?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
h. Walking several blocks?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
i. Walking one block?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
j. Bathing or dressing yourself?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

3. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	NO, NONE OF THE TIME	YES, A LITTLE OF THE TIME	YES, SOME OF THE TIME	YES, MOST OF THE TIME	YES, ALL OF THE TIME
a. Cut down the amount of time you spent on work or other activities.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
b. Accomplished less than you would like	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
c. Were limited in the kind of work or other activities.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
d. Had difficulty performing the work or other activities (for example, it took extra effort).	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

4. During the past 4 weeks, have you had any of the following problems with your work or other daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	NO, NONE OF THE TIME	YES, A LITTLE OF THE TIME	YES, SOME OF THE TIME	YES, MOST OF THE TIME	YES, ALL OF THE TIME
a. Cut down the amount of time you spent on work or other activities.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
b. Accomplished less than you would like.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
c. Didn't do work or other activities as carefully as usual.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

5. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

<input type="radio"/> NOT AT ALL	<input type="radio"/> SLIGHTLY	<input type="radio"/> MODERATELY	<input type="radio"/> QUITE A BIT	<input type="radio"/> EXTREMELY
-------------------------------------	-----------------------------------	-------------------------------------	--------------------------------------	------------------------------------

6. How much bodily pain have you had during the past 4 weeks?

<input type="radio"/> NONE	<input type="radio"/> VERY MILD	<input type="radio"/> MILD	<input type="radio"/> MODERATE	<input type="radio"/> SEVERE	<input type="radio"/> VERY SEVERE
-------------------------------	------------------------------------	-------------------------------	-----------------------------------	---------------------------------	--------------------------------------

7. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and house work)?

<input type="radio"/> NOT AT ALL	<input type="radio"/> A LITTLE BIT	<input type="radio"/> MODERATELY	<input type="radio"/> QUITE A BIT	<input type="radio"/> EXTREMELY
-------------------------------------	---------------------------------------	-------------------------------------	--------------------------------------	------------------------------------

8. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks:

	ALL OF THE TIME	MOST OF THE TIME	A GOOD BIT OF THE TIME	SOME OF THE TIME	A LITTLE OF THE TIME	NONE OF THE TIME
a. Did you feel full of pep?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
b. Have you been a very nervous person?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
c. Have you felt so down in the dumps that nothing could cheer you up?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
d. Have you felt calm and peaceful?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
e. Did you have a lot of energy?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

PLEASE CONTINUE

Continued from page 2...

How much of the time during the past 4 weeks:

	ALL OF THE TIME	MOST OF THE TIME	A GOOD BIT OF THE TIME	SOME OF THE TIME	A LITTLE OF THE TIME	NONE OF THE TIME
f. Have you felt downhearted and blue?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
g. Did you feel worn out?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
h. Have you been a happy person?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
i. Did you feel tired?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

9. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

<input type="radio"/> ALL OF THE TIME	<input type="radio"/> MOST OF THE TIME	<input type="radio"/> SOME OF THE TIME	<input type="radio"/> A LITTLE OF THE TIME	<input type="radio"/> NONE OF THE TIME
---	--	--	--	--

10. Please choose the answer that best describes how true or false each of the following statements is for you.

	DEFINITELY TRUE	MOSTLY TRUE	NOT SURE	MOSTLY FALSE	DEFINITELY FALSE
a. I seem to get sick a lot easier than other people.	<input type="radio"/>				
b. I am as healthy as anybody I know.	<input type="radio"/>				
c. I expect my health to get worse.	<input type="radio"/>				
d. My health is excellent.	<input type="radio"/>				

Now we'd like to ask you some questions about how your health may have changed.

11. Compared to one year ago, how would you rate your physical health in general now?

<input type="radio"/> MUCH BETTER	<input type="radio"/> SOMEWHAT BETTER	<input type="radio"/> ABOUT THE SAME	<input type="radio"/> SOMEWHAT WORSE	<input type="radio"/> MUCH WORSE
---	---	--	--	--

12. Compared to one year ago, how would you rate your emotional problems (such as feeling anxious, depressed or irritable) now?

<input type="radio"/> MUCH BETTER	<input type="radio"/> SOMEWHAT BETTER	<input type="radio"/> ABOUT THE SAME	<input type="radio"/> SOMEWHAT WORSE	<input type="radio"/> MUCH WORSE
---	---	--	--	--

SC Signature _____ Date _____

VA COOPERATIVE STUDY #556
The Effectiveness of rTMS in Depressed VA Patients

Site ____ Participant # _____ Alpha Code _____ Date ____/____/____ MM / DD / YYYY

Form 28 - NEUROPSYCHOLOGICAL BATTERY

Circle Visit Below:

Baseline

End of Active Treatment

Final Follow up Visit

SELF-RATING SCALE OF MEMORY FUNCTION

Please circle the number that best describes how you feel about each statement.

1. Compared to before I began to feel bad and had to go to the hospital, my ability to search through my mind and recall names of memories I know are there is:

-4	-3	-2	-1	0	1	2	3	4
Worse than ever before				Same as before				Better than before

2. Compared to before I began to feel bad and had to go to the hospital, I think my relatives and acquaintances now judge my memory to be:

-4	-3	-2	-1	0	1	2	3	4
Worse than ever before				Same as before				Better than before

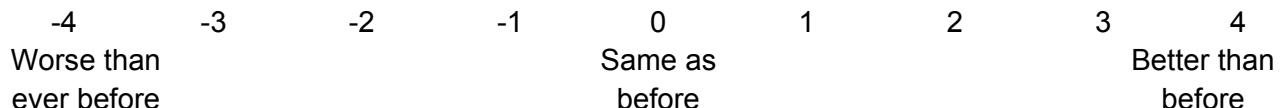
3. Compared to before I began to feel bad and had to go to the hospital, my ability to recall things when I really try is:

-4	-3	-2	-1	0	1	2	3	4
Worse than ever before				Same as before				Better than before

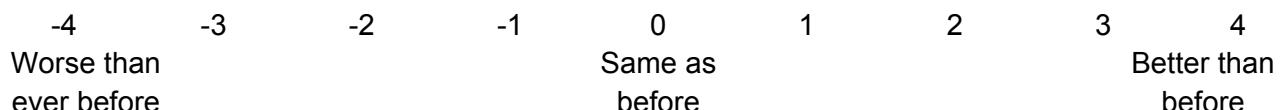
4. Compared to before I began to feel bad and had to go to the hospital, my ability to hold in my memory things that I have learned is:

-4	-3	-2	-1	0	1	2	3	4
Worse than ever before				Same as before				Better than before

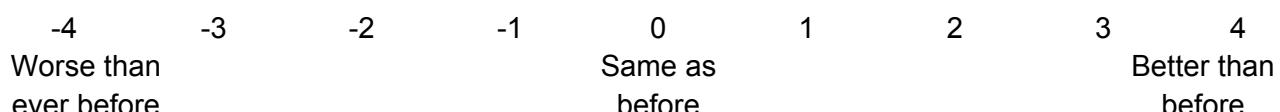
5. Compared to before I began to feel bad and had to go to the hospital, if I were asked about it a month from now, my ability to remember facts from this form I am filling out would be:



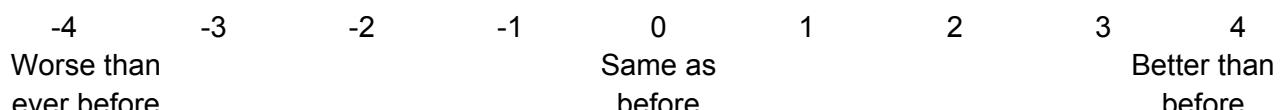
6. Compared to before I began to feel bad and had to go to the hospital, the tendency for a past memory to be "on the tip of my tongue," but not available to me is:



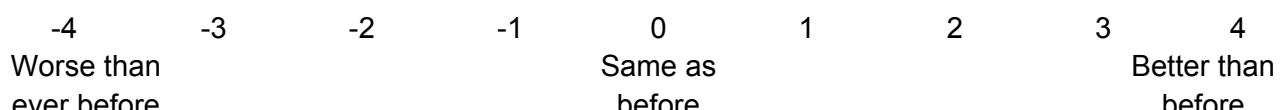
7. Compared to before I began to feel bad and had to go to the hospital, my ability to recall things that happened a long time ago is:



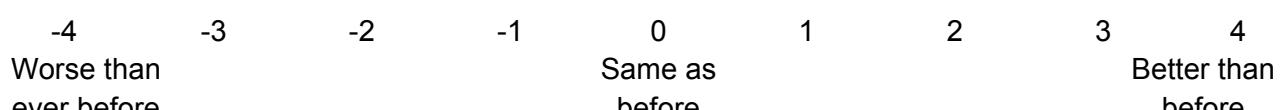
8. Compared to before I began to feel bad and had to go to the hospital, my ability to remember the names and faces of people I meet is:



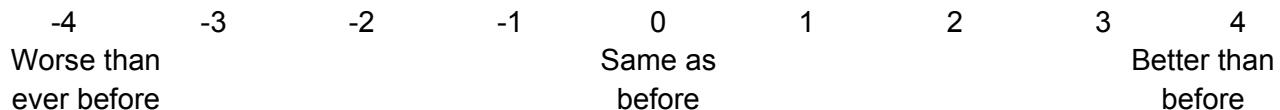
9. Compared to before I began to feel bad and had to go to the hospital, my ability to remember what I was doing after I have taken my mind off it for a few minutes is:



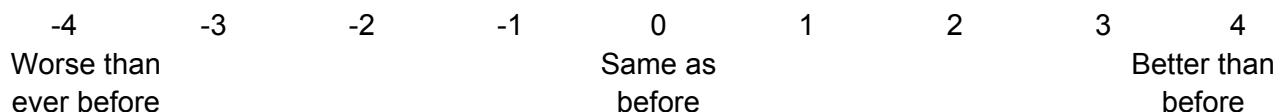
10. Compared to before I began to feel bad and had to go to the hospital, my ability to remember things that have happened more than a year ago is:



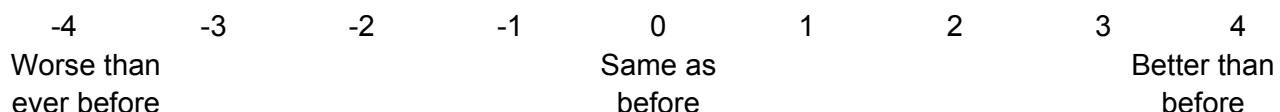
11. Compared to before I began to feel bad and had to go to the hospital, my ability now to remember what I read and what I watch on television is:



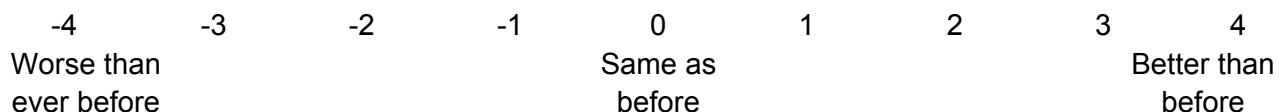
12. Compared to before I began to feel bad and had to go to the hospital, my ability to recall things that happened during my childhood is:



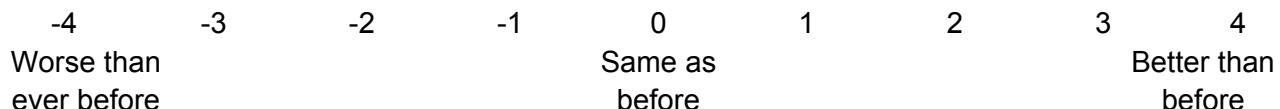
13. Compared to before I began to feel bad and had to go to the hospital, my ability to know when the things I am paying attention to are going to stick in my memory is:



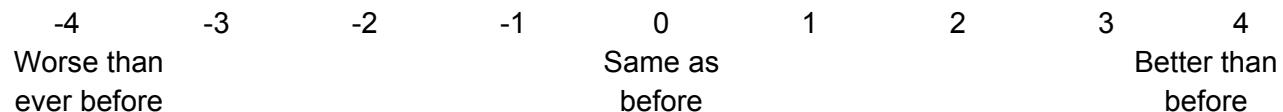
14. Compared to before I began to feel bad and had to go to the hospital, my ability to make sense out of what people explain to me is:



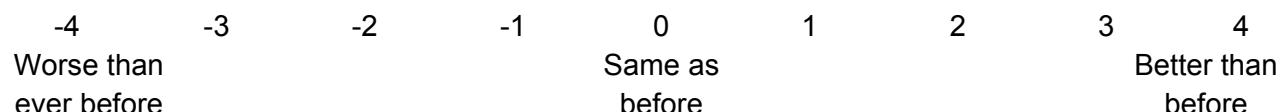
15. Compared to before I began to feel bad and had to go to the hospital, my ability to reach back in my memory and recall what happened a few minutes ago is:



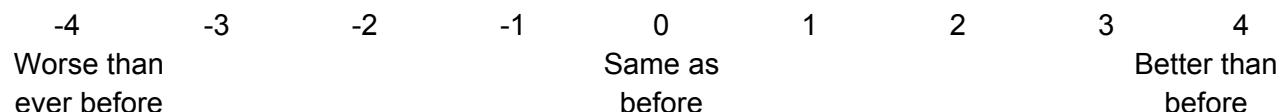
16. Compared to before I began to feel bad and had to go to the hospital, my ability to pay attention to what goes on around me is:



17. Compared to before I began to feel bad and had to go to the hospital, my general alertness to things happening around me is:



18. Compared to before I began to feel bad and had to go to the hospital, my ability to follow what people are saying is:



DEMOGRAPHIC INFORMATION

19. Age.....

20. Dominant hand (*Circle One*)..... Right Left

21. Years of education.....

MEDICAL HISTORY

22. Head injury (*Circle One*)..... Yes No

If Yes,

a. enter the date that the event appeared to have begun MM / DD / YYYY ____

b. enter the date that the event resolved MM / DD / YYYY ____

c. was there a loss of consciousness? (*Circle One*)..... Yes No

d. If Yes, how long was the loss of consciousness (*Circle One Below*)

1 = LOC 0-30 minutes

2 = LOC more than 30 minutes but less than 24 hours

3 = LOC more than 24 hours

23. Neurological illness (*Circle One*)..... Yes No

If Yes,

a. enter the date that the event appeared to have begun MM / DD / YYYY ____

b. enter the date that the event resolved MM / DD / YYYY ____

24. Learning disability (*Circle One*)..... Yes No

25. Substance abuse (*Circle One*)..... Yes No

If Yes,

a. enter the date that the event appeared to have begun MM / DD / YYYY ____

b. enter the date that the event resolved MM / DD / YYYY ____

26. Previous neuropsychological testing (*Circle One*)..... Yes No

If Yes,

a. If yes, enter the date of prior neuropsychological testing MM / DD / YYYY ____

27. Any tests familiar to patient (*Circle One*)..... Yes No

Site ____ Participant # _____ Alpha Code # _____ Date ____/____/____

28. Did participant report any significant event that may impact his/her performance on the neuropsychological battery? (Circle One)..... Yes No
(i.e., recent illness, stressful life event, poor sleep, etc.)

RATING SCALES

Score

29. Effort Rating.....

- 1 = inadequate effort (on one or more tests)
- 2 = somewhat inadequate (while patient tries, he/she doesn't really "push" for good performance)
- 3 = good performance (patient "pushes" to provide good performance)

30. Anxiety Rating (range 0 – 10)

31. Pain Rating (range 0 – 10)

Site ____ Participant # _____ Alpha Code # _____ Date ____/____/____

MEASURES	MISSING DATA Code Accordingly	RAW SCORE	COMMENTS
32.			
a. RAVLT Trial I	____	____	_____
b. RAVLT Trial II	____	____	_____
c. RAVLT Trial III	____	____	_____
d. RAVLT Trial IV	____	____	_____
e. RAVLT Trial V	____	____	_____
f. RAVLT Trial B	____	____	_____
g. RAVLT Trial VI	____	____	_____
h. RAVLT Delayed Recall	____	____	_____
i. RAVLT Recognition	____	____	_____
j. RAVLT False Positives	____	____	_____
k. RAVLT Trial I-V Total	____	____	_____
33. SDMT Written Score	____	____	_____
		/ _____	
34.			
a. TMT-A Time	____	____	_____
b. TMT-A Number of Errors	____	____	_____
c. TMT-B Time	____	____	_____
d. TMT-B Number of Errors	____	____	_____
35. JLO Total Correct	____	____	_____
36.			
a. COWAT F Number Correct	____	____	_____
b. COWAT F Perseverations	____	____	_____
c. COWAT F Intrusions	____	____	_____
d. COWAT F Variants	____	____	_____
e. COWAT A Number Correct	____	____	_____
f. COWAT A Perseverations	____	____	_____
g. COWAT A Intrusions	____	____	_____
h. COWAT A Variants	____	____	_____

Site ____ Participant # _____ Alpha Code # _____ Date ____/____/____

MEASURES	MISSING DATA Code Accordingly	RAW SCORE	COMMENTS
i. COWAT S Number Correct	____	____	_____
j. COWAT S Perseverations	____	____	_____
k. COWAT S Intrusions	____	____	_____
l. COWAT S Variants	____	____	_____
m. COWAT Total FAS Correct	____	____	_____
n. COWAT Total FAS Perseverations	____	____	_____
o. COWAT Total FAS Intrusions	____	____	_____
p. COWAT Total FAS Variants	____	____	_____
q. COWAT Total AN Correct	____	____	_____
r. COWAT Total AN Perseverations	____	____	_____
s. COWAT Total AN Intrusions	____	____	_____
t. COWAT Total AN Variants	____	____	_____
37.			
a. Stroop Word Score	____	____	_____
b. Stroop Color Score	____	____	_____
c. Stroop Color-Word Score	____	____	_____
38. NAART Number of Errors	____	____	_____

CODES:

U = answer if unknown F = rater forgot to obtain data L = record of test result was lost

M = if patient missed appointment R = patient refused to provide an answer

T = patient was not testable or was unable to provide information I = invalid data

SC Signature _____ Date _____

VA COOPERATIVE STUDY #556
The Effectiveness of rTMS in Depressed VA Patients

Site ____ Participant # _____ Alpha Code _____ Date ____/____/____

Form 29 – The Drug Abuse Screening Test (DAST)

<u>Circle Visit Below:</u>		
Screening	End of Active Treatment	Final Follow-up Visit

Directions: The following questions concern information about your involvement with drugs. Drug abuse refers to (1) the use of prescribed or “over-the-counter” drugs in excess of the directions, and (2) any non-medical use of drugs. Consider the past month and carefully read each statement. Then decide whether your answer is YES or NO and circle the appropriate answer. Please be sure to answer every question.

1. Have you used drugs other than those required for medical reasons?	Yes	No
2. Have you abused prescription drugs?	Yes	No
3. Do you abuse more than one drug at a time?	Yes	No
4. Can you get through the week without using drugs (other than those required for medical reasons)?	Yes	No
5. Are you always able to stop using drugs when you want to?	Yes	No
6. Do you abuse drugs on continuous basis?	Yes	No
7. Do you try to limit your drug use to certain situations?	Yes	No
8. Have you had “blackouts” or “flashbacks” as a result of drug use?	Yes	No
9. Do you ever feel bad about your drug abuse?	Yes	No
10. Does your spouse (or parents) ever complain about your involvement with drugs?	Yes	No
11. Do your friends or relatives know or suspect you abuse drugs?	Yes	No
12. Has drug abuse ever created problems between you and your spouse?	Yes	No
13. Has any family member ever sought help for problems related to your drug use?	Yes	No
14. Have you ever lost friends because of your use of drugs?	Yes	No

Site ____ Participant # _____ Alpha Code _____ Date ___/___/___

15. Have you ever neglected your family or missed work because of your use of drugs?	Yes	No
16. Have you ever been in trouble at work because of drug abuse?	Yes	No
17. Have you ever lost a job because of drug abuse?	Yes	No
18. Have you ever gotten into fights when under the influence of drugs?	Yes	No
19. Have you ever been arrested because of unusual behavior while under the influence of drugs?	Yes	No
20. Have you ever been arrested for driving while under the influence of drugs?	Yes	No
21. Have you engaged in illegal activities in order to obtain drug?	Yes	No
22. Have you ever been arrested for possession of illegal drugs?	Yes	No
23. Have you ever experienced withdrawal symptoms as a result of heavy drug intake?	Yes	No
24. Have you had medical problems as a result of your drug use (e.g., memory loss, hepatitis, convulsions, bleeding, etc.)?	Yes	No
25. Have you ever gone to anyone for help for a drug problem?	Yes	No
26. Have you ever been in a hospital for medical problems related to your drug use?	Yes	No
27. Have you ever been involved in a treatment program specifically related to drug use?	Yes	No
28. Have you been treated as an outpatient for problems related to drug abuse?	Yes	No

SC Signature _____ Date _____

VA COOPERATIVE STUDY #556
The Effectiveness of rTMS in Depressed VA Patients

Site ____ Participant # _____ Alpha Code _____ Date ____/____/____ MM / DD / YYYY

Form 30 – PCL-M

Circle Visit Below:

Baseline

End of Active Treatment

Final Follow-up Visit

INSTRUCTIONS: Below is a list of problems and complaints that veterans sometimes have in response to stressful military experiences. Please read each one carefully, then circle one of the numbers to the right to indicate how much you have been bothered by that problem in the past month.

		Not at all	A little bit	Moderately	Quite a bit	Extremely
1. Repeated, disturbing <i>memories, thoughts, or images</i> of a stressful military experience?		1	2	3	4	5
2. Repeated, disturbing <i>dreams</i> of a stressful military experience?		1	2	3	4	5
3. Suddenly <i>acting or feeling</i> as if a stressful military experience <i>were happening again</i> (as if you were reliving it)?		1	2	3	4	5
4. Feeling <i>very upset</i> when <i>something reminded you</i> of a stressful military experience?		1	2	3	4	5
5. Having <i>physical reactions</i> (e.g., heart pounding, trouble breathing, sweating) when <i>something reminded you</i> of a stressful military experience?		1	2	3	4	5
6. Avoiding <i>thinking about</i> or <i>talking about</i> a stressful military experience or avoiding <i>having feelings</i> related to it?		1	2	3	4	5
7. Avoiding <i>activities or situations</i> because <i>they reminded you</i> of a stressful military experience?		1	2	3	4	5
8. Trouble <i>remembering important parts</i> of a stressful military experience?		1	2	3	4	5
9. <i>Loss of interest</i> in activities that you used to enjoy?		1	2	3	4	5
10. Feeling <i>distant</i> or <i>cut off</i> from other people?		1	2	3	4	5
11. Feeling <i>emotionally numb</i> or being unable to have loving feelings for those close to you?		1	2	3	4	5
12. Feeling as if your <i>future</i> will somehow be <i>cut short</i> ?		1	2	3	4	5
13. Trouble <i>falling</i> or <i>staying asleep</i> ?		1	2	3	4	5
14. Feeling <i>irritable</i> or having <i>angry outbursts</i> ?		1	2	3	4	5
15. Having <i>difficulty concentrating</i> ?		1	2	3	4	5
16. Being "super-alert" or watchful or on guard?		1	2	3	4	5
17. Feeling <i>jumpy</i> or easily startled?		1	2	3	4	5

PCL-M for DSM-IV (11/1/94) Weathers, Litz, Huska, & Keane

National Center for PTSD - Behavioral Science Division

SC Signature _____ Date _____

VA COOPERATIVE STUDY #556
The Effectiveness of rTMS in Depressed VA Patients

Site ____ Participant # _____ Alpha Code _____ Date ____/____/____

Form 31 Michigan Alcohol Screening Test

<u>Circle Visit Below:</u>		
Screening	End of Active Treatment	Final Follow-up Visit

The following questions concern information about your use of alcohol. Consider the past month and carefully read each question. Then decide whether your answer is YES or No and circle the appropriate answer. Please be sure to answer every question.

1. Do you feel you are a normal drinker?	Yes	No
2. Have you ever awakened the morning after some drinking the night before and found that you could not remember a part of the evening before?	Yes	No
3. Does any near relative or close friend ever worry or complain about your drinking?	Yes	No
4. Can you stop drinking without difficulty after one or two drinks?	Yes	No
5. Do you ever feel guilty about your drinking?	Yes	No
6. Do friends or relatives think you are a normal drinker?	Yes	No
7. Do you ever try to limit your drinking to certain times of the day or to certain places?	Yes	No
8. Are you always able to stop drinking when you want to?	Yes	No
9. Have you ever attended a meeting of Alcoholics Anonymous (AA)?	Yes	No
10. Have you ever gotten into fights when drinking?	Yes	No
11. Has drinking ever created problems between you and a near relative or close friend?	Yes	No
12. Has any family member or close friend ever gone to anyone for help about your drinking?	Yes	No
13. Have you ever lost friends because of your drinking?	Yes	No
14. Have you ever gotten into trouble at work because of drinking?	Yes	No
15. Have you ever lost a job because of drinking?	Yes	No

Site ____ Participant # _____ Alpha Code _____ Date MM / DD / YYYY _____

16. Have you ever neglected your obligations, your family, or your work for two or more days in a row because you were drinking?	Yes	No
17. Do you ever drink before noon?	Yes	No
18. Have you ever been told you have liver trouble? Cirrhosis?	Yes	No
19. Have you ever had delirium tremens (D.T's), severe shaking, heard voices or seen things that weren't there after heavy drinking?	Yes	No
20. Have you ever gone to anyone for help about your drinking?	Yes	No
21. Have you ever been in a hospital because of drinking?	Yes	No
22. Have you ever been a patient in a psychiatric hospital or on a psychiatric ward of a general hospital where drinking was part of the problem?	Yes	No
23. Have you ever been seen at a psychiatric or mental health clinic, or gone to a doctor, social worker, or clergyman for help with an emotional problem in which drinking had played a part?	Yes	No
24. Have you been arrested, even for a few hours, because of drunk behavior?	Yes	No
25. Have you ever been arrested for drunk driving or driving after drinking?	Yes	No

SC Signature _____ Date _____

VA COOPERATIVE STUDY #556
The Effectiveness of rTMS in Depressed VA Patients

Site ____ Participant # _____ Alpha Code _____ Date ____/____/____ MM / DD / YYYY

Form 32 – STAXI-2

Circle Visit Below:

Screening

Acute Treatment Phase Sessions: 5 10 15 20 25 30

Taper Week: 1 2 3

Follow-up Phase Weeks: 4 8 12 16 20 24

Gender (*Circle One*) Male Female

1. How I Feel Right Now

1. I am furious

Not at all Somewhat Moderately so Very much so

2. I feel irritated

Not at all Somewhat Moderately so Very much so

3. I feel angry

Not at all Somewhat Moderately so Very much so

4. I feel like yelling at somebody

Not at all Somewhat Moderately so Very much so

5. I feel like breaking things

Not at all Somewhat Moderately so Very much so

6. I am mad

Not at all Somewhat Moderately so Very much so

7. I feel like banging on the table

Not at all Somewhat Moderately so Very much so

Site ____ Participant# _____ Alpha Code _____ Date ____/____/____ MM / DD / YYYY

8. I feel like hitting someone
 Not at all Somewhat Moderately so Very much so

9. I feel like swearing
 Not at all Somewhat Moderately so Very much so

10. I feel annoyed
 Not at all Somewhat Moderately so Very much so

11. I feel like kicking somebody
 Not at all Somewhat Moderately so Very much so

12. I feel like cursing out loud
 Not at all Somewhat Moderately so Very much so

13. I feel like screaming
 Not at all Somewhat Moderately so Very much so

14. I feel like pounding somebody
 Not at all Somewhat Moderately so Very much so

15. I feel like shouting out loud
 Not at all Somewhat Moderately so Very much so

2. How I Generally Feel

16. I am quick tempered
 Almost never Sometimes Often Almost always

17. I have a fiery temper
 Almost never Sometimes Often Almost always

18. I am a hotheaded person

Almost never Sometimes Often Almost always

19. I get angry when I'm slowed down by others' mistakes

Almost never Sometimes Often Almost always

20. I feel annoyed when I am not given recognition for doing good work

Almost never Sometimes Often Almost always

21. I fly off the handle

Almost never Sometimes Often Almost always

22. When I get mad, I say nasty things

Almost never Sometimes Often Almost always

23. It makes me furious when I am criticized in front of others

Almost never Sometimes Often Almost always

24. When I get frustrated, I feel like hitting someone

Almost never Sometimes Often Almost always

25. I feel infuriated when I do a good job and get a poor evaluation

Almost never Sometimes Often Almost always

3. How I Generally React or Behave When Angry or Furious

26. I control my temper

Almost never Sometimes Often Almost always

27. I express my anger

Almost never Sometimes Often Almost always

Site ____ Participant# _____ Alpha Code _____ Date ____/____/____ MM / DD / YYYY

28. I take a deep breath and relax

Almost never Sometimes Often Almost always

29. I keep things in

Almost never Sometimes Often Almost always

30. I am patient with others

Almost never Sometimes Often Almost always

31. If someone annoys me, I'm apt to tell him or her how I feel

Almost never Sometimes Often Almost always

32. I try to calm myself as soon as possible

Almost never Sometimes Often Almost always

33. I pout or sulk

Almost never Sometimes Often Almost always

34. I control my urge to express my angry feelings

Almost never Sometimes Often Almost always

35. I lose my temper

Almost never Sometimes Often Almost always

36. I try to simmer down

Almost never Sometimes Often Almost always

37. I withdraw from people

Almost never Sometimes Often Almost always

38. I keep my cool

Almost never Sometimes Often Almost always

39. I make sarcastic remarks to others

Almost never Sometimes Often Almost always

40. I try to soothe my angry feelings

Almost never Sometimes Often Almost always

41. I boil inside, but I don't show it

Almost never Sometimes Often Almost always

42. I control my behavior

Almost never Sometimes Often Almost always

43. I do things like slam doors

Almost never Sometimes Often Almost always

44. I endeavor to become calm again

Almost never Sometimes Often Almost always

45. I tend to harbor grudges that I don't tell anyone about

Almost never Sometimes Often Almost always

46. I can stop myself from losing my temper

Almost never Sometimes Often Almost always

47. I argue with others

Almost never Sometimes Often Almost always

48. I reduce my anger as soon as possible

Almost never Sometimes Often Almost always

49. I am secretly quite critical of others

Almost never Sometimes Often Almost always

Site ____ Participant# _____ Alpha Code _____ Date ____/____/____ MM DD YYYY

50. I try to be tolerant and understanding

Almost never Sometimes Often Almost always

51. I strike out at whatever infuriates me

Almost never Sometimes Often Almost always

52. I do something relaxing to calm down

Almost never Sometimes Often Almost always

53. I am angrier than I am willing to admit

Almost never Sometimes Often Almost always

54. I control my angry feelings

Almost never Sometimes Often Almost always

55. I say nasty things

Almost never Sometimes Often Almost always

56. I try to relax

Almost never Sometimes Often Almost always

57. I'm irritated a great deal more than people are aware of

Almost never Sometimes Often Almost always

SC Signature _____ Date _____

VA COOPERATIVE STUDY #556
The Effectiveness of rTMS in Depressed VA Patients

Site ____ Participant # _____ Alpha Code _____ Date ____/____/____ MM/ DD/ YYYY

Form 33 – Urine Toxicology Screen/Alcohol Test

Circle Visit Below:				
Screening				
Acute Treatment Phase Blocks:	2	4	6	
Taper Phase Week:	2			
Follow-up Phase Weeks:	4	12	20	

I. Urine Drug Test

Dip Card A

		Results		
		Negative	Positive	No Result
1.	Methamphetamine (MET) and Ecstasy (ECS)			
2.	Amphetamine (AMP) and Methylenedioxymethamphetamine (MDA)			
3.	Marijuana (THC)			
4.	Cocaine (COC)			
5.	Opiates (OPI)*			

Dip Card B

1.	Barbiturates (BAR)*			
2.	Benzodiazepines (BZD)*			
3.	Phencyclidine (PCP)			
4.	Methadone (MTD)*			
5.	Oxycodone (OXY)*			

II. Alcohol Test

1.	Alcohol			
		Negative	Positive	No Result

* Opiates, barbiturates, benzodiazepines, methadone, and oxycodone, and THC may be positive if the patient is using these medications in accordance with a valid prescription.

VA COOPERATIVE STUDY #556
The Effectiveness of rTMS in Depressed VA Patients

Site ____ Participant # _____ Alpha Code _____ Date _____ / _____ / _____

MM DD YYYY

Form 34 – STUDY COMPLETION / TERMINATION

Complete this form when patient completes the study or when it is determined that patient will not be returning for study visits.

1. Did participant complete study? No Yes

2. Date of study termination or completion. Mo____ Day____ Yr_____

3. Major reason for not completing study?
01 = Completer - end of study
02 = Withdrew consent
03 = Moved
04 = Unable to return for appointments
05 = Incarceration
06 = Lost to follow-up, no response to contacts
07 = Deceased (Complete Adverse Event form pack) AE Reference # _____
(Date of death) Mo____ Day____ Yr_____

- 08 = Intolerance of burden of visits, interviews
09 = Administrative discharge
10 = Pregnancy
11 = Adverse medical event _____
(Complete Adverse Event form pack) AE Reference # _____

- 12 = Lack of effectiveness
13 = Other medical illness, specify _____
14 = Other psychiatric problem, specify _____
15 = Other, specify _____

4. Was care transferred to primary Psychiatrist? No Yes
4a. If No, why? _____

5. Does the participant believe that the treatment was effective in treating their depression?
(Circle One) Not at all Slightly Moderately Considerably Extremely

VA COOPERATIVE STUDY #556
The Effectiveness of rTMS in Depressed VA Patients

Site ____ Participant # _____ Alpha Code _____ Date ____/____/____

Form 35 - Control Questionnaire

Participant complete:

Before First Treatment Session After First Treatment Session End of the Study

End of the Study completed by:

Local Site Investigator TMS Treater Study Coordinator

1. Please indicate your best guess as to which treatment group the participant was assigned?

Real rTMS Sham

2. How confident are you that your guess is correct?

Extremely

Considerably

Moderately

Slightly

Not at all

Signature _____ Date _____

Participant completed (SC sign for Participant completed form)

VA COOPERATIVE STUDY #556
The Effectiveness of rTMS in Depressed VA Patients

Site ____ Participant # _____ Alpha Code _____ Date ____/____/____

Form 36 – Protocol Deviation

Complete for each protocol deviation

1. Protocol Deviation _____

- 01 = Adverse Event not reported
- 02 = SAE/UADE not reported
- 03 = SAE/UADE reported late
- 04 = Participant not monitored for AE/SAE/UADE
- 05 = Did not follow instructions from IRB or other review bodies/committees
- 06 = Confidentiality or privacy breach
- 07 = Loss of source documents/samples/source media
- 08 = Improper enrollment of a member of a vulnerable population
- 09 = Inappropriate participant randomization
- 10 = Ineligible participant enrolled
- 11 = Pregnancy test not performed prior to enrollment of female participant
- 12 = Participant in more than one simultaneous interventional trial
- 13 = Inappropriately modified informed consent/HIPAA
- 14 = Informed Consent/HIPAA documentation completed incorrectly
- 15 = Informed Consent/HIPAA documentation is incomplete
- 16 = Informed Consent/HIPAA not obtained prior to study procedures
- 17 = Reconsent/HIPAA reauthorization not obtained in timely manner
- 18 = Used incorrect informed consent/HIPAA version
- 19 = Drug/Device accountability issue
- 20 = Inappropriate intervention unblinding
- 21 = Intervention used by non-study individual
- 22 = Performed activities not allowed by protocol
- 23 = Performed study procedure at incorrect interval
- 24 = Required study procedure not performed per protocol
- 25 = Study activities performed by inappropriate personnel
- 26 = Study intervention not administered per protocol
- 27 = Participant non-compliance

Site ____ Participant # _____ Alpha Code _____ Date MM / DD / YYYY ____

99 = Other, provide description and reason: _____

2. Date of Deviation: MM / DD / YYYY ____

3. Comment: _____

VA COOPERATIVE STUDY #556
The Effectiveness of rTMS in Depressed VA Patients

FORM 37A – ADVERSE EVENT (AE)

FOR COLLECTING ADVERSE EVENTS (AEs) AND ADVERSE DEVICE EVENTS (ADEs) DEFINED IN THE PROTOCOL

Site Participant # Alpha Code

Date of Report: (mm-dd-yyyy): - - -

1. Adverse Event (s) Being Reported (enter the diagnosis if known; otherwise enter a sign or symptom):

2. AE start date/time (record the date/time the AE began) (mm-dd-yyyy): - - -
 Time: : (military time) (Time field optional) Check if date/time is an estimate.

3. Following the Adverse Event was the use of the Study Device:

Not Changed Changed (briefly describe the change)
 Temporarily Interrupted Withdrawn NA

4. If use of the Study Device was Interrupted or Withdrawn, did the Patient Improve?

Yes No Not yet resolved NA

5. If use of the Study Device was Interrupted or Withdrawn, do you Plan to Restart use of the Device?

Yes (or have already) Undecided at this Time No NA

6. If Study Device was Restarted, did the AE Reappear? Yes No NA

7. Outcome (check **one** of the following six possible responses):

Fatal: date of death (mm-dd-yyyy): - - - Check if date is an estimate.

Recovering/ Resolving (The subject has a good prognosis and is in the process of recovering or the problem is being resolved) Ongoing – create and submit Follow-up in Adverse Event formpack at least every 30 days until AE is resolved or the study ends, whichever occurs first.

Not Recovered/ Not Resolved (The subject has not recovered yet and the prognosis is unsure or the problem has not been resolved and the resolution is unclear) Ongoing - create and submit Follow-up in Adverse Event formpack at least every 30 days until AE is resolved or the study ends, whichever occurs first.

Recovered/ Resolved (The subject/problem has completely recovered)
Stop Date: (date/ time the AE ended) (mm-dd-yyyy): - - -
 Time: : (military time) (time field is optional) Check if date/time is an estimate.

Recovered / Resolved with Sequelae (The subject/problem has recovered as much as possible, but is not completely resolved) **Stop Date:** (date/ time the AE ended) (mm-dd-yyyy): - - -
 Time: : (military time) (time field is optional) Check if date/time is an estimate.

Unknown

8. Severity of AE: Mild Moderate Severe

Site ____ Participant # _____ Alpha Code _____ Date MM / DD / YYYY ____

9. Is the AE Attributable to the rTMS device?

Not attributed Possibly attributed Yes, attributed

10. Is the AE Attributable to the rTMS treatment?

Not attributed Possibly attributed Yes, attributed

11. Is the AE Attributable to disease progression of depression?

Not attributed Possibly attributed Yes, attributed

12. Is the AE Attributable to medications used to treat depression?

Not attributed Possibly attributed Yes, attributed

13. Is the AE Attributable to Other Patient-Related Conditions?

Not attributed Possibly attributed Yes, attributed

14. Is this event serious? (All seizure and suicide attempts are considered SAE for the purpose of this study.)

Yes If 'Yes' complete SAE section of Adverse Event formpack No

Comment (optional):

VA COOPERATIVE STUDY #556
The Effectiveness of rTMS in Depressed VA Patients

FORM 37B – SERIOUS ADVERSE EVENT (SAE)

FOR REPORTING ALL SERIOUS ADVERSE EVENTS (SAEs) AND UNANTICIPATED ADVERSE DEVICE EFFECT (UADE).
ALL SEIZURE AND SUICIDE ATTEMPTS ARE CONSIDERED SAEs IN THIS STUDY.

Site <input type="text"/> <input type="text"/> Participant # <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> Alpha Code <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
<p>Start Date: (date/ time the SAE began) (mm-dd-yyyy): <input type="text"/> - <input type="text"/> - <input type="text"/> - <input type="text"/> - <input type="text"/> Time: <input type="text"/> : <input type="text"/> (military time) (time field is optional) <input type="checkbox"/> Check if date/time is an estimate.</p>
<p>15. Serious Event Type: Check ALL that apply: <input type="checkbox"/> Death <input type="checkbox"/> Life-threatening <input type="checkbox"/> Congenital anomaly/Birth defect <input type="checkbox"/> Inpatient hospitalization or prolongation of existing hospitalization <input type="checkbox"/> Persistent or significant disability/Incapacity <input type="checkbox"/> Any other condition that may jeopardize the subject and require medical or surgical treatment to prevent one of the above outcomes</p>
<p>16. Date Site Investigator became aware of the event: (mm-dd-yyyy): <input type="text"/> - <input type="text"/> - <input type="text"/> - <input type="text"/> - <input type="text"/></p>
<p>17. Describe the Serious Adverse Event, including Treatment of the Event: (Describe patient's condition just prior to, during and after event – if known give the duration and outcome of this event – DO NOT include past medical history)</p> <hr/> <hr/> <hr/>
<p>18. When did SAE occur relative to randomization? <input type="checkbox"/> Pre-Randomization <input type="checkbox"/> Post-Randomization</p>
<p>19. Pertinent Medical History (Include pre-existing medical conditions and adverse events previously reported): <hr/><hr/><hr/></p>
<p>20. Concomitant Medications taken at the time of the SAE start date: 1. <input type="text"/> 2. <input type="text"/> 3. <input type="text"/> 4. <input type="text"/> 5. <input type="text"/> 6. <input type="text"/> 7. <input type="text"/> 8. <input type="text"/> 9. <input type="text"/></p>
<p>21. Pertinent Test Results / Laboratory Data (normal and abnormal) / Date: <hr/><hr/><hr/></p>
<p>22. Comment: <hr/><hr/><hr/></p>

Attach additional pages, if needed.

Page of

**COMPLETE IN ADVERSE EVENT FORMPACK WITHIN 72 HRS
OF INVESTIGATOR RECEIVING SAE NOTIFICATION**

VA COOPERATIVE STUDY #556
The Effectiveness of rTMS in Depressed VA Patients

FORM 37c – AE/SAE FOLLOW-UP

Submit at least every 30 days for events that are Recovering/ Resolving or Not Recovered/Not Resolved

Site

Participant #

Alpha Code

1. Date of Follow-up Report (mm-dd-yyyy): _____ - _____ - _____

2. Indicate whether the diagnosis being reported has changed from the initial AE/SAE report (e.g., event originally reported as chest pain, but final diagnosis is MI): Yes No

If yes, indicate the change in the AE/SAE being reported (enter only the diagnosis if known; otherwise enter a sign or symptom. Do not enter 'death' or 'hospitalization' as an event).

3. Has the severity of this AE/SAE changed from the initial report? Yes No

If yes, indicate the appropriate severity: Mild Moderate Severe

4. Has the Serious Classification of the event changed? Yes No

(All seizure and suicide attempts are considered SAE for the purpose of this study.)

If yes, complete SAE questions below.

(a) Serious Event Type: Death Life-threatening Congenital anomaly/Birth defect
(Mark all that apply) Inpatient hospitalization or prolongation of existing hospitalization
 Persistent or significant disability/Incapacity
 Any other condition that may jeopardize the subject and require medical or surgical treatment to prevent one of the above outcomes

(b) Describe the Serious Adverse Event, including Treatment of the Event: (Describe patient's condition just prior to, during and after event – if known give the duration and outcome of this event – DO NOT include past medical history)

(c) Pertinent Medical History (Include pre-existing medical conditions and adverse events previously reported):

(d) Pertinent Test Results / Laboratory Data (normal and abnormal)

Date: (mm-dd-yyyy): _____ - _____ - _____

5. Is there additional new information to report? Yes No
If yes, please specify: (use this section to provide new information):

6. Is the AE/SAE Attributable to the rTMS device?
 Not attributed Possibly attributed Yes, attributed

7. Is the AE/SAE Attributable to the rTMS treatment?
 Not attributed Possibly attributed Yes, attributed

8. Is the AE/SAE Attributable to disease progression of depression?
 Not attributed Possibly attributed Yes, attributed

9. Is the AE/SAE Attributable to medications used to treat depression?
 Not attributed Possibly attributed Yes, attributed

10. Is the AE/SAE Attributable to other patient-related conditions?
 Not attributed Possibly attributed Yes, attributed

11. Outcome (check **one** of the following six possible responses):

Fatal: date of death (mm-dd-yyyy): ____ - ____ - ____ Check if date is an estimate.

Recovering/ Resolving (The subject has a good prognosis and is in the process of recovering or the problem is being resolved) Ongoing – create and submit Follow-up in Adverse Event formpack at least every 30 days until AE is resolved or the study ends, whichever occurs first.

Not Recovered/ Not Resolved (The subject has not recovered yet and the prognosis is unsure or the problem has not been resolved and the resolution is unclear) Ongoing - create and submit Follow-up in Adverse Event formpack at least every 30 days until AE is resolved or the study ends, whichever occurs first.

Recovered/ Resolved (The subject/problem has completely recovered)
Stop Date: (date/ time the AE ended) (mm-dd-yyyy): ____ - ____ - ____
Time: ____ : ____ (military time) (time field is optional) Check if date/time is an estimate.

Recovered / Resolved with Sequelae (The subject/problem has recovered as much as possible, but is not completely resolved) **Stop Date:** (date/ time the AE ended) (mm-dd-yyyy): ____ - ____ - ____
Time: ____ : ____ (military time) (time field is optional) Check if date/time is an estimate.

Unknown

Site ____ Participant # ____ Alpha Code ____ Date ____ / ____ / ____
____ MM ____ DD ____ YYYY

12. Since the last report of this event, was the use of the Study Device:

Unchanged Changed (briefly describe the change) _____
 Temporarily interrupted Permanently Withdrawn NA

13. If use of the Study Device was Interrupted or Withdrawn, did the patient improve?

Yes No Not yet resolved NA

14. If use of the Study Device was Interrupted or Withdrawn, do you plan to restart use of the Device?

Yes (or have already) Undecided at this Time No NA

15. If Study Device was Restarted, did the AE/SAE Reappear? Yes No NA

Comments: _____

Attach additional pages, if needed.

Page ____ of ____

VA COOPERATIVE STUDY #556
The Effectiveness of rTMS in Depressed VA Patients

Site ____ Participant # _____ Alpha Code _____ Date ____/____/____

Form 86 – Informed Consent Confirmation

COMPLETE AT SCREENING ONLY

1. Did participant sign the Informed Consent Form? No Yes

If Yes,

a. then provide social security number: _____ - _____ - _____
b. then provide last name _____

2. Date Consent Signed ____/____/____

3. Patient Consented By: _____ Role: _____

Consent Form Questions

Please circle the answers to the Consent Form Questions below.

1)	True	False	7)	True	False
2)	True	False	8)	True	False
3)	True	False	9)	True	False
4)	True	False	10)	True	False
5)	True	False	11)	True	False
6)	True	False			

APPENDIX F

Device Handling Procedures

“The Effectiveness of Repetitive Transcranial Magnetic Stimulation (rTMS) in Depressed VA Patients”

DEVICE HANDLING PROCEDURES

IDE # G100005

Revised May 2012

Prepared by:

THE DEPARTMENT OF VETERANS AFFAIRS
COOPERATIVE STUDIES PROGRAM CLINICAL RESEARCH PHARMACY
COORDINATING CENTER (151-I)

2401 Centre Ave. SE
Albuquerque, NM 87106-4180

This document provides general information on investigator responsibilities and details on materials shipped for use in this trial. For information on how to use the device, consult the TMS Operator’s Manual.

Contents

1. INTRODUCTION AND PURPOSE	3
2. RESPONSIBILITIES OF THE PARTICIPATING INVESTIGATOR	3
3. DESCRIPTION OF CLINICAL TRIAL DEVICES	4
4. CLINICAL TRIAL DEVICES AND CLINICAL TRIAL AIDS	4
5. VERIFICATION OF rTMS DEVICE	5
6. REPLACEMENT OF EXPIRED/DAMAGED DEVICES	5
7. STORAGE REQUIREMENTS	5
8. REQUIRED DOCUMENTATION	5
9. DEVICE RETURN POLICY	5

1. INTRODUCTION AND PURPOSE

Each site investigator (SI) is responsible for a complete and accurate accounting of all study devices and other materials received by the site. The VA Cooperative Studies Program Clinical Research Pharmacy Coordinating Center (PCC) in Albuquerque, New Mexico will provide instructions and assistance as necessary to assure proper use of and accountability for all study materials. Each site must observe local policies and applicable state and federal regulations concerning study devices.

The device used in this study is the MagPro R30 Magnetic Stimulator, manufactured by Tonica Elektronik A/S.

2. RESPONSIBILITIES OF THE PARTICIPATING INVESTIGATOR

The SI at each site is responsible for:

2.1 Providing PCC with the following documents:

2.1.1 Investigator's Signed Agreement (ISA): The PCC will provide each SI with a partially completed "Investigator's Signed Agreement" form. This form must be completed, signed, and returned to the PCC prior to the shipment of any clinical trial devices to your center.

2.1.2 Curriculum Vitae: A signed and dated copy of the investigator's updated curriculum vitae (CV) must be attached to each "Investigator's Signed Agreement."

2.1.3 Research Committee Approval: A signed letter from the Associate Chief of Staff (ACOS) for Research and Development or other authorized individual indicating CSP #556 has been approved at your center. The letter must list the name of the SI who is responsible for the clinical trial. A copy of this document must be received before PCC will arrange shipment of the clinical trial device to your center.

2.2 Retaining all study-related documents until notified by the CSP Coordinating Center concerning the disposition of the documents. CSP studies remain active for five years after the last patient follow-up.

2.3 The SI, any subinvestigator, and any other personnel associated with the study will not represent that device used in CSP #556 is safe or effective for the purpose for which it is being investigated.

2.4 The site investigator will use the investigational device only with subjects under the investigator's personal supervision or under the supervision of a sub investigator listed on the Site Investigator's Agreement (SIA). The investigational device may be used only for the purpose of this study.

3. DESCRIPTION OF CLINICAL TRIAL DEVICES

3.1 Clinical Trial Device - The device used in this study is the MagPro R30 Magnetic Stimulator for repetitive transcranial magnetic stimulation (rTMS) in treating Treatment-Resistant Major Depression (TRMD). The device is programmed to (a) determine a patient's motor threshold and (b) deliver active or sham magnetic stimulation, depending the participant's treatment assignment. An Operator's Manual with instructions for the use of the MagPro R30 will be sent prior to the first randomization and will be available on the study SharePoint site.

4. CLINICAL TRIAL DEVICES AND CLINICAL TRIAL AIDS

4.1 RTMS device and associated equipment. Following receipt of all required documentation (Section 2.1), the PCC will arrange for shipment, installation, and training of the rTMS device by the manufacturer.

4.2 Audiometer. Following receipt of all required documentation the PCC will ship one Earscan 3 screening audiometer to each site. Each audiometer includes a manual which is also available at <http://www.earscan.com/earscan3m.aspx>.

4.3 Alcohol and drug test kits. Following receipt of all required documentation and in anticipation of imminent randomization, PCC will ship commercially-available drug and alcohol tests to each site. These will be used in participants as specified in the protocol. These tests must be stored at room temperature in a locked room. Directions for use are included with each test. To reorder, sites should contact PCC via email, fax or phone.

4.4 Patient ID Cards – PCC will ship patient identification (ID) cards to each site. At the randomization visit, this wallet-sized ID card should be filled out and given to the subject with instructions to present the card to any clinician seen for medical treatment while participating in CSP #556. If additional Patient ID cards are needed, the site coordinator should contact PCC via email, fax or phone.

CSP 556 Patient ID card (Printing on Both Sides of the Card)

<p>CSP #556 PATIENT IDENTIFICATION CARD</p> <p>Patient's Name _____ Address _____ Phone # _____ Subject ID #: _____ Subject Treatment #: _____</p> <p>I am participating in a clinical trial being conducted at the _____ During this trial I will have repetitive transcranial magnetic stimulation (rTMS) or sham treatment that may decrease my depression symptoms. Please contact the physician or nurse listed on the backside of this card if I require medical attention that might be affected by my participation in this trial or if you have questions regarding the trial.</p>	<p>IN CASE OF EMERGENCY, Please Notify:</p> <p>Site Investigator: _____ Name _____ Work number _____ Nurse: _____ Name _____ Work number _____</p> <p>National Clinical Trial Chairs: Jerome Yesavage, M.D. 650-852-3287 Mark George, M.D. 843-876-5142 J. Kaci Fairchild, Ph.D. 650-493-5000 x63432</p> <p>Pharmacy Coordinating Center: 505-248-3203 (24 hrs/7 days per week) Study Biostatistician: (410) 642-2411 ext 5283</p> <p><i>This card should be shown to any health care professional treating you for any reason.</i></p>
---	---

4.5 Electrodes. Following receipt of all required documentation and in anticipation of imminent randomization, PCC will ship two types of electrodes to each site. Stimulating electrodes will be used to mimic the sensation of active TMS. Recording electrodes will be used to evaluate motor threshold. See Operators Manual for complete information. If more electrodes are needed, sites should contact PCC by email, fax, or phone.

4.6 Ancillary supplies. PCC will provide all supplies listed on the table below once required documentation is received and sites are ready to start the study.

Supply	Description of use	Resupply
Fabric caps	Various sizes of fabric caps to be used for the correct placement of the rTMS coil.	Contact PCC
Styrofoam sheets	Boxes of Styrofoam sheets used to cushion a patients head from the rTMS coil	Not provided. If more sheets are needed, sites should order using their site budget.
Earphone covers	Disposable covers to place on the earphones of the audiometer for each patient use	Contact PCC

5. VERIFICATION OF rTMS DEVICE

Each device will be delivered to a site and tested for functionality by the MagVenture technicians. Each device will also be verified by PCC Quality Compliance personnel for performance of active and sham treatments.

6. REPLACEMENT OF NONFUNCTIONAL/DAMAGED DEVICES

If a device is damaged or broken, sites should contact the COTR at PCC and the device manufacturer to arrange for repair or replacement.

7. STORAGE REQUIREMENTS

CSP #556 clinical trial devices and ancillary supplies must be kept in a secure, locked area. Each rTMS device must be housed in a room that is approximately 8'x15' and has a dedicated 20 amp circuit.

8. REQUIRED DOCUMENTATION

A complete and accurate record of all clinical trial devices received from PCC is the responsibility of the Site Investigator (SI). The SI and Site Coordinator will maintain records to meet the requirements of the FDA, VA CSP, and the manufacturer.

9. DEVICE RETURN POLICY

At the end of the clinical trial PCC will instruct the site as to the disposition of the device.

APPENDIX G

Investigator's Brochure

Investigator's Brochure
for
VA Cooperative Studies Program Study, CSP #556

“The Effectiveness of Repetitive Transcranial Magnetic Stimulation (rTMS) in Depressed VA Patients”

STUDY DEVICE:
MagPro R30 Magnetic Stimulator

Revised November 30, 2015

Prepared by:
Department of Veterans Affairs
Cooperative Studies Program Clinical
Research Pharmacy Coordinating Center (151-I)
2401 Centre Ave. SE
Albuquerque, NM 87106

This section contains information, pertinent to the safety and effectiveness of repetitive transcranial stimulation (rTMS).

MagPro R30 Magnetic Stimulator

rTMS stimulates and induces firing in cortical neurons by producing brief pulses of an intense magnetic field, which ultimately leads to neuronal summation and depolarization¹. At present, the MagPro R30 device is FDA approved for the stimulation of peripheral nerves and muscles. It has also been studied for potential usefulness in treating depression, as is discussed below.

Summary of Relevant Clinical Studies

There have been a large number of published trials of rTMS for the treatment of depression^{2 3-10 8,11,12 13-31 32-36 24 28 15 20 14 27,31,37-40}. Because small participant pools have been a frequent limitation, several meta-analyses have been conducted in order to assess the value of rTMS as a treatment for depression, each using different base references and statistical methods^{33,36,41,42}.

In many of the trials evaluated in these meta-analyses, participants had failed prior medication trials. Thus, the participants represented in the published literature are, in general, a pre-selected group of more difficult to treat patients than those seen in typical studies of new antidepressant medications. Still, the conclusion of each of these five published meta-analyses has been the same: daily prefrontal rTMS delivered over several weeks has antidepressant effects greater than that obtained with placebo.

In a meta-analysis by Burt et al. of 23 published comparisons for controlled rTMS prefrontal antidepressant trials containing both treatment-resistant and non-treatment-resistant subjects, the authors found that rTMS had a combined effect size of 0.67, considered to be a moderate to large antidepressant effect³². In a sub-analysis, rTMS was compared with ECT. The effect size for rTMS in these studies was greater than in the studies comparing rTMS to sham, which may indicate a participant selection bias. The authors infer that rTMS may be most effective in the patients who also satisfy clinical predictors for positive ECT response.

A meta-analysis conducted using the Cochrane library guidelines was performed using literature published prior to 2001⁴². This stringent meta-analysis included 14 trials suitable for analysis and found that left prefrontal high-frequency rTMS at two weeks produced significantly greater improvements in the Hamilton Rating Scale than did sham treatment. However, a comparison of rTMS in general (i.e., not limited to high-frequency left prefrontal treatment) did not show a statistically significant difference.

A 2008 meta-analysis by Lam and colleagues⁴³ evaluated 24 randomized, sham-controlled studies containing 1092 patients with treatment-resistant depression. The analysis found a standardized mean difference of 0.48 for rTMS. Active treatment produced a response rate of 25% and remission rate of 9% compared to 17% and 6% respectively for placebo. The effect was robust and very few patients withdrew from the trial for adverse effects (2% withdrawal rate for active, 1.5% for placebo). However, most studies evaluated had a short follow-up time of 1-3 weeks, with no studies that evaluated response beyond 9 weeks. We hope that the current study can answer questions about long-term response.

Side Effects and Complications

Routine rTMS is usually mildly uncomfortable, but in some cases, particularly when applied over certain peripheral or cranial nerves, the treatment can be painful. TMS treatment produces a sensation on the head that most patients tolerate without problems. The painfulness is linked to the intensity of stimulation, which varies from subject to subject because dosing is based on individual patients' motor thresholds. Thus, some patients with high motor thresholds receive higher dose TMS than do other patients, and there

is a rough correlation of painfulness with intensity of stimulation. The rate of self-reported discomfort is generally low and the overall rate of discontinuation of treatment due to pain is estimated at <2%^{26,27}. Further, pain tends to diminish over time, with one study finding a 48% decrease in painfulness from baseline over the course of 15 sessions²⁷.

Headache appears to be a common but generally mild side effect of TMS. While pain associated with rTMS usually disappears rapidly, muscle headaches may occasionally persist for a few hours after stimulation⁴⁴. These headaches are not severe may respond to treatment with acetaminophen or ibuprofen²⁶.

The primary safety concern with rTMS is the risk of seizure induction. Rossi et. al systematically reviewed the literature for reports of seizures and found 16 cases. Of these, seven had occurred prior to the establishment of safety guidelines in 1998 and five were associated with rTMS treatment performed outside of the currently recommended safety guidelines adhered to in the current trial⁴⁵. In addition, another seizure in a participant who had consumed excessive alcohol the night prior to the event has been reported in the medical literature after the publication of Rossi⁴⁶.

Of the four seizures that appear to have been induced by treatment considered within current safety parameters, two may actually represent non-epileptic events. Clinical features of one of these events may be more consistent with convulsive syncope; in the other case, lack of response to anti-epileptic drugs and a normal neurological exam and EEG indicate that the event may have actually been a pseudoseizure. Even if all four events were true seizures, these reported cases have occurred within a sample size of thousands. Thus, the risk of seizure in non-epileptic patients is estimated at less than 1%⁴⁵.

rTMS is generally regarded as safe and without lasting side effects⁴⁵. There have been no significant cognitive^{47,48}, neurological⁴⁹ or cardiovascular sequelae reported as a result of rTMS. Immediately following an rTMS session similar to the ones proposed in this protocol, participants tested do not show significant neurocognitive side effects. Participants are free to return to work or drive themselves home.

rTMS may produce sounds at >120 dB, a level known to produce hearing loss; thus, hearing protection is required for all participants and treaters. There are a few published accounts of temporary and, in one case involving inadequate hearing protection, permanent hearing loss. One report found that mean group threshold at 1 kHz rose from 9.0 to 14.0 dB in five depressed patients treated for six weeks; however, this was not statistically significant. The same study noted measured hearing loss in one patient at 6-8 kHz (15 dB change) and another patient at 3-4 kHz (20 dB change). Retesting of the patient with more severe hearing loss found that hearing had returned to baseline a month later⁵⁰. Another study showed slight, transient changes in hearing in two normal volunteers⁵¹. Hearing returned to normal within four hours. In addition, permanent hearing loss (30 dB at 4 kHz) has been reported in one individual whose earplugs had fallen out during treatment⁵².

In addition to these case reports, there have been two studies that specifically examine hearing changes in patients exposed to rTMS. The first, a study of single pulse rTMS, did not find any hearing loss⁵³. A more recent study of a single session of rTMS with healthy volunteers found that, while there was no change in hearing threshold (as measured by pure-tone audiometry), there was a slight temporary alteration in transiently evoked otoacoustic emissions, a more sensitive measure of cochlear functioning. The effect was significant only in subjects who were least protected by earplugs and persisted for less than one hour⁵⁴.

To date, all reported cases of hearing loss are mild and all but the case involving inadequate auditory protection have been transient. In accordance with the current TMS guidelines⁴⁵, all participants and treaters will wear the provided foam earplugs and over-ear headphones to minimize potential ear damage while maintaining the blind. Also in accordance with these guidelines, the risks of participation to patients

CSP #556, "The Effectiveness of rTMS in Depressed VA Patients"

Version 4.6, November 2015

Appendix G Device Information Report (Investigator's Brochure)

receiving ototoxic medication and those with pre-existing noise-induced hearing loss should be carefully considered prior to enrollment in this study. Patients considered at high risk of further hearing loss may be excluded at the clinician's discretion. When such patients are included, particular care should be given in ensuring that hearing protection is properly placed prior to each treatment. Patients who complain of hearing loss, tinnitus, or aural fullness following rTMS treatment should be referred for further audiometric testing prior to receiving further stimulation.

There has been one case report of posterior vitreous detachment (PVD) and retinal tear in a 60-year-old woman which appears to have occurred during or immediately after the patient's 11th RTMS treatment for depression⁵⁵. Stimulation for this patient was right-sided and given at 110% of motor threshold for periods of 1000 seconds (16.6 minutes). The patient, who had experience eye twitching and discomfort during previous treatment sessions, reported new floaters in her right eye which were determined to be related to PVD with a small retinal tear. The authors of this report hypothesize that the tear may have been triggered by the mechanical trauma of rapid contraction of extraocular muscles in response to TMS treatment. The patient was thought to be at increased risk for PVD due to her age and because the patient's motor threshold location resulted in a treatment position closer to her eye than in previous treatment sessions.

The stimulation duration in this case was considerably longer than is planned in this trial (3 trains of 1000 seconds separated by one minute intertrain intervals compared to 4 second trains with 10 second intervals); nevertheless, investigators should be aware of the possibility of PVD and retinal tears, particularly in patients over age 60. Excessive activity of the extraocular muscles, beyond the expected stimulation of periorbital muscles, should be monitored and the presence of new floaters, flashes of light, decreased vision, or eye discomfort following treatment should initiate immediate investigation.

Acute psychiatric changes including treatment-emergent changes have been reported in some patients treated with rTMS including cases which occurred in patients without a history of mania or psychosis⁵⁶. However, few cases have been reported and the rate of manic switching is not significantly different between active and sham treatment (0.84% and 0.73% respectively)⁵⁷.

The VA has long been concerned with the issue of suicide in veterans and has funded a special MIRECC in VISN 19 to perform research on this issue and with whom this protocol has been developed. A major risk in treating seriously depressed patients is the risk of suicide. Even more difficult, many of these patients have a background of having made multiple attempts. Thus, monitoring suicide attempts, and less serious gestures, is of paramount importance. In the recently completed industry trial suicidal ideation as indexed by the HRSD Item 3 on suicidal ideation increased in 3% of sham patients over 6 weeks and did not increase in active rTMS patients. The findings of increased suicidal ideation in some sham patients as well as the fact that the population of TRMD patients as a whole are at elevated risk for suicide require that certain preventive measures be taken (Section X.B.7). Both suicidal ideation (Section VI.G.13) and behavior (Section VI.G.18) will be monitored.

In summary, the short-term adverse events expected in this trial are mild discomfort at the site of stimulation, transient tension-type headaches on the day of stimulation, and concerns about high-frequency hearing loss. A risk exists for suicide in these patients, however, extensive precautions have been planned in collaboration with experts on suicide from the VISN 19 MIRECC and it is felt that inclusion of such patients in this protocol is consistent with providing new treatment options for these difficult patients.

Risk Minimization

The risks associated with the procedures will be minimized as follows:

- 1) An independent group of physicians representing the Data Monitoring Committee (DMC) will monitor the data. The DMC will also provide an independent statistical review of the data.
- 2) All investigators and site personnel will be trained in the use of the device and in the protection of human subjects.
- 3) Treatments will be conducted as outlined in the protocol, and adverse events will be collected and reviewed for patient safety.
- 4) Assessments required in the protocol, including substance abuse and suicidality, etc are summarized on page 37 of the submitted protocol and discussed in the subsequent pages of the protocol.
- 5) Suicidality Risk Minimization - A common practice is to stop a treatment if a patient makes a suicide attempt. Because this may occur early in treatment, before a patient is adequately treated (in the active group), we would elect to continue treatment with the patient in an inpatient unit if the patient agrees to continue the trial. Discharge would be based on the patient's ability to adhere to a modified safety plan (listing behaviors and strategies in the event of increasing suicidal impulses, including returning to the ER). We will develop a safety plan agreed upon with the clinician and the patient as a condition of entry into the study. Failure of the patient to comply with the safety plan will require stopping study treatments and aggressively treating the suicidality.

As a condition of participation, we will insist that those patients with a history of suicidality have all firearms either removed from their residence or placed under lock and key, including trigger locks, with guns and ammunition locked separately and the keys given to another family member or friend. Suicide is an impulsive act and since our patients know how to use firearms effectively, the decision to make a suicide attempt will more likely be fatal if a firearm is available. Thus, another stopping point will be a violation of the firearms agreement and/or the procurement of a new firearm during the study.

Another way we are attempting to decrease the suicide risk to the patient is to enable the patient to continue in treatment with his/her outpatient clinician and to continue taking all medication except those which would convey an increased risk of seizures (which would likely have resulted in the patient's having been excluded). Should the patient drop out of outpatient treatment or if we receive information from the clinician that the patient is imminently suicidal, we will institute appropriate safety measures and discontinue study treatments if a major change in medication or treatment is necessary. Similarly, any patient who is so imminently suicidal (or homicidal) that he would require involuntary treatment, would no longer meet criteria for continuing study treatments.

- 6) Drug Abuse Risk Minimization - Another stopping point will be the acute abuse of alcohol, OTC medication, opiates, or street drugs by the patient. Under the exclusion criteria, we have listed substance abuse within the previous 90 days because evaluating withdrawal symptoms or cravings in the context of a depression study complicates the evaluation. Furthermore alcohol withdrawal, cocaine and stimulant abuse, and barbiturate withdrawal are all associated with an increased risk of seizures. More critically, actively abusing drugs or alcohol is associated with a higher risk of completed suicide. Thus, beginning to abuse alcohol or drugs could well be a prelude to a completed suicide and must be immediately addressed.

List of Contraindicated Drugs

1. Bohning DE. Introduction and Overview of TMS Physics. *Transcranial Magnetic Stimulation in Neuropsychiatry*. Washington DC: American Psychiatric Press:13-44.

CSP #556, "The Effectiveness of rTMS in Depressed VA Patients"

Version 4.6, November 2015

Appendix G Device Information Report (Investigator's Brochure)

2. Sackeim HA, Prudic J, Devanand DP, Decina P, Kerr B, Malitz S. The impact of medication resistance and continuation pharmacotherapy on relapse following response to electroconvulsive therapy in major depression. *J Clin Psychopharmacol*. Apr 1990;10(2):96-104.
3. Barker AF, IL; Jarratt, JA; Jalinous, R. Magnetic stimulation of the human nervous system: an introduction and basic principles. In: Chokroverty S, ed. *Magnetic Stimulation in Clinical Neurophysiology*. Boston: Butterworth's; 1989:55-72.
4. Barker AT, Jalinous R, Freeston IL. Non-invasive magnetic stimulation of human motor cortex. *Lancet*. May 11 1985;1(8437):1106-1107.
5. Barker AT, Freeston IL, Jalinous R, Jarratt JA. Magnetic stimulation of the human brain and peripheral nervous system: an introduction and the results of an initial clinical evaluation. *Neurosurgery*. Jan 1987;20(1):100-109.
6. Roth BJ, Cohen LG, Hallett M. The Electric Field Induced During Magnetic Stimulation. In: Lecy WJC, R.Q.; Barker, A.T.; Rothwell, J., ed. *Magnetic Motor Stimulation: Basic Principles and Clinical Experience (EEG Suppl. 43)*. Amsterdam: Elsevier Science Publishers; 1991:268-278.
7. Roth BJ, Cohen LG, Hallett M. The electric field induced during magnetic stimulation. *Electroencephalogr Clin Neurophysiol Suppl*. 1991;43:268-278.
8. Roth Y, Zangen A, Hallett M. A coil design for transcranial magnetic stimulation of deep brain regions. *J Clin Neurophysiol*. Aug 2002;19(4):361-370.
9. Bohning DE, Pecheny AP, Epstein CM, Speer AM, Vincent DJ, George MS. In-Vivo Three Dimensional Transcranial Magnetic Stimulation (TMS) Field Mapping with MRI. *Neuroimage*. 1997;5:S522.
10. Davey KR, Cheng CH, Epstein CM. Prediction of magnetically induced electric fields in biological tissue. *IEEE Trans Biomed Eng*. May 1991;38(5):418-422.
11. Bohning DE. Introduction and Overview of TMS Physics. In: George MSB, R.H., ed. *Transcranial Magnetic Stimulation in Neuropsychiatry*. Washington, DC: American Psychiatric Press; 2000:13-44.
12. Roth BJ, Momen S, Turner R. Algorithm for the design of magnetic stimulation coils. *Med Biol Eng Comput*. Mar 1994;32(2):214-216.
13. Avery DH. Transcranial magnetic stimulation in the treatment of depression. *Essent Psychopharmacol*. 2001;4:37-48.
14. Avery DH, Claypoole K, Robinson L, et al. Repetitive transcranial magnetic stimulation in the treatment of medication-resistant depression: preliminary data. *J Nerv Ment Dis*. Feb 1999;187(2):114-117.
15. Berman RM, Narasimhan M, Sanacora G, et al. A randomized clinical trial of repetitive transcranial magnetic stimulation in the treatment of major depression. *Biol Psychiatry*. Feb 15 2000;47(4):332-337.
16. Feinsod M, Kreinin B, Chistyakov A, Klein E. Preliminary evidence for a beneficial effect of low-frequency, repetitive transcranial magnetic stimulation in patients with major depression and schizophrenia. *Depress Anxiety*. 1998;7(2):65-68.
17. Garcia-Toro M, Pascual-Leone A, Romera M, et al. Prefrontal repetitive transcranial magnetic stimulation as add-on treatment in depression. *Journal of Neurology, Neurosurgery & Psychiatry*. 2001;71:546-548.
18. George MS, Wassermann EM, Williams WA, et al. Daily repetitive transcranial magnetic stimulation (rTMS) improves mood in depression. *Neuroreport*. Oct 2 1995;6(14):1853-1856.

19. George MS, Wassermann EM, Kimbrell TA, et al. Mood improvement following daily left prefrontal repetitive transcranial magnetic stimulation in patients with depression: a placebo-controlled crossover trial. *Am J Psychiatry*. Dec 1997;154(12):1752-1756.
20. George MS, Nahas Z, Molloy M, et al. A controlled trial of daily left prefrontal cortex TMS for treating depression. *Biol Psychiatry*. Nov 15 2000;48(10):962-970.
21. Grisaru N, Yarovslavsky U, Arbarbanel J, Lamberg T, Belmaker RH. Transcranial magnetic stimulation in depression and schizophrenia. *European Neuropsychopharmacology*. 1994(4):287-288.
22. Hoflich G, Kasper S, Hufnagel A, Ruhrmann S, Moller HJ. Application of transcranial magnetic stimulation in the treatment of drug-resistant major depression. *Human Psychopharmacology*. 1993;8:361-365.
23. Janicak PG, Dowd SM, Martis B, et al. Repetitive transcranial magnetic stimulation versus electroconvulsive therapy for major depression: preliminary results of a randomized trial. *Biol Psychiatry*. Apr 15 2002;51(8):659-667.
24. Klein E, Kreinin I, Chistyakov A, et al. Therapeutic efficacy of right prefrontal slow repetitive transcranial magnetic stimulation in major depression: a double-blind controlled study. *Arch Gen Psychiatry*. Apr 1999;56(4):315-320.
25. Kolbinger HM, Hoflich G, Hufnagel A, Moller HJ, S K. Transcranial magnetic stimulation (TMS) in the treatment of major depression: a pilot study. *Human Psychopharmacology*. 1995;10:305-310.
26. Loo C, Mitchell P, Sachdev P, McDermont B, Parker G, Gandevia S. Double-blind controlled investigation of transcranial magnetic stimulation for the treatment of resistant major depression. *Am J Psychiatry*. Jun 1999;156(6):946-948.
27. Nahas Z, Kozel FA, Li X, Anderson B, George MS. Left prefrontal transcranial magnetic stimulation (TMS) treatment of depression in bipolar affective disorder: a pilot study of acute safety and efficacy. *Bipolar Disord*. Feb 2003;5(1):40-47.
28. Padberg F, Zwanzger P, Thoma H, et al. Repetitive transcranial magnetic stimulation (rTMS) in pharmacotherapy-refractory major depression: comparative study of fast, slow and sham rTMS. *Psychiatry Res*. Nov 29 1999;88(3):163-171.
29. Padberg F, Zwanzger P, Keck ME, et al. Repetitive transcranial magnetic stimulation (rTMS) in major depression: relation between efficacy and stimulation intensity. *Neuropsychopharmacology*. Oct 2002;27(4):638-645.
30. Padberg F, Schule C, Zwanzger P, et al. Relation between responses to repetitive transcranial magnetic stimulation and partial sleep deprivation in major depression. *Journal of Psychiatric Research*. 2002(36):131-135.
31. Szuba MP, O'Reardon JP, Rai AS, et al. Acute mood and thyroid stimulating hormone effects of transcranial magnetic stimulation in major depression. *Biol Psychiatry*. Jul 1 2001;50(1):22-27.
32. Burt T, Lisanby SH, Sackeim HA. Neuropsychiatric applications of transcranial magnetic stimulation: a meta analysis. *Int J Neuropsychopharmacol*. Mar 2002;5(1):73-103.
33. Holtzheimer PE, 3rd, Russo J, Avery DH. A meta-analysis of repetitive transcranial magnetic stimulation in the treatment of depression. *Psychopharmacol Bull*. Autumn 2001;35(4):149-169.
34. Kozel FA, George MS. Meta-analysis of left prefrontal repetitive transcranial magnetic stimulation (rTMS) to treat depression. *Journal of Psychiatric Practice*. 2002;8:270-275.

35. Martin JLR, Barbanoj MJ, Schlaepfer TE, Clos S PV, Kulisevsky J, A G. Transcranial magnetic stimulation for treating depression (Cochrane Review). In (eds.): The Cochrane Library. Oxford: Update Software, 2002.

36. McNamara B, Ray JL, Arthurs OJ, Boniface S. Transcranial magnetic stimulation for depression and other psychiatric disorders. *Psychol Med*. Oct 2001;31(7):1141-1146.

37. Garcia-Toro M, Pascual-Leone A, Romera M, et al. Prefrontal repetitive transcranial magnetic stimulation as add on treatment in depression. *J Neurol Neurosurg Psychiatry*. Oct 2001;71(4):546-548.

38. Janicak PG, Dowd S, Rado J, et al. Repetitive transcranial magnetic stimulation versus electroconvulsive therapy: efficacy of treatment in nonpsychotic patients with depression. *Am J Psychiatry*. Jul 2007;164(7):1118; author reply 1118-1119.

39. Padberg F, Schule C. Relation between responses to repetitive transcranial magnetic stimulation and partial sleep deprivation in major depression. *neuropsychopharmacology*. 2002;27(4):638-645.

40. Padberg F, Moller HJ. Repetitive transcranial magnetic stimulation : does it have potential in the treatment of depression? *CNS Drugs*. 2003;17(6):383-403.

41. Kozel FA, George MS. Meta-analysis of left prefrontal repetitive transcranial magnetic stimulation (rTMS) to treat depression. *J Psychiatr Pract*. Sep 2002;8(5):270-275.

42. Martin JL, Barbanoj MJ, Schlaepfer TE, et al. Transcranial magnetic stimulation for treating depression. *Cochrane Database Syst Rev*. 2002(2):CD003493.

43. Lam RW, Chan P, Wilkins-Ho M, Yatham LN. Repetitive transcranial magnetic stimulation for treatment-resistant depression: a systematic review and metaanalysis. *Can J Psychiatry*. Sep 2008;53(9):621-631.

44. Loo CK, McFarquhar TF, Mitchell PB. A review of the safety of repetitive transcranial magnetic stimulation as a clinical treatment for depression. *Int J Neuropsychopharmacol*. Feb 2008;11(1):131-147.

45. Rossi S, Hallett M, Rossini PM, Pascual-Leone A. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clin Neurophysiol*. Dec 2009;120(12):2008-2039.

46. Levkovitz Y, Isserles M, Padberg F, et al. Efficacy and safety of deep transcranial magnetic stimulation for major depression: a prospective multicenter randomized controlled trial. *World psychiatry : official journal of the World Psychiatric Association*. Feb 2015;14(1):64-73.

47. Triggs WJ, McCoy KJ, Greer R, et al. Effects of left frontal transcranial magnetic stimulation on depressed mood, cognition, and corticomotor threshold. *Biol Psychiatry*. Jun 1 1999;45(11):1440-1446.

48. Little JT, Kimbrell TA, Wassermann EM, et al. Cognitive effects of 1- and 20-hertz repetitive transcranial magnetic stimulation in depression: preliminary report. *Neuropsychiatry Neuropsychol Behav Neurol*. Apr 2000;13(2):119-124.

49. Nahas Z, DeBrux C, Chandler V, et al. Lack of significant changes on magnetic resonance scans before and after 2 weeks of daily left prefrontal repetitive transcranial magnetic stimulation for depression. *J ECT*. Dec 2000;16(4):380-390.

50. Loo C, Sachdev P, Elsayed H, et al. Effects of a 2- to 4-week course of repetitive transcranial magnetic stimulation (rTMS) on neuropsychologic functioning, electroencephalogram, and auditory threshold in depressed patients. *Biol Psychiatry*. Apr 1 2001;49(7):615-623.

51. Pascual-Leone A, Houser CM, Reese K, et al. Safety of rapid-rate transcranial magnetic stimulation in normal volunteers. *Electroencephalogr Clin Neurophysiol*. Apr 1993;89(2):120-130.
52. Zangen A, Roth Y, Voller B, Hallett M. Transcranial magnetic stimulation of deep brain regions: evidence for efficacy of the H-coil. *Clin Neurophysiol*. Apr 2005;116(4):775-779.
53. Pascual-Leone A, Cohen LG, Shotland LI, et al. No evidence of hearing loss in humans due to transcranial magnetic stimulation. *Neurology*. Mar 1992;42(3 Pt 1):647-651.
54. Tringali S, Perrot X, Collet L, Moulin A. Repetitive transcranial magnetic stimulation: hearing safety considerations. *Brain Stimul*. Jul 26 2011.
55. Kung S, Ahuja Y, Iezzi R, Sampson SM. Posterior vitreous detachment and retinal tear after repetitive transcranial magnetic stimulation. *Brain Stimul*. Sep 6 2011.
56. Sakkas P, Mihalopoulou P, Mourtzouhou P, et al. Induction of mania by rTMS: report of two cases. *Eur Psychiatry*. Jun 2003;18(4):196-198.
57. Xia G, Gajwani P, Muzina DJ, et al. Treatment-emergent mania in unipolar and bipolar depression: focus on repetitive transcranial magnetic stimulation. *Int J Neuropsychopharmacol*. Feb 2008;11(1):119-130.

Contraindicated drugs are listed in **Appendix H - List of Exclusionary Drugs**

MagVenture rTMS solution

- for advanced clinical research, requiring double blinded testing.

System Setup

MagVenture's rTMS solution includes a complete setup including magnetic stimulator, comfortable chair, head rest system, motor threshold determination, head caps, positioning/repositioning system, fixation of magnetic coil, sham concept and magnetic coil.



MagPro R30



The MagPro R30 is an advanced high performance magnetic stimulator designed primarily for clinical use. The stimulator is often used for Transcranial Magnetic Stimulation (TMS) and repetitive Transcranial Magnetic Stimulation (rTMS) research.

With the repetition rate up to 30 pulses per second the MagPro R30 covers most protocol settings.

List of Core Specifications and Features

- Repetition Rate up to 30 pulses per second
- Pulse width 280 μ s with Biphasic Waveform
- Pulses in Train: 1-1000
- Number of Trains: 1-500
- Inter Train Interval: 1-120s

Treatment Chair



For optimal comfort a chair is part of the solution.
Possible to adjust seat height and tilting for best possible comfort.

Head rest for easy positioning of patient head during treatment.

Only 85 kg.

Airpump and Vacuum pillow



Airpump unit for vacuum pillows for easy support of patients head during magnetic stimulation.

The vacuum pillow consists of an airtight shell containing granules of polystyrene.



Super Flexible Arm

The flexible arm is used for easy positioning of the coil.

The arm has three joints. Two ball joints, of which two can rotate in multiple directions and one central joint can rotate in one direction. All three joints can be locked and unlocked by a single grip on the central handle. This allows a very flexible positioning of the coils.



Trolley



A Trolley is available to ease the mobility of the MagPro R30 stimulator.

For installations in countries with 100-120V mains, the 110V/230V Power Supply Option must be used.



Motor Threshold (MT)

As an important part of all research and clinical studies the Motor Threshold (MT) level for the patient must be determined.

To determine the motor threshold the C-B60 Coil is used for stimulating the motor cortex and the MEP Monitor for measurement of the resulting Motor Evoked Potential.

C-B60 Coil

Before performing the research study with the Cool-B65-A/P Coil the motor threshold for each patient must be found.

For this purpose the C-B60 Coil can be used. The magnetic field from this coil is equal to the active side of the Cool-B65-A/P Coil.

Built-in amplitude controls on the coil handle. This together with the small weight makes it very flexible and easy to operate with one hand.

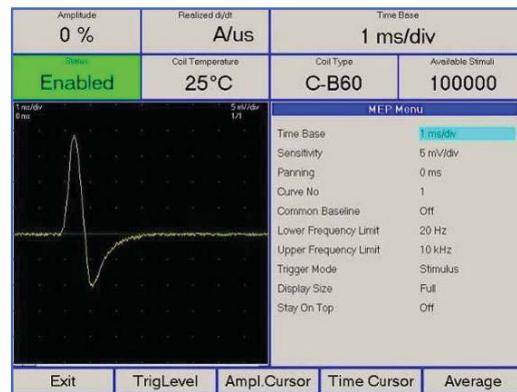
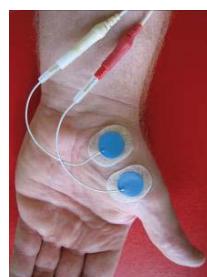
- Max initial dB/dt: 32 kT/s near the coil surface
- Active pulse width: 280 μ s (Biphasic)



MEP Monitor

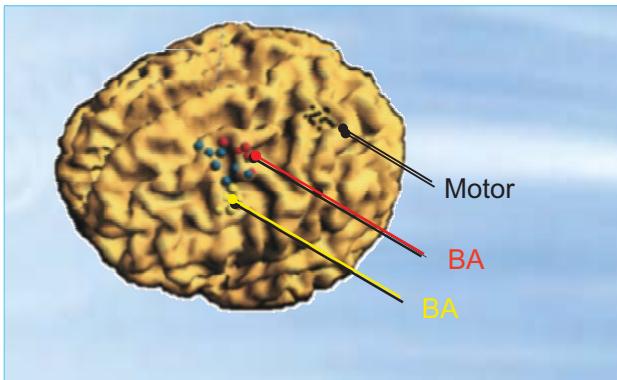


With this 1 channel EMG Amplifier connected to the MagPro it is possible to measure the Motor Evoked Potential (MEP) signals. With the MEP Monitor it is easy to find the motor threshold level.



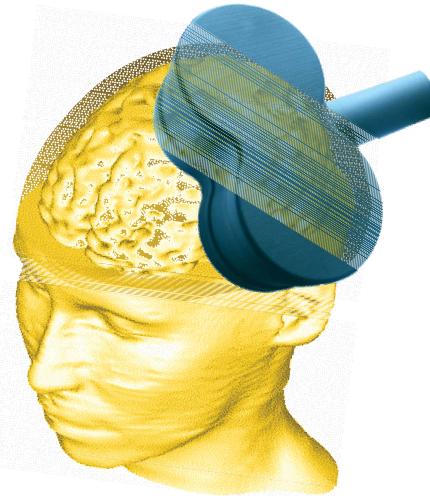
Positioning / Repositioning concept

For treatment of depression with rTMS the stimulation is applied over the dorsolateral prefrontal cortex (DLPFC). The treatment sessions normally takes 30-40 minutes and is repeated 10-20 times for each patient with one session per day.



Target: DLPFC-Brodman area

Location of Cool-B65 A/P coil



MagVentures solution is a simple, rugged, cost effective and easy to use design.

- Fixation of the coil during treatment with use of a strong and flexible arm.
- Determination of DLPFC area during motor threshold measurement based on “5 cm” rule. Possibility to use 4.5 cm, 5.5 cm and 6 cm steps too depending of patient head size.
- Simple, fast and easy to operate. Operational by nursing staff.
- Use of personal cap for each patient. Caps in different sizes to fit different head sizes.
- Cost effective solution compared to real navigation systems.
- Adjustable chair for optimal comfort of patient during treatment.
- Use of vacuum pillow to fixate the patients head.
- Complete system and chair are mobile and possible to move around. Low weight compared to systems with special “dental” chair and big navigation system.
- Coil positioning/repositioning within $\pm 10\text{mm}$ accuracy possible.

Head caps



Textile head caps available in different sizes to fit different head sizes.

One head cap is selected for each patient.

The head cap will be used during the motor threshold determination and marking of the treatment spot.

Procedure for marking of the treatment spot during Motor Threshold determination

During the Motor Threshold determination the later treatment spot (5 cm rule) is marked on the head cap by use of a coil C-B60 with special marking plate.

For positioning the coil on the head of the patient a bathing cap made of silicone is used. The cap has fixation mark on the front which is placed in line with the nasion. The cap is wrapped back on the head of the patient and it is secured that the cap is tight on to the front of the skull. The cap has a fold in the centre from front to back. This fold must follow the patient heads centerline.

The distance from the edge of the cap in front to the nasion is measured and documented for the patient. A good idea is to write the distance on the cap on the front. This distance must be controlled at each session for the patient for right location of cap.

Procedure:

- The patient is placed in the treatment chair
- The patients head size is measured or estimated in order to select a proper head cap size
- The head cap is mounted on the patient
- Check that the centerline on the cap is in line with the patients head
- The distance from nasion to the head cap is measured and noted. Use of glasses can help measure this distance for untrained users. A good idea is to write the distance on the cap on the front. This distance must be controlled at each session for the patient for right location of cap.
- The motor threshold point and MT level is now to be found by using a C-B60 coil with the special marking plate mounted upon it. A MEP-unit can optionally be used to monitor EMG-activity on APB. Make sure the coil is rotated in a 45° angle to the centerline of the head.
- The MT stimulation level is noted
- Using the marking plate on the C-B60 coil the stimulation point is marked with a thin felt tip pen.
- This marking will be used to positioning and repositioning the Cool-B65 A/P coil during following treatments.



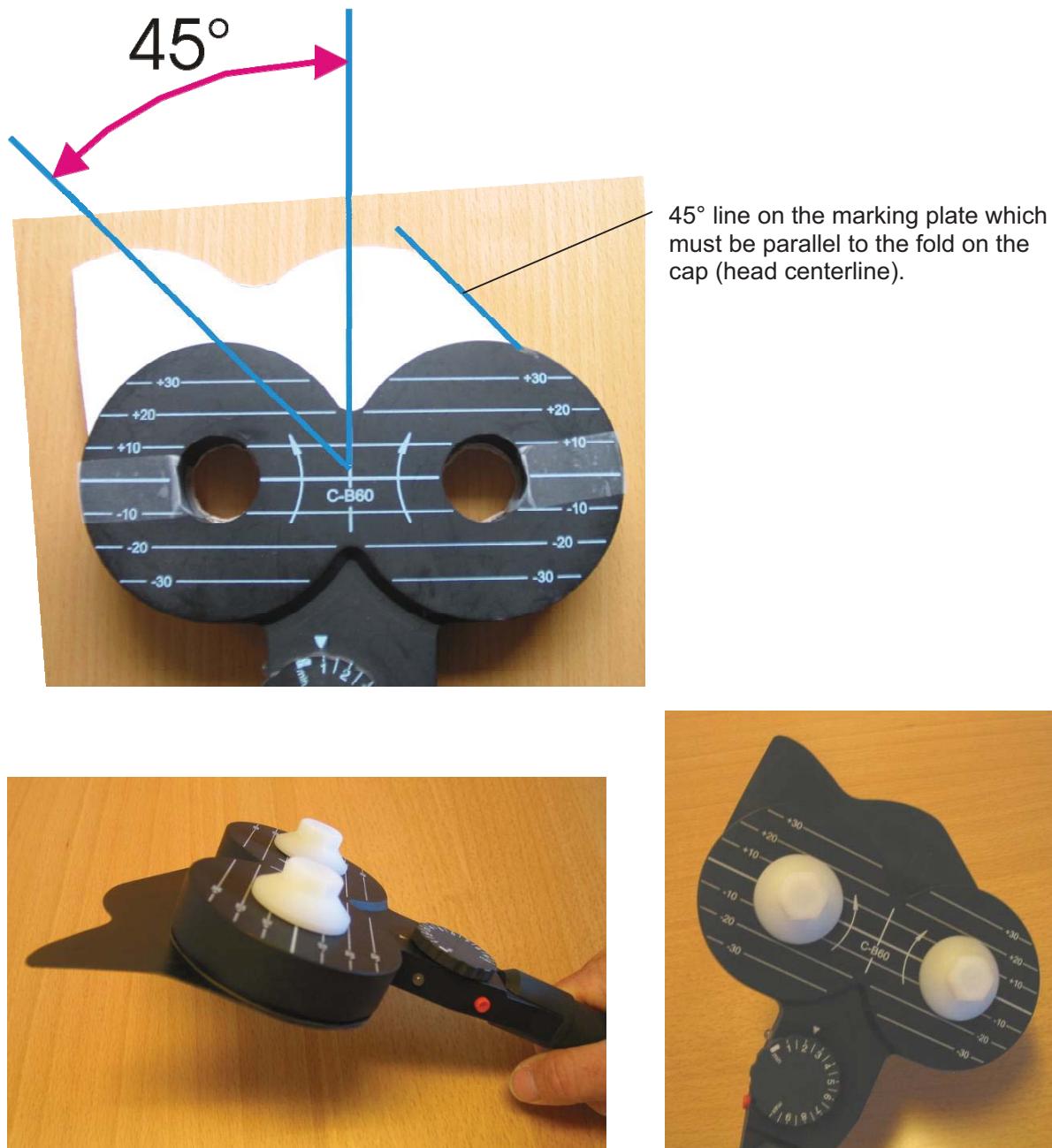
Measurement of distance to nasion



Marking of treatment spot

Coil C-B60 with marking plate

The marking plate is mounted on the C-B60 coil in an angle of 45° to the centerline on the top of the head.



Cool-B65-A/P Coil

The Cool-B65-A/P Coil is especially designed for advanced clinical studies where double blinded research experiments are required. The Cool-B65-A/P is capable to be used both as an active (A) coil and as a placebo (P) coil, without operator or patient knowledge.

The Cool-B65-A/P Coil is based on the Cool-B65 Coil. The Cool-B65 Coil has been on the market for more than 4 years and is used for many applications requiring a high number of stimuli, e.g. Treatment of Depression.

Cool-B65



Cool-B65-A/P



- The Cool-B65-A/P has a symmetrical mechanical design and no labeling on the coil indicating the active or placebo side. With this setup it is not possible for the operator to see or hear which side is used.
- Built-in orientation switch, used for the software to determine which side the operator shall use
- Output for current stimulation surface electrodes
- Max initial dB/dt: 32 kT/s near the coil surface on the active side, same as Cool-B65 Coil.
- The magnetic field near the coil surface on the placebo side is <5% of active side
- Active pulse width: 280µs (Biphasic)
- Protocol: 2pps Setup: Output=100%:
Number of stimulations before warm-up: > 20,000 pulses
- Typical Protocol: 60 trains @ 50 pulses/train @ 10pps @ Inter Train Interval: 25s @ Output=120% of MT.
Performance: Number of stimulations before warm-up: > 10,000 pulses (i.e. more than 3 patients on a row).
- Larger ergonomic handle
- All cables and cooling tubes combined in one cable

Lifetime



Due to mechanical, magnetically and thermal stress on the coil-winding inside the Cool-B65-A/P Coil, the lifetime of the coil is limited.

The lifetime is defined as maximum 5 years or Equivalent Pulse Value (EPV) of maximum 18.000.000 stimulations whichever occurs first.

When the coil reach the limit it will stop working and it has to be replaced with a new coil. The coil is handled as "electronic waste" and is not serviceable when it has reached the limit.

The EPV value is dependent on stimulation current waveform and amplitude. See example below.

Running a protocol of 3000 pulses at 75% MagPro indicated output power, using standard biphasic pulses:

The EPV is 4, and the 3000 pulses is equivalent to 12.000 EPV's. Providing a lifetime of 4.500.000 stimuli corresponding to 1.500 run of the protocol !

Benefits with Cool-B65-A/P for placebo studies

- It is possible with same coil to perform active stimulation and placebo stimulation
- No change in mechanical design and weight from side to side
- No change in sound level during stimulation in active and placebo mode
- Heating up of the coil is the same in active and placebo mode
- No labeling on the coil telling which is active side and which is placebo side
- Output current stimulator for surface electrodes on the patient for sensory sham

External Cooler Unit



- The Cool-B65-A/P is connected to an external Cooler Unit for circulation of liquid fluid as cooling media.
- Low noise system with very high performance.

Sham Noise Generator



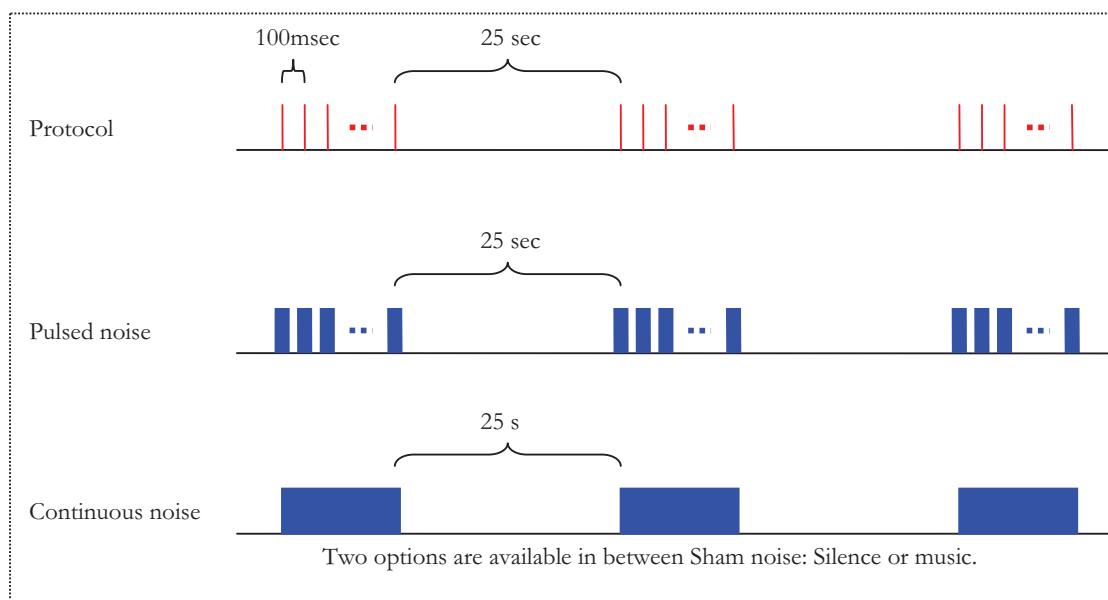
The sound level from the coil during active stimulation and placebo is the same. But to sham the noise during the operation 100%, both patient and operator are connected to the Sham Noise Generator.

Headsets on both patient and operator are connected to the Sham Noise Generator. When a magnetic stimulation pulse is fired; a pulse of sham noise is send into the ears. This sham noise pulse will hide the click noise from the coil for the patient and operator; even at 100% stimulus intensity.

Use your ipod, and connect it to the Sham Noise Generator to make the patient feel comfortable with music during the treatment.



Earphone Headset



With the Sham Noise Generator it is possible to adjust the sound volume of the white noise and the duration of the pulse.

Constant Current Stimulation of skin



The Cool-B65-A/P Coil has a current stimulation outlet for surface electrodes. With this setup it is possible to place electrodes on the patient skin beneath the magnetic stimulation coil.

A current stimulation pulse will be sent to the electrodes synchronous with the magnetic stimulation, giving a sensory feeling in the skin for the patient, again to sham the use of placebo side or active side.



Procedure for treatment sessions

- The patient is placed in the treatment chair
- The treatment program is loaded into the MagPro
- Surface electrodes (2) are placed on the patient's left forehead above the eyebrows
- The patients dedicated treatment cap is placed symmetrically on the head.
- The patient is now to be rested in the treatment chair.
- The patient takes on the headset from the sham noise generator
- The patients head and neck is now fixed by positioning and activating the vacuum pillow.
- The Cool-B65 A/P-coil must turn right according to the instructions indicated on the display either: "Coil Ready" or "Flip coil"
- The Cool-B65 A/P-coil is now positioned by adjusting the mechanical arm to the marking on the cap.
- The stimulation level is adjusted as prescribed in the treatment protocol
- The stimulation sequence can now begin, and the operator should regularly visual control that the stimulation point is maintained.
- After treatment session the MagPro is disabled and Exit is pressed
- The coil is removed from the head and the cap can be removed from the head and stored until the next treatment.



Setting up double blinded studies

For clinical research, double blinded studies are often required to verify the efficacy of the selected methods and protocols. Since magnetic stimulation is a technique, producing a remarkably sound, vibration and sensation, blinding of the patient and the person administering the treatment is difficult. The rTMS solution from MagVenture offers a variety of means to accomplish the blinding:

“Blinding” of the patient...

It is a preferred method to adjust the amplitude of the magnetic field, used for rTMS, in a fixed relation to the motor threshold (MT) of the individual patient. Finding the MT is well described in the literature, and can easily be done by the use of e.g. the C-B60 coil shown above. If required, connect the APB to the input of the build-in EMG-amplifier (MEP-unit) to identify the response. Then slowly turn up the amplitude of the MagPro to find the threshold.

Finding the individual MT is associated with a distinct sensation with the patient. Thus, continuing with providing a treatment or sham immediately after finding the MT might lead to some discussion with the patient as to whether or not the treatment is “felt at all”. And in this way there is a risk of jeopardizing the actual “blinding” of the experiment. However, if the MT is established in a separate session, this discussion can be somewhat attenuated.

In order not to damage the patients hearing, the patient should wear some means of ear protection during the treatment. To blind the patient to the acoustic click noise originating from the stimulus, we encourage the use of “sham noise”. The “Sham Noise Generator” shown above generates a short pulse of white noise every time a stimulus is provided, thus masking the click noise from the coil. This amazing effect is very effective and masks the clicking sound all the way up to a 100% stimulator output.

The sound and the sound level from the A/P-coil during Active-stimulation or Sham-stimulation is the same.

The magnetic field originating from the stimulation coil stimulates a mild skin sensation when passing from the coil winding in to the brain. When using sham stimulation this effect is not present: To blind the patient to the sensation, a current stimulator is build in to the handle of the A/P-coil, and surface electrodes are placed just below the stimulation coil. For every magnetic stimulus a synchronous current stimulus is provided inducing an equivalent skin sensation. The current stimulator should be used both when using sham and active stimuli to insure blinding of the operator.

“Blinding” of the Operator....

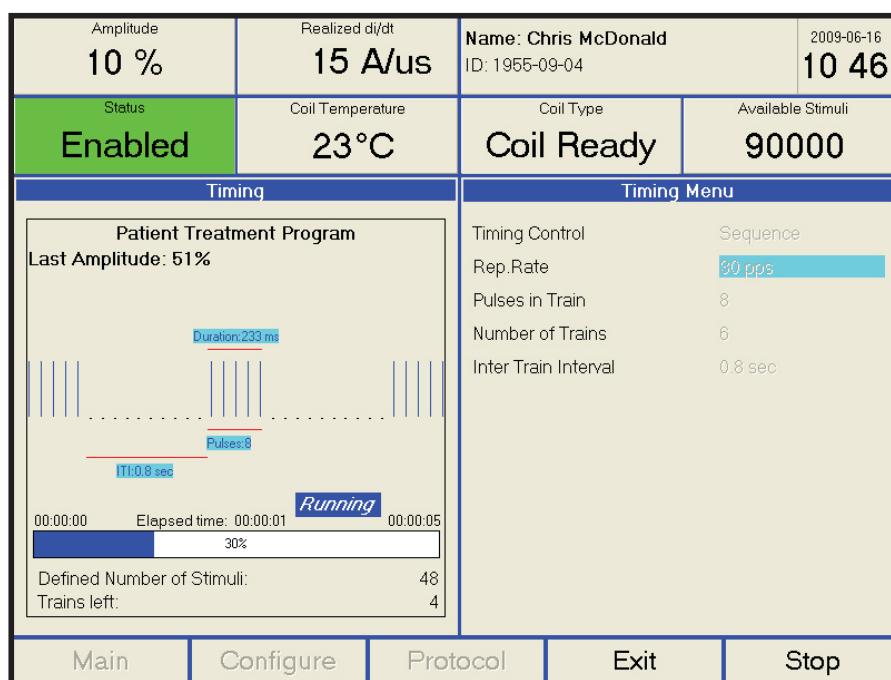
We encourage the use of the multifunctional liquid cooled A/P coil. As described above, the A/P coil provides Active or Placebo stimulation, depending on which side is turned up/down. The coil winding is placed near one side and turning this side against the patient induces active stimulation. In the opposing end of the coil housing a shielding system is integrated to attenuate the field and also to balance the weight of the coil. When the coil is flipped 180 degrees, the distance from the coil winding to the patients head is much increased. The resulting remaining magnetic field is attenuated by the shield, and less than 10% of the active field is left in the Sham position.

The encapsulation of the A/P-coil is completely symmetrical, with no markers revealing which side is active and which is sham.

The A/P coil is equipped with a small orientation-sensing device. This device reports to MagPro which side of the coil is turned towards the patient, and in this way MagPro can detect if active or sham treatment is taking place.

It is not possible to start the treatment before the correct coil is inserted and the correct side is turned towards the patient. The MagPro will display the messages “Incorrect Coil” and “Flip Coil” if the actual setup does not match the specified setup stored.

When the coil is in-place, the MagPro is enabled and the amplitude adjusted to the agreed amplitude. Pressing the Start button will initialize the full sequence. When the treatment is ended successfully (or interrupted for some reason), a line with treatment information is stored.



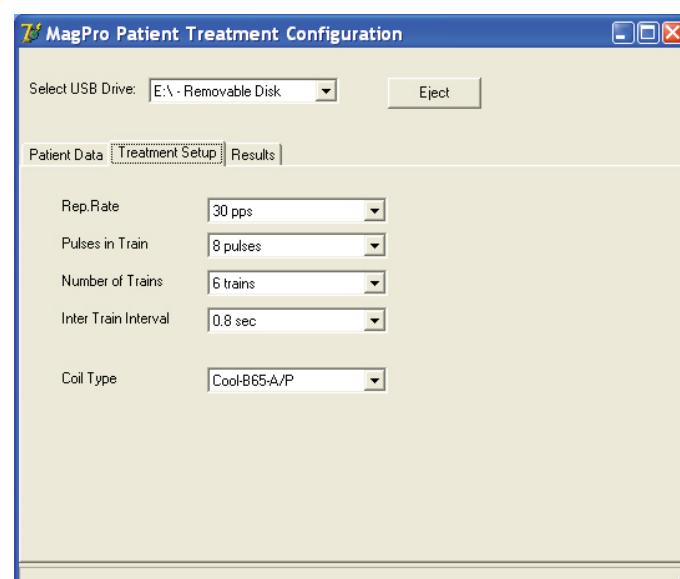
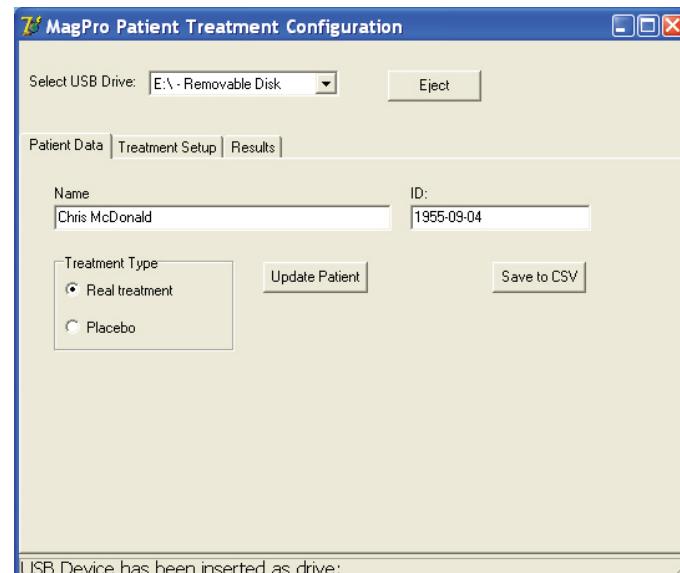
Controlling studies

When a clinical research project has been approved by local IRB's and the FDA the basic protocol parameters intended to be used in the study are usually fixed. From a device-point of view, this includes the magnetic pulse treatment parameters like number of pulse trains, total of number pulses, repetition rate, inter train interval, theta-burst pulse setup and relation to individual Motor Threshold. In some cases, also a specification of the type, form and size of coil.

Often a wide range of requirements must be fulfilled before a patient meets the pre-inclusion criteria's for the rTMS-study. Patients meeting such criteria's are usually referred to additional screening tests, and then it must be decided by the study-master if this patient should have sham or active treatment.

MagVenture offers a Program to control and configure the treatment and analyze the results. This program runs on a standard PC and allows the study-master to configure individual patients. On the first page (see right), the patient data are entered and it is selected if the treatment should be active or sham.

On the tab "Treatment Data" the basic settings are made (rep.rate coil type etc.). These settings are most likely to be identical for the full study and they are therefore saved after the first definition.



The tab “Results” is used by the study-master for analysis. Every line represents a session and clearly identifies the used settings, the amplitude, coil data and the number of stimuli provided.

At the Results tab a trace of every session is made. One line is added to the results file every time the treatment is ended or if the timing is for some reason interrupted.

MagPro Patient Treatment Configuration

Select USB Drive: E:\ - Removable Disk

Patient Data | Treatment Setup | **Results**

Date	Rep Rate	Pulses in train	Number of trains	Inter Train Interval	Coil Type	Amplitude	% fulfilled
2009-06-01	5 pps	10 pulses	5 trains	1.0 sec	Cool-B65-A/P	52%	100%
2009-06-02	5 pps	20 pulses	15 trains	10.0 sec	Cool-B65-A/P	51%	100%
2009-06-03	5 pps	30 pulses	25 trains	20.0 sec	Cool-B65-A/P	53%	100%
2009-06-04	5 pps	40 pulses	35 trains	30.0 sec	Cool-B65-A/P	52%	100%
2009-06-05	5 pps	50 pulses	45 trains	40.0 sec	Cool-B65-A/P	54%	100%
2009-06-06	5 pps	60 pulses	55 trains	50.0 sec	Cool-B65-A/P	50%	100%
2009-06-07	5 pps	70 pulses	65 trains	60.0 sec	Cool-B65-A/P	51%	100%
2009-06-08	5 pps	80 pulses	75 trains	70.0 sec	Cool-B65-A/P	53%	100%
2009-06-09	5 pps	90 pulses	85 trains	80.0 sec	Cool-B65-A/P	52%	100%
2009-06-10	5 pps	99 pulses	95 trains	90.0 sec	Cool-B65-A/P	51%	100%

APPENDIX H

LIST OF EXCLUSIONARY DRUGS

This list of exclusionary drugs shall be reviewed and updated as needed and at least annually based on new information such as new marketed drugs. Citations are available upon request.

Amoxapine

Bupropion (at doses >300mg/day)

Clomipramine

Clozapine

Dantrolene

Disulfiram

Flumazenil

Ginkgo Biloba

Ginseng

Haloperidol

Illicit Drugs

Heroin

Ecstasy

LSD

Other illicit drugs

Isoniazid

Ketamine

Levodopa

Lidocaine and other local anesthetics

Loxapine

Maprotiline

Mefenamic acid (>1000mg)

Meperidine

Nelarabine

Olanzapine

Phenothiazines

Chlorpromazine

Fluphenazine

Perphenazine

Prochlorperazine

Promethazine

Thioridazine

Trifluoperazine

Piroxicam (> 20mg)

Stimulants

Amphetamine

Armodafinil

Benzphetamine

Cocaine

Dexmethylphenidate

Dextroamphetamine

Diethylpropion

Ephedra /Ephedrine containing herbal products

Lisdexamfetamine

Methylphenidate
Methamphetamine
Modafinil
Phendimetrazine
Phencyclidine (PCP)
Phentermine
Phenylpropanolamine
Pseudoephedrine
St John's Wort
Theophylline
Tiagabine
Tramadol
Vincristine

APPENDIX I

SEIZURE PROTOCOL AND FOLLOW-UP

Seizure Protocol and Follow-Up Procedures

Managing emergencies (syncope and seizures)

First: Stop the TMS session and remove the coil

Each TMS laboratory must institute an explicit plan for dealing with syncope and seizures, and every member of the TMS team must be familiar with it. There must be a place where the subject can lie down. All team members must be familiar with the means of summoning emergency medical help and when to call for it. Additionally, in laboratories performing rTMS at >1Hz, life-support equipment should be available.

Syncope usually is very brief. Seizures potentially induced by TMS, as well as seizures in general, are also brief (typically < 60 s) and without serious physical sequelae. Thus, efforts should be focused on preventing complications of the seizure or syncope rather than starting any specific medication, which is not required unless status epilepticus (which has been never described following rTMS) occurs. In most cases it is enough to lay the subject down. Supine position with the legs elevated is appropriate for suspected syncope. In case of seizures, attention must be taken to minimize the risk of aspiration and left lateral decubitus position is desirable. The description of additional medical emergency procedures to treat seizure complications go beyond the scope of the current guidelines.

Subjects who experience seizures with rTMS should be informed of the fact that they are not at a greater risk for further seizures than before. For some individuals, however, the potential psychological effects of having had a seizure can be significant and should not be ignored or minimized. Informed consent documents discuss the possibility of a seizure, and investigators must ensure that the subjects understand its implications. Both medical and psychological support must be provided to patients and normal subjects who have rTMS-induced seizures.

It is possible that the report of a seizure in a patient's medical record could be misinterpreted or used as a pretext for the denial of employment or medical insurance. Subjects of research studies should be informed of this possibility, and investigators must make certain that documentation of seizures is done in such a way that jeopardizes subjects to the minimum extent possible. Additional documentary support of a healthy subject's claim that a provoked seizure carries no adverse prognosis must be provided when appropriate.

Protocol for seizures

All personnel conducting TMS studies must be familiar with the Lab Policy for a seizure.

Responding to a seizure-

Sample protocol (UC Irvine protocol, courtesy, Steve Cramer, MD)

- If alone, call for help—
- If two people are present, the first stays with the subject and the second should go to get a nurse, who will call 911
- Immediately page MD if not physically present
- Remove harmful objects from the person's surrounding area
- If the person is in a chair, gently pull chair back away from metal instruments
- Loosen tight clothing from around the neck
- Cushion the head as much as possible
- Do NOT place fingers or any other objects in or near the person's mouth
- Do not attempt to hold the person down
- Remain calm, seizures almost always stop after a few minutes
- Observe what is happening, how long, etc—this can help the person later
- If a person is having trouble breathing, turn them on their side, provide oxygen mask
- After a seizure, stay with the person until paramedics arrive
- If there is concern for injury, do not move the person

Safety Equipment

Basic BLS supplies

Oxygen

Face masks

Crash cart-with medications readily available

Follow-up seizures

After a patient has been stabilized from a seizure during a TMS treatment, a neurologist will need to be contacted immediately, and the patient will be seen by a neurologist as soon as possible. Additionally, patients will have the following blood chemistries drawn as ordered by the MD.

Full metabolic screen (CBC, serum electrolytes including calcium and potassium)

Serum prolactin level, with the time noted when the serum was drawn relative to the seizure (that is, how many minutes or hours after the seizure was the sample drawn).

A urine sample should be collected and sent for a urine drug screen

The neurologist will likely schedule the patient for a brain scan (MRI or CT) and an EEG.

The above workup may provide an understanding of precipitating factors involved in the seizure, and whether follow-up care is needed.

If the workup is unrevealing, then it would be assumed that this was a TMS induced seizure with no sequelae, and a letter can be sent to the patient as in the Appendix.

If at any point during study participation, a participant has a seizure (not including syncope), that participant will be withdrawn from study treatments immediately (they will still be followed for protocol assessments). All seizures (not including syncope) will be considered serious adverse events and as such, will be reported using **Form 37 Adverse Event** in SharePoint and IRB **Form 119 Report of Serious Adverse Events and Unanticipated Problems** to the VA Central IRB using its website for the most-recent version:

<http://www.research.va.gov/vacentralirb/forms/investigator-forms.cfm>

What follows is a proposed letter to patient regarding seizure from the rTMS study.

Attachment: Letter to patients regarding seizure

Dear (patient's name)

On ____ (date) you experienced a seizure after you were given a study treatment of repeated transcranial magnetic stimulation (rTMS) as part of CSP #556, "The Effectiveness of rTMS in Depressed VA Patients". This letter is provided to explain the seizure occurrence to you and other health care providers.

Although seizures are rare when patients receive rTMS, they may occur. We assure you that this seizure probably occurred as result of the experimental treatment and does not indicate that you have any disease or other health or physical problem.

Please contact us at _____ if you have any further questions regarding this event.

Appendix J

Removed

APPENDIX K

rTMS TREATMENT REGIMEN

APPENDIX K: rTMS TREATMENT REGIMEN

This appendix contains the procedure for the administration of rTMS treatment, including subject preparation, determination of motor threshold, and the actual administration of the stimulus. Additional information on the rTMS device, coils, chair; and equipment; cap marking system; rTMS Research Software; MEP Monitor; and Sham Noise Generator; can be found in the manufacturer's datasheets. See Appendix G Device Information.

1. Procedures Prior to Treatment Administration

There will be a number of procedures that will occur prior to treatment:

- The patient will be asked to remove glasses, earrings or any jewelry around the neck.
- The patient will remove wallets from their pockets if they contain magnetic media (e.g., credit cards).
- The patient will empty their bladder to avoid treatment interruption.
- The patient will be provided with ear protection.
- It will be necessary to determine motor threshold for each patient before starting the course of treatment:
 - The SI will locate and determine the Motor Threshold (MT) as part of the Screening Phase. The marking cap system is used for repeatability of the coil placement.
 - On the first day prior to the first treatment, the administrator will determine the MT. The actual "hands on" procedures will be

standardized by training provided to each administrator prior to the start of the study.

- In addition to the initial determination of MT, it will also be determined at the first session of each 5-session block and of each taper treatment block.

2. *Motor Threshold location and determination*

To determine the necessary level of power that must be used, the establishment of a “motor threshold” (MT) is the most commonly employed technique (Kiers et al. 1993; Pridmore et al. 1998). The MT is usually defined as the minimum amount of electricity needed to produce movement in the contralateral thumb, when the coil is placed in the appropriate spot over the primary motor cortex (Pascual-Leone et al. 1993). The MT determining method has been improved with the use of an electromyograph (EMG) that is easier to teach, train, and operationalize than the visual method. In the recently completed NIH TMS trial, 3 of 4 sites used the EMG method, while one site used visual movement. The TMS vendor has incorporated a sophisticated EMG system within the TMS device and will provide the necessary software. A procedure called Maximum-Likelihood Strategy using Parameter Estimation by Sequential Testing MLS-PEST is a mathematical algorithm that is a promising alternative to traditional, time-consuming methods for determining MT. Because the EMG-PEST method is totally automated, it may prove useful in studies using MT as a quickly changing variable, as well as in large-scale clinical trials (Mishory et al. 2004). Dr. George’s Brain Stimulation Lab has developed simple algorithms to use with the EMG system that can make MT determination rather rapid (8 pulses) and highly reproducible, essentially reducing and eliminating operator error, and almost like an automatic blood pressure cuff.

MT will be determined using Motor Evoked Potential (MEP) and the Parametric Estimation by Sequential Testing (PEST) procedure along with the CB60 coil. Refer to the MEP Monitor Use Guide in Appendix G Device Information.

3. *Treatment Administration*

Treatment will be administered following these procedures:

- A qualified registered nurse, nurse practitioner, or physician assistant will administer the treatment as well as determine all MT's, except for the one done at screening.
- The treatment administrator and all study personnel will be masked to the treatment.
- All treatments will be conducted in a business-like manner minimizing personal contact with the patient.
- The Cool-B65 A/P coil is used for treatments.
- The treatment location will be 6 cm anterior (i.e., forward) to the hand motor area stimulation point identified above, on a para-sagittal line, using the marking cap procedure.
- The rTMS device utilized will have a rigid arm-holder for positioning the rTMS coil on the person's head, and a head-holding system to maintain consistent and reproducible head orientation through the multiple treatment sessions.
- The rTMS treatment and sham group will receive the following dose of rTMS delivered over the left prefrontal cortex:
 - Power: 120% of motor threshold as separately determined for each participant prior to treatment/placebo sessions.
 - Pulse frequency: 10 Hz
 - Length of each pulse train: 4 seconds
 - Time between pulse trains: 10 seconds

- Length of treatment: 25 minutes
- Units of 5 sessions will be delivered over one week's time. These units of 5 sessions can be delivered over a minimum of 5 calendar days and a maximum of 12 calendar days.
- Patients will receive a minimum of 20 sessions of treatment and a maximum of 30 sessions. This will total 4000 pulses per session or 80,000 pulses for 20 sessions or 120,000 pulses for total 30 sessions, respectively.
- For those individuals not showing clinical response, they will continue getting their initial treatment (sham or active) up to 30 sessions maximum.
- Although the treatment will be administered at 120% MT, at the beginning of each treatment session, and after a treatment pause, there will be a 'ramp up' beginning at 80% of the therapeutic dose and increasing by 5% with each pulse train to facilitate comfort of the subject. The treatment will require one 25 minute session per day.

4. Monitoring for Adverse Events

- Possible Seizure Activity.
 - During the treatment procedure, the treatment administrator must observe the patient closely for any sign of imminent seizure activity or muscle twitching. The administrator must be an individual trained to be perceptive to warning signs, and familiar with the emergency management of seizure activity. Emergency equipment (oxygen, suction, CPR equipment) must be readily available for the treatment suite.

- Other Adverse Events.
 - During the treatment procedure, the administrator will assess for and record any adverse events.
 - Prior to leaving the facility following each treatment, the patient will be assessed for the occurrence of adverse events by a qualified individual who is masked to the subject's assigned treatment group.
 - Patient should be routinely queried at each visit as to whether they have experienced any adverse events. Reports of significant, possible related adverse events such as changes in hearing or vision should prompt adverse event reporting and further evaluation to ensure that no patient is placed at excessive risk.

5. *Interruptions*

Every attempt shall be made to complete each treatment session as per the protocol. Interruptions during the treatment are allowed as needed for patient comfort or convenience by using the “pause” selection on the device. However, in the event that an incomplete treatment is given, this information will be recorded. Total number of treatments will be recorded. Since this is an “intent to treat” design, patients that miss treatments are not removed from the study. However, post-hoc analyses will examine the effects of compliance on overall outcome.

6. *Evaluations*

Patients are first tested for “remission” after the first 20 sessions of treatment and then again at the 25th and 30th sessions. Remission is defined as a decrease in Hamilton Rating Scale for Depression *to 10 or less*. If a patient enters “remission” after 20 sessions, then they enter a 24-week follow-up period. If a patient does not enter “remission” at the end of 20 sessions, they are offered an additional 5 sessions of treatment and retested for “remission.” This procedure may continue for a

maximum of 10 additional sessions resulting in a total of 30 sessions. Patients who do not show a treatment response at the end of 30 sessions of treatment or who drop out during treatment will be considered a treatment “failure”.

At the end of the acute treatment phase, all patients will be entered into a 24 week follow-up phase. Participants who remit will receive a 3 week treatment taper at the beginning of the follow-up phase. The taper will include 3 treatment sessions in the first week, 2 in the second week and 1 in the last week of the taper.

7. *Sham (Control) rTMS Treatment*

Sham (Control) treatment will be accomplished by using the Cool-B65-A/P coil that functions both as an active (A) and placebo (P) coil. It has a symmetrical mechanical design and no labeling on the coil indicates the active or placebo side. Consequently it is not possible for the operator to see or hear which side is used.

8. *Masking*

Every attempt will be made to mask the patient and the treatment administrator to the treatment group assignment, as will all personnel at each clinical site. Each site will be supplied with 2 coils; one C-B60 coil for MT determination and one Cool-B65 A/P coil for treatment.

Additionally, for each treatment session, whether sham or active, each patient shall wear scalp electrodes through which, in the case of sham treatments, a low-voltage, low electric current (2 – 20ma at no more than 100V) will be passed in order to provide cutaneous stimulation that mimics the sensation of actual rTMS. At the same time, the Sham Noise Generator is used in order to hide the click noise. When a magnetic stimulation pulse is fired, white noise is sent to the ears of the patient. This sham noise pulse will hide the click noise from the coil for the patient. The treatment administrator also receives the sham noise.

To further assess the adequacy of the mask, rTMS administrators, clinical raters, and patients will complete a Control Questionnaire at the time of the final study visit to assess their “best guess” as to treatment condition, and their level of confidence in

this guess. Successful blinding of experienced rTMS administrators determined to break the blind with this method has been piloted by Drs. George and Nahas, and found to be successful.

APPENDIX L

Ethics: Belmont Report

The Belmont Report

Office of the Secretary

Ethical Principles and Guidelines for the Protection of Human Subjects of Research

The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

April 18, 1979

AGENCY: Department of Health, Education, and Welfare.

ACTION: Notice of Report for Public Comment.

SUMMARY: On July 12, 1974, the National Research Act (Pub. L. 93-348) was signed into law, thereby creating the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. One of the charges to the Commission was to identify the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects and to develop guidelines which should be followed to assure that such research is conducted in accordance with those principles. In carrying out the above, the Commission was directed to consider: **(i)** the boundaries between biomedical and behavioral research and the accepted and routine practice of medicine, **(ii)** the role of assessment of risk-benefit criteria in the determination of the appropriateness of research involving human subjects, **(iii)** appropriate guidelines for the selection of human subjects for participation in such research and **(iv)** the nature and definition of informed consent in various research settings.

The Belmont Report attempts to summarize the basic ethical principles identified by the Commission in the course of its deliberations. It is the outgrowth of an intensive four-day period of discussions that were held in February 1976 at the Smithsonian Institution's Belmont Conference Center supplemented by the monthly deliberations of the Commission that were held over a period of nearly four years. It is a statement of basic ethical principles and guidelines that should assist in resolving the ethical problems that surround the conduct of research with human subjects. By publishing the Report in the Federal Register, and providing reprints upon request, the Secretary intends that it may be made readily available to scientists, members of Institutional Review Boards, and Federal employees. The two-volume Appendix, containing the lengthy reports of experts and specialists who assisted the Commission in fulfilling this part of its charge, is available as DHEW Publication No. (OS) 78-0013 and No. (OS) 78-0014, for sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402.

Unlike most other reports of the Commission, the Belmont Report does not make specific recommendations for administrative action by the Secretary of Health, Education, and Welfare. Rather, the Commission recommended that the Belmont Report be adopted in its entirety, as a statement of the Department's policy. The Department requests public comment on this recommendation.

**National Commission for the Protection of Human Subjects
of Biomedical and Behavioral Research**

Members of the Commission

Kenneth John Ryan, M.D., Chairman, Chief of Staff, Boston Hospital for Women.

Joseph V. Brady, Ph.D., Professor of Behavioral Biology, Johns Hopkins University.

Robert E. Cooke, M.D., President, Medical College of Pennsylvania.

Dorothy I. Height, President, National Council of Negro Women, Inc.

Albert R. Jonsen, Ph.D., Associate Professor of Bioethics, University of California at San Francisco.

Patricia King, J.D., Associate Professor of Law, Georgetown University Law Center.

Karen Lebacqz, Ph.D., Associate Professor of Christian Ethics, Pacific School of Religion.

**** David W. Louisell, J.D., Professor of Law, University of California at Berkeley.*

Donald W. Seldin, M.D., Professor and Chairman, Department of Internal Medicine, University of Texas at Dallas.

****Eliot Stellar, Ph.D., Provost of the University and Professor of Physiological Psychology, University of Pennsylvania.*

**** Robert H. Turtle, LL.B., Attorney, VomBaur, Coburn, Simmons & Turtle, Washington, D.C.*

**** Deceased.*

Table of Contents

Ethical Principles and Guidelines for Research Involving Human Subjects

A. Boundaries Between Practice and Research

B. Basic Ethical Principles

1. Respect for Persons
2. Beneficence
3. Justice

C. Applications

1. Informed Consent
2. Assessment of Risk and Benefits
3. Selection of Subjects

Ethical Principles & Guidelines for Research Involving Human Subjects

Scientific research has produced substantial social benefits. It has also posed some troubling ethical questions. Public attention was drawn to these questions by reported abuses of human subjects in biomedical experiments, especially during the Second World War. During the Nuremberg War Crime Trials, the Nuremberg code was drafted as a set of standards for judging physicians and scientists who had conducted biomedical experiments on concentration camp prisoners. This code became the prototype of many later codes⁽¹⁾ intended to assure that research involving human subjects would be carried out in an ethical manner.

The codes consist of rules, some general, others specific, that guide the investigators or the reviewers of research in their work. Such rules often are inadequate to cover complex situations; at times they come into conflict, and they are frequently difficult to interpret or apply. Broader ethical principles will provide a basis on which specific rules may be formulated, criticized and interpreted.

Three principles, or general prescriptive judgments, that are relevant to research involving human subjects are identified in this statement. Other principles may also be relevant. These three are comprehensive, however, and are stated at a level of generalization that should assist scientists, subjects, reviewers and interested citizens to understand the ethical issues inherent in research involving human subjects. These principles cannot always be applied so as to resolve beyond dispute particular ethical problems. The objective is to provide an analytical framework that will guide the resolution of ethical problems arising from research involving human subjects.

This statement consists of a distinction between research and practice, a discussion of the three basic ethical principles, and remarks about the application of these principles.

Part A: Boundaries Between Practice & Research

A. Boundaries Between Practice and Research

It is important to distinguish between biomedical and behavioral research, on the one hand, and the practice of accepted therapy on the other, in order to know what activities ought to undergo review for the protection of human subjects of research. The distinction between research and practice is blurred partly because both often occur together (as in research designed to evaluate a therapy) and partly because notable departures from standard practice are often called "experimental" when the terms "experimental" and "research" are not carefully defined.

For the most part, the term "practice" refers to interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success. The purpose of medical or behavioral practice is to provide diagnosis, preventive treatment or therapy to particular individuals.⁽²⁾ By contrast, the term "research" designates an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge (expressed, for example, in theories, principles, and

statements of relationships). Research is usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective.

When a clinician departs in a significant way from standard or accepted practice, the innovation does not, in and of itself, constitute research. The fact that a procedure is "experimental," in the sense of new, untested or different, does not automatically place it in the category of research. Radically new procedures of this description should, however, be made the object of formal research at an early stage in order to determine whether they are safe and effective. Thus, it is the responsibility of medical practice committees, for example, to insist that a major innovation be incorporated into a formal research project.⁽³⁾

Research and practice may be carried on together when research is designed to evaluate the safety and efficacy of a therapy. This need not cause any confusion regarding whether or not the activity requires review; the general rule is that if there is any element of research in an activity, that activity should undergo review for the protection of human subjects.

Part B: Basic Ethical Principles

B. Basic Ethical Principles

The expression "basic ethical principles" refers to those general judgments that serve as a basic justification for the many particular ethical prescriptions and evaluations of human actions. Three basic principles, among those generally accepted in our cultural tradition, are particularly relevant to the ethics of research involving human subjects: the principles of respect of persons, beneficence and justice.

1. Respect for Persons.—Respect for persons incorporates at least two ethical convictions: first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection. The principle of respect for persons thus divides into two separate moral requirements: the requirement to acknowledge autonomy and the requirement to protect those with diminished autonomy.

An autonomous person is an individual capable of deliberation about personal goals and of acting under the direction of such deliberation. To respect autonomy is to give weight to autonomous persons' considered opinions and choices while refraining from obstructing their actions unless they are clearly detrimental to others. To show lack of respect for an autonomous agent is to repudiate that person's considered judgments, to deny an individual the freedom to act on those considered judgments, or to withhold information necessary to make a considered judgment, when there are no compelling reasons to do so.

However, not every human being is capable of self-determination. The capacity for self-determination matures during an individual's life, and some individuals lose this capacity wholly or in part because of illness, mental disability, or circumstances that severely restrict liberty. Respect for the immature and the incapacitated may require protecting them as they mature or while they are incapacitated.

Some persons are in need of extensive protection, even to the point of excluding them from activities which may harm them; other persons require little protection beyond making sure they undertake activities freely and with awareness of possible adverse consequence. The extent of protection afforded should depend upon the risk of harm and the likelihood of benefit. The judgment that any individual lacks autonomy should be periodically reevaluated and will vary in different situations.

In most cases of research involving human subjects, respect for persons demands that subjects enter into the research voluntarily and with adequate information. In some situations, however, application of the principle is not obvious. The involvement of prisoners as subjects of research provides an instructive example. On the one hand, it would seem that the principle of respect for persons requires that prisoners not be deprived of the opportunity to volunteer for research. On the other hand, under prison conditions they may be subtly coerced or unduly influenced to engage in research activities for which they would not otherwise volunteer. Respect for persons would then dictate that prisoners be protected. Whether to allow prisoners to "volunteer" or to "protect" them presents a dilemma. Respecting persons, in most hard cases, is often a matter of balancing competing claims urged by the principle of respect itself.

2. Beneficence.—Persons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well-being. Such treatment falls under the principle of beneficence. The term "beneficence" is often understood to cover acts of kindness or charity that go beyond strict obligation. In this document, beneficence is understood in a stronger sense, as an obligation. Two general rules have been formulated as complementary expressions of beneficent actions in this sense: **(1)** do not harm and **(2)** maximize possible benefits and minimize possible harms.

The Hippocratic maxim "do no harm" has long been a fundamental principle of medical ethics. Claude Bernard extended it to the realm of research, saying that one should not injure one person regardless of the benefits that might come to others. However, even avoiding harm requires learning what is harmful; and, in the process of obtaining this information, persons may be exposed to risk of harm. Further, the Hippocratic Oath requires physicians to benefit their patients "according to their best judgment." Learning what will in fact benefit may require exposing persons to risk. The problem posed by these imperatives is to decide when it is justifiable to seek certain benefits despite the risks involved, and when the benefits should be foregone because of the risks.

The obligations of beneficence affect both individual investigators and society at large, because they extend both to particular research projects and to the entire enterprise of research. In the case of particular projects, investigators and members of their institutions are obliged to give forethought to the maximization of benefits and the reduction of risk that might occur from the research investigation. In the case of scientific research in general, members of the larger society are obliged to recognize the longer term benefits and risks that may result from the improvement of knowledge and from the development of novel medical, psychotherapeutic, and social procedures.

The principle of beneficence often occupies a well-defined justifying role in many areas of research involving human subjects. An example is found in research involving children. Effective ways of treating childhood diseases and fostering healthy development are benefits that serve to justify research involving children—even when individual research subjects are not direct beneficiaries. Research also makes it possible to avoid the harm that may result from the application of previously accepted routine practices that on closer investigation turn out to be dangerous. But the role of the principle of beneficence is not always so unambiguous. A difficult ethical problem remains, for example, about research that presents more than minimal risk without immediate prospect of direct benefit to the children involved. Some have argued that such research is inadmissible, while others have pointed out that this limit would rule out much research promising great benefit to children in the future. Here again, as with all hard cases, the different claims covered by the principle of beneficence may come into conflict and force difficult choices.

3. Justice.—Who ought to receive the benefits of research and bear its burdens? This is a question of justice, in the sense of "fairness in distribution" or "what is deserved." An injustice occurs when some benefit to which a person is entitled is denied without good reason or when some burden is imposed unduly. Another way of conceiving the principle of justice is that equals ought to be treated equally. However, this statement requires explication. Who is equal and who is unequal? What considerations justify departure from equal distribution? Almost all commentators allow that distinctions based on experience, age, deprivation, competence, merit and position do sometimes constitute criteria justifying differential treatment for certain purposes. It is necessary, then, to explain in what respects people should be treated equally. There are several widely accepted formulations of just ways to distribute burdens and benefits. Each formulation mentions some relevant property on the basis of which burdens and benefits should be distributed. These formulations are (1) to each person an equal share, (2) to each person according to individual need, (3) to each person according to individual effort, (4) to each person according to societal contribution, and (5) to each person according to merit.

Questions of justice have long been associated with social practices such as punishment, taxation and political representation. Until recently these questions have not generally been associated with scientific research. However, they are foreshadowed even in the earliest reflections on the ethics of research involving human subjects. For example, during the 19th and early 20th centuries the burdens of serving as research subjects fell largely upon poor ward patients, while the benefits of improved medical care flowed primarily to private patients. Subsequently, the exploitation of unwilling prisoners as research subjects in Nazi concentration camps was condemned as a particularly flagrant injustice. In this country, in the 1940's, the Tuskegee syphilis study used disadvantaged, rural black men to study the untreated course of a disease that is by no means confined to that population. These subjects were deprived of demonstrably effective treatment in order not to interrupt the project, long after such treatment became generally available.

Against this historical background, it can be seen how conceptions of justice are relevant to research involving human subjects. For example, the selection of research subjects needs to be scrutinized in order to determine whether some classes (e.g., welfare patients, particular racial and ethnic minorities, or persons confined to institutions) are being systematically selected

simply because of their easy availability, their compromised position, or their manipulability, rather than for reasons directly related to the problem being studied. Finally, whenever research supported by public funds leads to the development of therapeutic devices and procedures, justice demands both that these not provide advantages only to those who can afford them and that such research should not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research.

Part C: Applications

C. Applications

Applications of the general principles to the conduct of research leads to consideration of the following requirements: informed consent, risk/benefit assessment, and the selection of subjects of research.

1. Informed Consent.—Respect for persons requires that subjects, to the degree that they are capable, be given the opportunity to choose what shall or shall not happen to them. This opportunity is provided when adequate standards for informed consent are satisfied.

While the importance of informed consent is unquestioned, controversy prevails over the nature and possibility of an informed consent. Nonetheless, there is widespread agreement that the consent process can be analyzed as containing three elements: information, comprehension and voluntariness.

Information. Most codes of research establish specific items for disclosure intended to assure that subjects are given sufficient information. These items generally include: the research procedure, their purposes, risks and anticipated benefits, alternative procedures (where therapy is involved), and a statement offering the subject the opportunity to ask questions and to withdraw at any time from the research. Additional items have been proposed, including how subjects are selected, the person responsible for the research, etc.

However, a simple listing of items does not answer the question of what the standard should be for judging how much and what sort of information should be provided. One standard frequently invoked in medical practice, namely the information commonly provided by practitioners in the field or in the locale, is inadequate since research takes place precisely when a common understanding does not exist. Another standard, currently popular in malpractice law, requires the practitioner to reveal the information that reasonable persons would wish to know in order to make a decision regarding their care. This, too, seems insufficient since the research subject, being in essence a volunteer, may wish to know considerably more about risks gratuitously undertaken than do patients who deliver themselves into the hand of a clinician for needed care. It may be that a standard of "the reasonable volunteer" should be proposed: the extent and nature of information should be such that persons, knowing that the procedure is neither necessary for their care nor perhaps fully understood, can decide whether they wish to participate in the furthering of knowledge. Even when some direct benefit to them is anticipated, the subjects should understand clearly the range of risk and the voluntary nature of participation.

A special problem of consent arises where informing subjects of some pertinent aspect of the research is likely to impair the validity of the research. In many cases, it is sufficient to

CSP#556 "The Effectiveness of rTMS in Depressed VA Patients"

Version 4.0, September 2013

Appendix L, Ethics: Belmont Report

indicate to subjects that they are being invited to participate in research of which some features will not be revealed until the research is concluded. In all cases of research involving incomplete disclosure, such research is justified only if it is clear that (1) incomplete disclosure is truly necessary to accomplish the goals of the research, (2) there are no undisclosed risks to subjects that are more than minimal, and (3) there is an adequate plan for debriefing subjects, when appropriate, and for dissemination of research results to them. Information about risks should never be withheld for the purpose of eliciting the cooperation of subjects, and truthful answers should always be given to direct questions about the research. Care should be taken to distinguish cases in which disclosure would destroy or invalidate the research from cases in which disclosure would simply inconvenience the investigator.

Comprehension. The manner and context in which information is conveyed is as important as the information itself. For example, presenting information in a disorganized and rapid fashion, allowing too little time for consideration or curtailing opportunities for questioning, all may adversely affect a subject's ability to make an informed choice.

Because the subject's ability to understand is a function of intelligence, rationality, maturity and language, it is necessary to adapt the presentation of the information to the subject's capacities. Investigators are responsible for ascertaining that the subject has comprehended the information. While there is always an obligation to ascertain that the information about risk to subjects is complete and adequately comprehended, when the risks are more serious, that obligation increases. On occasion, it may be suitable to give some oral or written tests of comprehension.

Special provision may need to be made when comprehension is severely limited—for example, by conditions of immaturity or mental disability. Each class of subjects that one might consider as incompetent (e.g., infants and young children, mentally disable patients, the terminally ill and the comatose) should be considered on its own terms. Even for these persons, however, respect requires giving them the opportunity to choose to the extent they are able, whether or not to participate in research. The objections of these subjects to involvement should be honored, unless the research entails providing them a therapy unavailable elsewhere. Respect for persons also requires seeking the permission of other parties in order to protect the subjects from harm. Such persons are thus respected both by acknowledging their own wishes and by the use of third parties to protect them from harm.

The third parties chosen should be those who are most likely to understand the incompetent subject's situation and to act in that person's best interest. The person authorized to act on behalf of the subject should be given an opportunity to observe the research as it proceeds in order to be able to withdraw the subject from the research, if such action appears in the subject's best interest.

Voluntariness. An agreement to participate in research constitutes a valid consent only if voluntarily given. This element of informed consent requires conditions free of coercion and undue influence. Coercion occurs when an overt threat of harm is intentionally presented by one person to another in order to obtain compliance. Undue influence, by contrast, occurs through an offer of an excessive, unwarranted, inappropriate or improper reward or other overture in order

to obtain compliance. Also, inducements that would ordinarily be acceptable may become undue influences if the subject is especially vulnerable.

Unjustifiable pressures usually occur when persons in positions of authority or commanding influence—especially where possible sanctions are involved—urge a course of action for a subject. A continuum of such influencing factors exists, however, and it is impossible to state precisely where justifiable persuasion ends and undue influence begins. But undue influence would include actions such as manipulating a person's choice through the controlling influence of a close relative and threatening to withdraw health services to which an individual would otherwise be entitled.

2. Assessment of Risks and Benefits.—The assessment of risks and benefits requires a careful arrayal of relevant data, including, in some cases, alternative ways of obtaining the benefits sought in the research. Thus, the assessment presents both an opportunity and a responsibility to gather systematic and comprehensive information about proposed research. For the investigator, it is a means to examine whether the proposed research is properly designed. For a review committee, it is a method for determining whether the risks that will be presented to subjects are justified. For prospective subjects, the assessment will assist the determination whether or not to participate.

The Nature and Scope of Risks and Benefits. The requirement that research be justified on the basis of a favorable risk/benefit assessment bears a close relation to the principle of beneficence, just as the moral requirement that informed consent be obtained is derived primarily from the principle of respect for persons. The term "risk" refers to a possibility that harm may occur. However, when expressions such as "small risk" or "high risk" are used, they usually refer (often ambiguously) both to the chance (probability) of experiencing a harm and the severity (magnitude) of the envisioned harm.

The term "benefit" is used in the research context to refer to something of positive value related to health or welfare. Unlike, "risk," "benefit" is not a term that expresses probabilities. Risk is properly contrasted to probability of benefits, and benefits are properly contrasted with harms rather than risks of harm. Accordingly, so-called risk/benefit assessments are concerned with the probabilities and magnitudes of possible harm and anticipated benefits. Many kinds of possible harms and benefits need to be taken into account. There are, for example, risks of psychological harm, physical harm, legal harm, social harm and economic harm and the corresponding benefits. While the most likely types of harms to research subjects are those of psychological or physical pain or injury, other possible kinds should not be overlooked.

Risks and benefits of research may affect the individual subjects, the families of the individual subjects, and society at large (or special groups of subjects in society). Previous codes and Federal regulations have required that risks to subjects be outweighed by the sum of both the anticipated benefit to the subject, if any, and the anticipated benefit to society in the form of knowledge to be gained from the research. In balancing these different elements, the risks and benefits affecting the immediate research subject will normally carry special weight. On the other hand, interests other than those of the subject may on some occasions be sufficient by themselves to justify the risks involved in the research, so long as the subjects' rights have been

protected. Beneficence thus requires that we protect against risk of harm to subjects and also that we be concerned about the loss of the substantial benefits that might be gained from research.

The Systematic Assessment of Risks and Benefits. It is commonly said that benefits and risks must be "balanced" and shown to be "in a favorable ratio." The metaphorical character of these terms draws attention to the difficulty of making precise judgments. Only on rare occasions will quantitative techniques be available for the scrutiny of research protocols. However, the idea of systematic, nonarbitrary analysis of risks and benefits should be emulated insofar as possible. This ideal requires those making decisions about the justifiability of research to be thorough in the accumulation and assessment of information about all aspects of the research, and to consider alternatives systematically. This procedure renders the assessment of research more rigorous and precise, while making communication between review board members and investigators less subject to misinterpretation, misinformation and conflicting judgments. Thus, there should first be a determination of the validity of the presuppositions of the research; then the nature, probability and magnitude of risk should be distinguished with as much clarity as possible. The method of ascertaining risks should be explicit, especially where there is no alternative to the use of such vague categories as small or slight risk. It should also be determined whether an investigator's estimates of the probability of harm or benefits are reasonable, as judged by known facts or other available studies.

Finally, assessment of the justifiability of research should reflect at least the following considerations: **(i)** Brutal or inhumane treatment of human subjects is never morally justified. **(ii)** Risks should be reduced to those necessary to achieve the research objective. It should be determined whether it is in fact necessary to use human subjects at all. Risk can perhaps never be entirely eliminated, but it can often be reduced by careful attention to alternative procedures. **(iii)** When research involves significant risk of serious impairment, review committees should be extraordinarily insistent on the justification of the risk (looking usually to the likelihood of benefit to the subject—or, in some rare cases, to the manifest voluntariness of the participation). **(iv)** When vulnerable populations are involved in research, the appropriateness of involving them should itself be demonstrated. A number of variables go into such judgments, including the nature and degree of risk, the condition of the particular population involved, and the nature and level of the anticipated benefits. **(v)** Relevant risks and benefits must be thoroughly arrayed in documents and procedures used in the informed consent process.

3. Selection of Subjects.—Just as the principle of respect for persons finds expression in the requirements for consent, and the principle of beneficence in risk/benefit assessment, the principle of justice gives rise to moral requirements that there be fair procedures and outcomes in the selection of research subjects.

Justice is relevant to the selection of subjects of research at two levels: the social and the individual. Individual justice in the selection of subjects would require that researchers exhibit fairness: thus, they should not offer potentially beneficial research only to some patients who are in their favor or select only "undesirable" persons for risky research. Social justice requires that distinction be drawn between classes of subjects that ought, and ought not, to participate in any particular kind of research, based on the ability of members of that class to bear burdens and on the appropriateness of placing further burdens on already burdened persons. Thus, it can be

considered a matter of social justice that there is an order of preference in the selection of classes of subjects (e.g., adults before children) and that some classes of potential subjects (e.g., the institutionalized mentally infirm or prisoners) may be involved as research subjects, if at all, only on certain conditions.

Injustice may appear in the selection of subjects, even if individual subjects are selected fairly by investigators and treated fairly in the course of research. Thus injustice arises from social, racial, sexual and cultural biases institutionalized in society. Thus, even if individual researchers are treating their research subjects fairly, and even if IRBs are taking care to assure that subjects are selected fairly within a particular institution, unjust social patterns may nevertheless appear in the overall distribution of the burdens and benefits of research. Although individual institutions or investigators may not be able to resolve a problem that is pervasive in their social setting, they can consider distributive justice in selecting research subjects.

Some populations, especially institutionalized ones, are already burdened in many ways by their infirmities and environments. When research is proposed that involves risks and does not include a therapeutic component, other less burdened classes of persons should be called upon first to accept these risks of research, except where the research is directly related to the specific conditions of the class involved. Also, even though public funds for research may often flow in the same directions as public funds for health care, it seems unfair that populations dependent on public health care constitute a pool of preferred research subjects if more advantaged populations are likely to be the recipients of the benefits.

One special instance of injustice results from the involvement of vulnerable subjects. Certain groups, such as racial minorities, the economically disadvantaged, the very sick, and the institutionalized may continually be sought as research subjects, owing to their ready availability in settings where research is conducted. Given their dependent status and their frequently compromised capacity for free consent, they should be protected against the danger of being involved in research solely for administrative convenience, or because they are easy to manipulate as a result of their illness or socioeconomic condition.

⁽¹⁾ Since 1945, various codes for the proper and responsible conduct of human experimentation in medical research have been adopted by different organizations. The best known of these codes are the Nuremberg Code of 1947, the Helsinki Declaration of 1964 (revised in 1975), and the 1971 Guidelines (codified into Federal Regulations in 1974) issued by the U.S. Department of Health, Education, and Welfare Codes for the conduct of social and behavioral research have also been adopted, the best known being that of the American Psychological Association, published in 1973.

⁽²⁾ Although practice usually involves interventions designed solely to enhance the well-being of a particular individual, interventions are sometimes applied to one individual for the enhancement of the well-being of another (e.g., blood donation, skin grafts, organ transplants) or an intervention may have the dual purpose of enhancing the well-being of a particular individual, and, at the same time, providing some benefit to others (e.g., vaccination, which protects both the person who is vaccinated and society generally). The fact that some forms of practice have elements other than immediate benefit to the individual receiving an intervention, however, should not confuse the general distinction between research and practice. Even when a procedure applied in practice may benefit some other person, it remains an intervention designed to enhance the well-being of a particular individual or groups of individuals; thus, it is practice and need not be reviewed as research.

⁽³⁾ Because the problems related to social experimentation may differ substantially from those of biomedical and behavioral research, the Commission specifically declines to make any policy determination regarding such research at this time. Rather, the Commission believes that the problem ought to be addressed by one of its successor bodies.

APPENDIX M

HEALTH ECONOMICS AND COST ANALYSIS

A. Overview

The proposed project will compare the effectiveness of rTMS to that of sham-rTMS among patients with treatment-resistant major depression participating in CSP 556. The economic analysis will comprise three parts: (1) cost-identification analysis to document the cost of the intervention; (2) a cost-consequences analysis to estimate its impact in both short- and long-term time horizons (i.e., 24-weeks post-treatment, and 4- to 12-months post-treatment, respectively); and (3) a cost-effectiveness analysis for rTMS therapy. The intervention cost-identification analysis will document the expected cost of the intervention to the VA in a typical site. The cost-consequences analysis will compare the difference in average total and average variable costs of care during a one-year period between rTMS therapy and usual outpatient depression care for treatment-resistant patients. The cost-effectiveness analysis will calculate the average incremental treatment cost per incremental depression remission for these same participants and time period. Remission is defined as a Hamilton depression score less than 10.

An economic analysis is central to CSP 556, because any future plan to implement rTMS technology within VHA will require estimates of the expected investment cost for new equipment, staff time, and other resources and because any decision to invest substantial new resources into rTMS therapy may depend on its expected effects on services utilization, cost, and patients' health status balanced against that investment.

A VA payer perspective will be adopted for the analyses. Although a broader societal viewpoint is often used in cost-effectiveness research,¹ the primary rationale for the economic analysis component in this study is to provide information to VA managers and administrators about the likely budgetary plus indirect health care resource impacts of rTMS implementation and diffusion. It is critical that VA administrators have preliminary evidence on economic impacts to inform their decisions about the extent and timing of any investment in rTMS technology. A secondary rationale is to demonstrate the cost-effectiveness of rTMS within an integrated system of care vis-à-vis usual care received by patients with treatment-resistant major depression. The planned cost-effectiveness analysis will provide information about the improvements in depressive symptoms that may result from an investment in rTMS as compared to standard care.

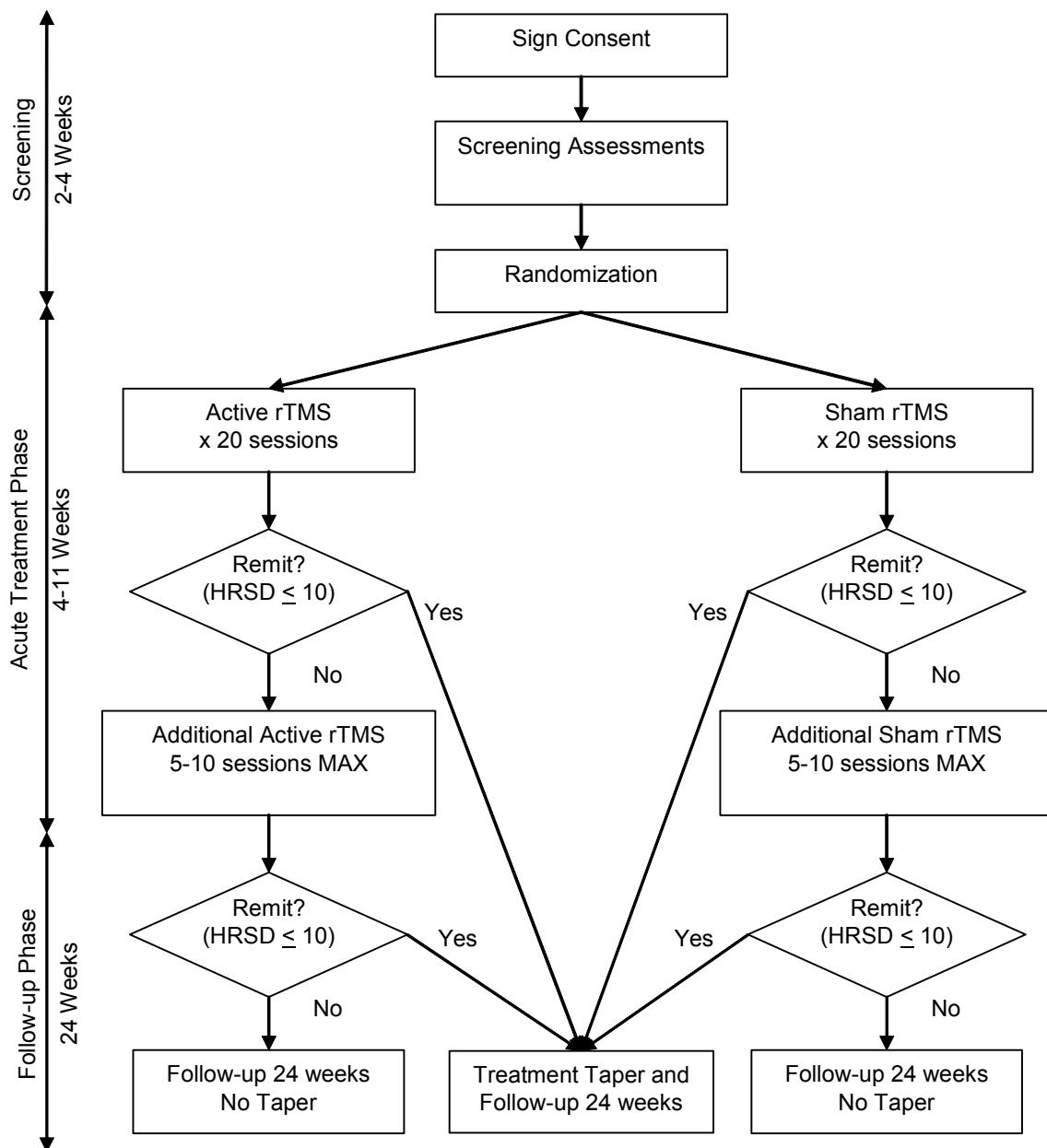
We will combine both micro-costing and gross (or "average") costing methodologies in deriving these cost estimates, as has been recommended for cost-effectiveness research in the

VA health care system.² We will use micro-costing methods to estimate the cost of rTMS therapy. We will use average costing methods for other health care costs. The more labor-intensive micro-costing method, where the quantity of each production input is counted, quantities are multiplied by input unit costs, and input costs are added together, is reserved for components of the analysis where precision is paramount or where alternatives are not available. Gross costing, where the average cost of finished products and services are used, is used for remaining components. Costs will be expressed in current-year dollars, or "nominal dollars". Past and future costs will be inflated and discounted, respectively, following recommended guidelines.

Three elements are needed to perform these cost and cost-effectiveness analyses: clinical outcomes, health care utilization data, and value data for assigning costs to utilization. The sources of information for these elements may be summarized as follows. Health outcomes will be determined from patient interviews. Health care utilization will be determined from national VA data systems and CSP study forms. Cost data will be extracted from national data systems when possible and from published sources or VA administrators as needed. The range of costs considered will include: direct inpatient and outpatient care costs; indirect costs for staff time; and direct and indirect costs associated with use of equipment and office space and with use of other physical and administrative resources.

A key component of the economic analysis is our strategy for estimating usual care costs in a comparison group representing "usual care." A customized imputation approach is required for this component, because the randomized trial does not include a "treatment as usual" study arm. Patients assigned to the trial's comparison or "placebo" group will receive sham rTMS. Sham treatment does not resemble usual care for treatment-resistant patients in the VA. Patients assigned to sham will attend up to 30 sham rTMS sessions (see **Figure 1**, "*Patient Flow in Study*"). Patients who do not achieve remission (HRSD<=10) after the first 20 sham rTMS sessions will attend additional sham rTMS sessions. Thus, the expected cost of usual care during the acute treatment phase of the trial, which will last from 4 to 11 weeks, must be imputed for all patients receiving sham rTMS. These imputed costs will be added together with actual costs during the follow-up phase to estimate the cost of usual care for treatment-resistant patients in the comparison group. We provide further details on the imputation method and related sensitivity analyses below.

Figure 1. Patient Flow in Study (in Main Proposal)



B. Objectives

It cannot be known *a priori* if rTMS therapy will increase or reduce usual VA health care costs associated with treatment-resistant depression. This innovation, rTMS, may increase costs during the acute treatment phase due to more frequent contact with outpatient providers, greater frequency of lab tests, use of an expensive rTMS medical device, and greater use of other resources. However, these extra costs could be partially or completely offset by savings from reduced likelihood of later hospitalization, reduced likelihood of receiving electroconvulsive therapy (ECT), reduced use of psychotropic medications, and/or reduced frequency of depression-related medical encounters. If rTMS therapy increases the likelihood of a full remission and/or reduces the likelihood of a recurrence, cost-offset effects will tend to accumulate over time. Because there is presently little evidence on the cost and effectiveness of rTMS in usual clinical settings, the magnitude of shorter and longer term potential cost differences between rTMS and usual care are unknown. Two hypotheses about the short-term (24-weeks post-treatment) and longer term (6- to 12-months post-treatment) cost consequences of rTMS therapy will therefore be tested:

1. Relative to usual care, total direct and indirect VA costs related to rTMS therapy for treatment-resistant depression will be less than total costs associated with usual care at 6-weeks post-treatment.
2. Relative to usual care, total direct and indirect VA costs related to rTMS therapy for treatment-resistant depression will be less than total costs associated with usual care at 6- to 12-months post-treatment.

The short-term 24-week period was chosen to coincide with the collection of clinical endpoints at the end of the CSP 556 follow-up phase. The longer term 6- to 12-month period was chosen to maximize the opportunity to observe cost offsets from rTMS. The reason for specifying 6- to 12-months rather than a single time period is that due to extant data lags we do not know in advance how long of a retrospective period will be available to us, given the potential variability in the timing of patient recruitment. Maximization of sample size is paramount to accurate cost estimation. Therefore, we will select the longest 6- to 12-month post-treatment period that will allow us to include the largest sample of study participants. We believe that nearly all patients will have completed treatment and will have 6-months post-treatment cost data available before the end of the three-year study. A longer cost consequence follow-up will be pursued, if the extant data are available. Cost consequences

results will be discussed in terms of statistical significance and the magnitude and types of differences (e.g., inpatient and outpatient).

We will then estimate the cost-effectiveness of rTMS therapy in producing a sustained remission from depression (HRSD \leq 10) at 24-weeks post-treatment. We will report the incremental cost of rTMS per incremental remission, which will provide a standardized measure of the cost-effectiveness of rTMS therapy relative to that of “usual outpatient care”. These estimates will allow us to test a third hypothesis:

3. Relative to usual care, rTMS therapy for treatment-resistant depression is cost-effective in producing a sustained remission from acute depressive symptoms, in outpatients.

We will calculate a 95% confidence region for all estimated cost-effectiveness ratios. The ratios will be discussed in light of the cost-effectiveness of antidepressant medication and ECT. Estimates for these alternative therapies are available from published studies.^{3, 4}

C. Background

1. Prevalence

In the VA there may be roughly 100,000 treatment-resistant patients.⁵⁻⁸ Prevalence estimates for treatment-resistant depression that are derived from general community samples indicate that up to 20% of patients with depression disorders are treatment-resistant.⁶⁻⁸ Even this number could underestimate the actual number of VA patients with treatment-resistant depression, where more difficult patients are often expected. First, many VA treatment-resistant patients may discontinue antidepressant medication use altogether, and therefore are not counted among current medication users. Second, the rate of treatment resistance among VA patients could be greater than in the community: VA patients could have higher rates of substance abuse and anxiety disorders, which are associated with higher rates of treatment resistance.⁹

2. Treatment Costs

Annual VA health care costs associated with treatment resistance among patients with depression could represent roughly \$580 million. In FY02, the VA spent approximately \$3 billion for medical and psychiatric care for patients with unipolar depression diagnoses, or approximately \$5,535 per depression patient.⁵ In community samples of patients with depression, health care costs among treatment-resistant patients are at least 2-times the mean costs of non-treatment-resistant patients.^{6, 7, 10, 11} This suggests treatment costs among

treatment-resistant patients in the VA could exceed the costs for non-treatment-resistant patients by more than \$5,800 per patient per year.

One goal of this proposed economic study is to establish some bounds for the likely cost impact of rTMS. The magnitude of any cost-offset depends on the effectiveness of rTMS compared with antidepressant or other therapy among treatment-resistant patients and on the relationship between depressive symptoms and services utilization. Recurrently elevated depressive symptoms may to some extent contribute to these patients' relatively higher psychiatric as well as general medical services costs. An effective therapy could potentially lower their psychiatric as well as their general medical care costs. However, these relationships have not been established in prior research, so the potential cost impacts of rTMS technology are unknown. Because of the extensive, standardized data systems in the VA, this investigation can be conducted during the CSP 556 trial.

A final important point is that an effective alternative to electro-convulsive therapy (ECT) would fill a void in the current VA treatment arsenal for patients who do not respond fully to antidepressant therapy. ECT is not offered at all VHA facilities. Access to ECT is also limited because of its high cost and because of administrative and logistical barriers, such as the need for ECT patients to receive anesthesia. rTMS could provide another treatment option, one that could be disseminated widely, both to larger as well as to smaller outpatient treatment settings. Thus, even though rTMS might increase VA's expenditures for depression care, rTMS could benefit the health of patients who currently have limited access to effective treatment.

3. Health Economics and Treatment Resistance

The health economics literature on treatment resistance consists of only a few studies. Virtually all have focused on its association with health care costs.^{6, 7, 10, 11} Prior studies have been based on estimates from private employer claims data, which may underestimate both its prevalence and its cost. The validity and reliability of measures of treatment resistance in administrative claims data have also not been verified. Obvious problems include reliance on an incomplete history of depression treatment, misidentification of depression based on claims diagnosis, and underreporting of depression diagnoses by physicians (e.g., due to concerns about insurance reimbursement). In the proposed CSP 556 study, treatment resistance will be determined through clinical interview, thereby allowing us to extend the literature on cost estimates using a more valid measure of cases. The correlation of clinical interview-based and administrative data-based case identification can also be examined, with estimates of the

systematic biases of claims-based case identification and associated costs of care derived from these data. These would be valuable contribution to this limited literature.

D. Analyses

1. Cost and Utilization Data

Data Sources. **Table 1** summarizes constituent components of utilization and cost and their corresponding data sources. Components are divided by whether they will be used to measure costs for active rTMS only (Tx Group = Active) or for both sham and active rTMS (Tx Group = Both). Health care utilization will be determined from national VA data systems, patient responses recorded on study forms, and study case report forms (adverse events, in particular). Cost estimates will be derived from national VA data systems, published sources, and accounting values provided by VA administrators.

We will use centralized VA databases to obtain the health care services used by the trial participants. From the database of VA inpatient hospital stays, the Patient Treatment File (PTF), we will obtain the date of discharge, days of stay in each ward (bedsection), including the number of days in intensive care, and the ICD-9 diagnoses (up to 10 codes) assigned to the stay. Then, we will obtain from the outpatient care file (OPC), the date of the visit, the location of care (stop code), and ICD-9 diagnoses (up to ten) and CPT codes (up to five) assigned to describe the visit and the type of provider. All major types of outpatient care are captured, including mental health and substance abuse as well as general medical services utilization. The cost of other care (including diagnostic tests) will be obtained from detailed utilization data, which is available from centralized VA Austin databases. National VA utilization databases (PTF and OPC) lack cost estimates, but they can be merged to the Health Economics Resource Center (HERC) average cost database, and accepted methods applied.

Table 1. Resource Utilization and Associated Costs

Tx Phase/Resource Category	Tx Group	Primary Source(s) and Notes
Pre-screening for patient safety	Active	Case report forms and provider wage rates
Treatment for rTMS-related adverse medical events	Active	Adverse events reporting forms, OPC and PTF, and administrative HERC files. We will link study data on adverse events with administrative data on services utilization and costs.
rTMS device and associated physical equipment costs	Active	Equipment prices will be obtained from study investigators. Average per session expense will be imputed using straight-line depreciation plus rental cost, with per session costs distributed across the equipment's useful lifetime.
Staff time during rTMS sessions	Active	Case report forms and provider wage rates
Staff time for planning ongoing rTMS care and for post-treatment services	Active	Provider reports
rTMS-related non-clinical administrative staff time	Active	Administrative staff reports
rTMS-related medical supplies	Active	Study investigators and administrative staff
rTMS-related electricity expense and other overhead	Active	Study investigators and administrative staff
Office space for rTMS sessions	Active	Study investigators and administrative staff. Imputed rental cost.
rTMS-related computer resource use	Active	Study investigators and administrative staff
Inpatient stays	Both	VA administrative HERC cost files
All non-rTMS outpatient visits	Both	VA administrative HERC cost files
Prescription medication	Both	DSS pharmacy extracts and Pharmacy Benefits Management (PBM) data.

Comparison of HERC & DSS Costs. Data from the VA administrative HERC average cost data files will be used to estimate most outpatient and inpatient costs.¹²⁻¹⁵ The HERC average cost data provide cost estimates; the true cost is unknown. For a second set of cost estimates, we will use the VA Decision Support System (DSS). DSS is a detailed cost allocation system that was implemented in 1997 across the VA. Although DSS is a sophisticated accounting tool that taps VA cost and utilization databases for “real time” managers’ use, its use by researchers is limited. Ongoing validation studies with DSS data show that the cost estimates need to be carefully reviewed to find administrative errors. Because DSS is not standardized nationally, we will use DSS as a secondary source of cost and utilization data in a sensitivity analysis. Recent research compared the HERC and DSS

cost estimates, and the research provides guidance on how to use DSS to test the sensitivity of the HERC data.¹⁶

Pharmacy Costs. The cost of outpatient prescription medications will come primarily from the DSS Pharmacy Extract. The DSS Pharmacy Extract is a relatively new data source that now covers all VA health care systems and medical centers. The DSS cost includes the medication and a dispensing fee that reflects labor and supply costs for the source of the prescription, either the VA study sites or the VA centralized mail order pharmacy. Preliminary analysis by VIREC suggests that these data are quite comparable to the VA Pharmacy Benefits Management (PBM) data, except that the PBM cost estimate does not include a dispensing fee. To verify the completeness and accuracy of DSS prescription records and associated costs, we will also access prescription data from the PBM database and compare them to DSS data. PBM prescription records could be more complete and accurate in some respects, particularly for inpatient stays. DSS inpatient pharmacy records have been aggregated; they contain one cost amount per day rather than separate records for each prescription. Also, we will compare PBM to DSS for reporting of diagnostic tests, which could be under-reported in DSS. Finally, we will compare the DSS pharmacy data with the study records on the dispensing of any medications to make sure that no double counting occurs.

2. *Identification of rTMS Intervention Costs*

The cost of the rTMS intervention will be estimated by aggregating the costs of component services and physical resources. Services costs will be derived from data on provider type, service type, and service duration using standard methods. Providers' nominal earnings will be multiplied by a loading factor (>1) to adjust for fringe benefit and overhead costs. Costs will be assigned to all physical resources, including donated office space and computer time, using standard resource valuation methods. The cost of physical resources (e.g., rTMS devices) will include depreciation costs plus the rental cost of capital. Resource prices will be obtained from published sources or will be obtained from VA administrators or resource suppliers.

3. *rTMS Cost Consequences*

We will estimate the average cost differences between active-rTMS and usual care during the acute treatment phase and the follow-up phase. Two analyses will be conducted, one for the period extending 24-weeks post-treatment and one for the period extending 6- to 12-months post-treatment. Total average direct and indirect health care costs for all inpatient and outpatient care will be included in our estimates. Will also produce separate estimates by study phase (treatment or follow-up), in order to isolate any post-treatment cost-offset effects. We will

collect utilization and cost data from HERC, DSS Pharmacy, PBM, and National Patient Care Database (OPC and PTF) files for at least a 30-month period, starting one year prior to the date of randomization and extending one year after the end of the treatment follow-up phase. For patients randomized to sham-rTMS, we will assume that health care utilization and costs during the post-treatment phase are representative of usual health care utilization and costs for these patients. An imputation approach (described in the next paragraph) will be used to estimate their cost of usual care during the acute treatment phase.

Usual Care Costs for Patients Randomized to Sham rTMS. As noted earlier, usual daily cost values will be imputed for patients in the comparison group. Imputation is necessary because our cost analysis requires an estimate of the difference between the cost of providing rTMS intervention and the cost of providing “usual services over a similar period of potential intervention time”. This “incremental cost” cannot be estimated by the difference in average health care costs during the acute treatment phase between the active- and sham-rTMS treatment groups. The estimator for the average incremental cost of rTMS can be expressed as $E(C | T_a) - E(C | T_u)$, where C is health care cost, T_a indicates receipt of active rTMS and T_u indicates receipt of usual care. In randomized trials, estimates of the second component of this expression, $E(C | T_u)$, are normally calculated as the average cost of care in the comparison group. In this trial that approach is problematic, because this trial will not include a “usual care” group, and the sham-rTMS group will potentially get protocol-driven additional days of care as compared to the active-rTMS group, if the latter is more effective.

Instead, we propose to estimate the cost of usual care for the sham-rTMS group during the pre-intervention acute treatment phase using HERC estimates of all (inpatient and outpatient) VA health care costs during the 6-month period immediately preceding the date of study recruitment. Using these cost estimates, we will calculate each patient’s *average estimated daily health care cost*. We will multiply these estimated daily cost values by the average duration (in days) of the acute treatment phase, measured from first to last day of rTMS therapy, among patients randomized to active-rTMS. The average duration represents the expected number of days of usual care that essentially will be foregone as a result of receiving active-rTMS. The product of the average daily health care cost value and the average duration will be our imputed value for the usual cost of care in the sham-rTMS treatment group during the acute treatment phase of the trial.

Mortality. Mortality information is potentially significant to this economic study because of the potential for patients who die to have very high health care costs just prior to expiring. Deaths will be identified by searching the VA Patient Treatment File and the VA Beneficiary

Identification and Record Locator System (BIRLS) death file. In sensitivity analyses, all analytical findings will be replicated leaving patients who died during the treatment or follow-up periods out of the analytical sample. The resulting estimates will be compared with results from the complete sample and any differences will be noted in our reporting of the research findings.

Inflation and Discounting. Dollar amounts in the study will be presented in terms of the price level as of the last year of data collection. We will adjust costs for inflation using the Consumer Price Index (CPI) for all urban consumers and all goods, the most common measure of nationwide inflation. The CPI is calculated on the basis of a basket of 305 items representing all goods and services purchased for everyday living by all urban residents. We will follow standard discounting methods, and discount health benefits and expenditures at a rate of 3% per year.¹ As noted earlier, HERC cost estimates are adjusted for regional differences in health care labor costs.

Discussion of the Rationale for Exclusion of non-VA Costs. As we noted above, we have chosen to limit our economic focus to VA health care costs only. Clearly, we have the opportunity to also collect data on non-VA health care costs. We recognize that a substantial proportion of these CSP 556 study participants' health care utilization may occur outside the VHA system and that it is generally desirable to measure non-VA treatment and caregiver costs. However, we believe that the gain in knowledge that could result from an effort to measure non-VA health care costs does not justify the additional research cost that would be required to obtain usable information on non-VA costs. In particular, we expect that Medicaid reimbursements account for a substantial proportion of non-VA expenditures among treatment-resistant VA patients. To obtain access to Medicaid data we would need to overcome numerous administrative hurdles, including gaining permission from each state's Medicaid agency. This has become a lengthy and sometimes infeasible process since the implementation of HIPAA privacy regulations. Access to private insurance claims is also potentially problematic, and working with claims from numerous private insurance carriers is onerous and labor intensive. Medicare files are available for VA patients, but Medicare may cover only a handful of patients in this study.

Estimation of non-VA patient and caregiver indirect costs is also potentially problematic, and therefore may not be justifiable given the required added research costs. Information on caregiver costs and patients' indirect costs is potentially unreliable due to several factors, including stigma associated with psychiatric problems and disability, difficult relationships between patients and family members, and cognitive problems. Although it is possible to address these issues through careful study planning and thorough data verification steps, the

additional expense and the risk that the resulting data would be incomplete and/or unreliable suggest that such an enterprise may not be justified in the current study.

4. Cost-Effectiveness Analysis

The remission outcomes data – where a sustained remission is defined as HRSD \leq 10 at 6-weeks post-treatment – will be used in conjunction with incremental treatment cost estimates to determine an incremental cost-effectiveness ratio (ICER) for the intervention. The resulting ICER will represent the estimated incremental cost per sustained remission, measured at 6-weeks post-treatment. The ratio will be expressed as: $ICER = [E(C | T_a) - E(C | T_u)] / [P(R | T_a) - P(R | T_u)]$, the difference in average acute treatment costs divided by the difference in probability of remission (R) between the two groups. Note that this assumes that the P(R) among patients receiving sham-rTMS is approximately equal to the probability of remission among usual care patients. A 95% confidence region surrounding cost-effectiveness ratios will be estimated using bootstrapping methods.¹⁷⁻¹⁹

The cost-effectiveness analysis could produce one of three major results: (1) rTMS may be cost neutral or less expensive and also more effective than usual depression care, indicating that its implementation is highly desirable; (2) rTMS might not be shown clinically effective in the VA, in which case its relative cost impact is irrelevant to VA decision-makers; (3) rTMS therapy will be more expensive than sham but will yield a greater likelihood of sustained remission. In this last case, the costs of a sustained remission will be compared with the cost of the main alternative treatment option, namely ECT. Estimates of ECT costs will be derived from the literature and from VA administrative sources.⁴

5. Sensitivity Analyses

We will test the sensitivity of our results to a number of assumptions. At a minimum, we expect them to include:

Discount and Inflation Rates. Costs incurred in earlier years must be inflated over time to maintain a steady level of purchasing power. They must also be inflated over time to reflect the discount rate, the rate at which people value money today over the same amount of money next year. The inflation rate, which we will measure by changes in the Consumer Price Index (CPI), could be varied in two ways for a sensitivity analysis. One is to use an alternative inflation measure, such as changes in the Gross Domestic Product Implicit Price deflator. We will use the CPI for main analyses and the Gross Domestic Product Implicit Price Deflator in the sensitivity analysis. A second approach is to vary the CPI by a small percentage, such as +/- 1.0% per year. Likewise, we will vary the assumed 3% discount rate by using alternative rates, such as 2% or 5%.

Usual Cost of Care. We will test our assumption that our imputed average costs in usual care for patients randomized to sham-rTMS are typical of treatment-resistant patients with major depression by comparing our average costs estimates for this group to a similar group of VA patients who are not participating in CSP 556. We will use Austin OPC-file data patients who were screened for participation in the study to estimate a propensity score for treatment-resistance among patients with a major depression diagnosis. The propensity score predictors will include an algorithm for possible treatment-resistance, which will be based on ICD-9 codes, number of changes in antidepressant medications in the past 12 months, treatment with a mood stabilizer, receipt of ECT, and other factors identified in extant studies.^{6, 7, 9, 10} Using this propensity score metric, we will identify treatment-resistant likely patients in the VA, and estimate their average health care costs and the variance of costs. Statistics for mean and variance will be compared with analogous sample parameters for patients randomized to sham. Based on these comparisons, we will define sensitivity ranges and apply them to our cost-effectiveness and cost-consequences estimates.

6. Power Analysis.

We do not present power analysis data. The extant literature provides too little information to make such an analysis informative. A key purpose of the cost-consequences analyses is to establish potential bounds for cost-offset effects resulting from rTMS, which are a necessary component of a power analysis. Also, the clinical study is adequately powered to detect a difference in health outcomes. We believe that an important finding of the economic study will be set of bounds for the potential cost-offsets that are associated with a depression remission among treatment-resistant patients with major depression. Whether or not these estimates reach statistical significance at conventional levels, they will provide critical information about the potential cost-effectiveness of expanded investment in emerging therapeutic technologies for treatment-resistant patients. They will be useful both in conducting future economic evaluation studies using the VA's large administrative databases as well as in ensuring that future cost-effectiveness studies in depression treatment are adequately powered.

E. Administrative policy

Economics data will be managed in the same way as the clinical data. We will adopt the same procedures and policies developed in the clinical study.

F. Project Coordination and Implementation Plan

1) Time Frame for Data Collection

The cost analysis will be conducted throughout the three-year RCT. The Gantt Chart describing the activities and the duration of each is shown below in **Table 2**.

Table 2 rTMS for Treatment-Resistant Major Depression Trial – Cost Analysis

Gantt Chart

Activity:	Year 1				Year 2				Year 3				Year 4				Year 5				Year 6				
	Quarter				Quarter				Quarter				Quarter				Quarter				Quarter				
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	
1. Establish data collection routine at local sites for Intervention Costs																									
2. Collect cost of production data on each subject																									
3. Extract prior-year VHA data for each enrolled subject																									
4. Extract post-year VHA data for each enrolled subject																									
5. Extract Medicare data for those using extensive non-VHA services																									
6. Analyze the cost of Intervention in each Facility																									
7. Analyze the healthcare use & cost in post-intervention year																									
8. Analyze the healthcare use & cost in pre- & post-intervention years																									
9. Analyze the cost-effectiveness																									
10. Prepare manuscripts, Final Report, etc.																									

2) Project Plan and Resource Requirements for Cost Analysis

The Cost Analysis Management Plan for this trial flows from the Gantt Chart of **Table 2**. Cost analysis will start prospective data collection of primary data collection concerning the intervention's implementation as soon as each site's IRB approves the study. In both study groups, the prior year of VHA utilization and VHA expenditures will be calculated to establish the pre-enrollment healthcare costs per patient and for each group. For each participant in the trial, VHA and Medicare utilization and expenses will be tracked and summarized for 6-months and one-year following their treatment follow-up date. For some portion of the sample, we anticipate having more than one-year of follow-up experience recorded in the AAC encounter data, which will permit modeling of longer-term impacts.

The cost analysis will be conducted centrally at the Perry Point Cooperative Studies Branch. The Investigator time will include: 12.5% of two Health Economists, and 80% of an advanced Outcomes Programmer throughout the six-year RCT. **At each site, the primary data**

collection effort will require 5% of a research coordinator to collect the Intervention's Costs of Implementation. This allows for the start-up and implementation period and the manuscript and final report generation periods in addition to the four-year data collection period described above in **Table 2**.

a) Investigative Team

Eric Slade, PhD is a Research Health Scientist at the MIRECC, VAMCS, Baltimore VAMC and is an Associate Professor in the Division of Services Research, Department of Psychiatry at the University of Maryland School of Medicine. He will serve as a Health Economist on the economic evaluation sub-study. His participation will require 12.5% FTE each year during the project. This will be Dr. Slade's first CSP project. He will collaborate with Dr. Bradham, who is on the same campus in the extraction and assembly of the necessary data for the planned analyses. He will assist in the development of the analytical products, manuscripts and final reports. Dr. Slade is currently engaged in numerous studies of mental health service use and cost, including several VA projects, and has more than 9 years of post-graduate experience as a health economist.

Douglas D. Bradham, Dr.P.H. is Associate Professor in the Department of Epidemiology and Preventive Medicine at the University of Maryland Medical School in Baltimore. He is a Senior CSP Health Economist located at the Perry Point CSP Coordinating Center and at the Baltimore VA Medical Center, which is the lead facility in the Veterans Affairs Maryland Health Care Systems (VAMHCS). Dr. Bradham is also the Director of The Capitol Network (VISN 5) HSR&D Center, located in the Baltimore-Washington regional area. His participation will require 12.5% FTE each year during the project. He will: (a) coordinate the extraction of the requisite data from the national VHA and Medicare data, and local VHA databases; (b) design the intervention cost-identification and healthcare use and expense identification analyses; (c) oversee the cost and use analyses; (d) collaborate with other investigators; (e) determine whether the Medicare data are warranted and obtain these Medicare data for each of these patient, where informed consents allow retrieval; and (f) consult with the Principal Investigators, investigators, data coordinators and others necessary to implement the cost analysis study. He will assist in the development of the analytical products, manuscripts and final reports.

Dr. Bradham has been engaged in the development of this project since the first planning meeting on May 9-10, 2005 and is fully committed to its success. Dr. Bradham has been conducting these types of health services impact studies since completing his doctoral work at the University of North Carolina in 1981 where he specialized in Health Economics and Health

Services Research. He has been at Baltimore since 1996 developing the infrastructure for HSR in VISN 5. He is an independently-funded investigator for VHA, and has been a member of the Scientific Review and Evaluation Boards for HSR&D and RR&D in the VHA. Dr. Bradham has been involved with CSP studies since 2001.

William J. Culpepper, MS, Ph.D. Candidate (80% FTE) - will provide expertise in: (a) extraction of the data from the national VHA and local VHA databases; (b) summarizing the intervention's healthcare use and expense identification process and analyses; (c) analyzing of both the cost and use analyses applying the HERC data and techniques; and (d) collaborate in the development of the manuscripts and reports. Mr. Culpepper had 10 years in outcomes research before joining Bradham in 2002, where he serves as Assistant Director. He will consult with Local VHA facility IRM personnel and programmers to coordinate and assemble all additional data from contributing sites, so that patient-specific event and episode data elements are available for the study periods. He will assist in the development of the analytical products, manuscripts and final reports. He facilitate the extraction the VHA, PBM, DSS and Medicare data for these patients and merge them into longitudinal analytic files, in order to prepare the final episodic utilization and cost data in a SAS-compatible format, which can be merged with other study data. All healthcare expense estimates will be summarized by setting, (e.g. inpatient, outpatient, ER, etc.) and expenditure components, (e.g., pharmacy, physicians, laboratory, adverse events) and total healthcare use, allowing for analysis by total and by type of setting (ER, ambulatory visit, hospital day, etc.) and by service (Psychiatric, Medical, Pharmacy, etc.). Mr. Culpepper and Dr. Bradham's staff have assisted Dr. Bradham in similar activities over the past three years in health services cost-of-care estimation techniques. He has co-authored manuscripts with Dr. Bradham.

b) Budget Justification:

Drs. Bradham and Slade are VHA employees and the portion of their VHA salary levels are used to estimate the budget requirements. Mr. Culpepper is a University of Maryland employee. His time will be acquired by IPA arrangement with the Department of Epidemiology and Preventive Medicine, where Dr. Bradham is his supervisor. The analytical work will be accomplished through the facilities at the Perry Point Coordinating Center and Dr. Bradham's offices at the University of Maryland, Department of Epidemiology and Preventive Medicine based on a Memorandum of Understanding.

Travel expenses are needed for all three Health Economics Investigators to attend the annual meeting for the trial, and for at least one professional meeting – the latter has been included in

the budget. Specialized computer expenses are anticipated to be consistent with VA Data Security Policy. Software updates are required for all three investigators bi-annually.

References

1. Gold MR, Siegel JE, Russell LB, Weinstein MC, eds. *Cost-Effectiveness in Health and Medicine*. Oxford: Oxford University Press; 1996.
2. Swindle R, Lukas CV, Meyer DA, Barnett PG, Hendricks AM. Cost analysis in the department of veterans affairs: Consensus and future directions. *Med Care*. 1999;37:AS3-8.
3. Berndt ER, Bir A, Busch SH, Frank RG, Normand SL. The medical treatment of depression, 1991-1996: Productive inefficiency, expected outcome variations, and price indexes. *J Health Econ*. 2002;21:373-396.
4. Kozel FA, George MS, Simpson KN. Decision analysis of the cost-effectiveness of repetitive transcranial magnetic stimulation versus electroconvulsive therapy for treatment of nonpsychotic severe depression. *CNS Spectr*. 2004;9:476-482.
5. Blow FC, Owen RE, eds. *Specialty Care for Veterans with Depression in the VHA: 2002 National Registry for Depression (NARDEP) Project Report*. Ann Arbor, MI: Serious Mental Illness Treatment Research and Evaluation Center; 2003.
6. Corey-Lisle PK, Birnbaum HG, Greenberg PE, Marynchenko MB, Claxton AJ. Identification of a claims data "signature" and economic consequences for treatment-resistant depression. *J Clin Psychiatry*. 2002;63:717-726.
7. Crown WH, Finkelstein S, Berndt ER, et al. The impact of treatment-resistant depression on health care utilization and costs. *J Clin Psychiatry*. 2002;63:963-971.
8. Thase ME. New approaches to managing difficult-to-treat depressions. *J Clin Psychiatry*. 2003;64 Suppl 1:3-4.
9. Kornstein SG, Schneider RK. Clinical features of treatment-resistant depression. *J Clin Psych*. 2001;62:18-25.
10. Greenberg P, Corey-Lisle PK, Birnbaum H, Marynchenko M, Claxton A. Economic implications of treatment-resistant depression among employees. *Pharmacoconomics*. 2004;22:363-373.
11. Russell JM, Hawkins K, Ozminkowski RJ, et al. The cost consequences of treatment-resistant depression. *J Clin Psychiatry*. 2004;65:341-347.
12. Phibbs CS, Bhandari A, Yu W, Barnett PG. Estimating the costs of VA ambulatory care. *Med Care Res Rev*. 2003;60(3 suppl.):54S-73S.
13. Yu W, Wagner TH, Chen S, Barnett PG. Average cost of VA rehabilitation, mental health, and long-term hospital stays. *Med Care Res Rev*. 2003;60:40S-53S.
14. Wagner TH, Chen S, Barnett PG. Using average cost methods to estimate encounter-level costs for medical-surgical stays in the VA. *Med Care Res Rev*. 2003;60:15S-36S.

15. Smith MW, Joseph GJ. Pharmacy data in the VA health care system. *Med Care Res Rev*. 2003;60(3):92S-123S.
16. Wagner TH, Velez J. *A comparison of inpatient costs from the HERC and DSS national data extract datasets*. Menlo Park, CA: VA Health Economics Resource Center; 2004.
17. Willan AR, O'Brien BJ. Sample size and power issues in estimating incremental cost-effectiveness ratios from clinical trials data. *Health Econ*. 1999;8:203-211.
18. O'Brien BJ, Drummond MF, Labelle RJ, Willan A. In search of power and significance: Issues in the design and analysis of stochastic cost-effectiveness studies in health care. *Med Care*. 1994;32:150-163.
19. Stinnett AA, Mullahy J. Net health benefits: A new framework for the analysis of uncertainty in cost-effectiveness analysis. *Med Decis Making*. 1998;18:S68-80.

Attachment 1: Study Intervention's Implementation Costs

The purpose of this form is to help you track the local expenses and resources used developing, testing, implementing and maintaining the Study's Intervention. Ideally, one form should be filed per month, even if there is no activity.

1. Site _____
2. Date ____ / ____ / _____. Please enter Date of Submission as mm/dd/yyyy
3. **Please list all Study meetings where the Intervention was discussed, by date (3.a), since last report.**

Classify by entering a check mark the following characteristics about the meeting: **3.b. purpose** (i.e., Development, Implementation, Maintenance) and **3.c. mode** of meeting, (i.e., Telephone, Face-to-face or Video).

Record in **3.d.** the total number of persons in attendance. For each personnel category attending (**3.e.**) indicate personnel grade (i.e., GS or Title 38, and level).

Finally, in **3.f.**, indicate approximate total time involved and the types of activity (**3.g.**), (i.e., Preparation, Conduct and Follow-up).

Example: A telephone conference attended by 5 people. Three are MDs (T38); one is NP (T38) and one is PhD researcher (GS-13). Total time for the meeting was 1 hour, but approximately 1.5 hours was spent by two attendees in preparation and 1 hour in follow-up to prior meeting.

Mtg .#	Date	Mode of Meeting			Total # @ Mtg.	Personnel Grade	Time Involved		Type of Activity			
							D	I	M	T	F	V
	(mm/dd/yyyy)					GS						
I	02/03/2004	X			X					5	2@11	2@NII I

Mt g. #	3.a.		3.b.		3.c.		3.d.		3.e.		3.f.		3.g.			
	Date	Purpose		Mode of Meeting		Total # @ Mtg.	Personnel Grade (# @ Grade)		Time Involved		Type of Activity			P	C	F
		(mm/dd/yyyy)	D	I	M		T	F	V	GS	T38	Hr	Min			
I																
II																
III																
IV																
V																
VI																
VII																
VIII																
IX																

X												
---	--	--	--	--	--	--	--	--	--	--	--	--

4. Please list all Equipment or Space required for the Intervention purchased or encumbered since last report.

In 4.a. please indicate date of purchase (or date of encumbrance).

In 4.b. please describe the equipment item by model name or number. If space allocated to intervention, then indicate room # and total square feet.

In 4.c. please describe the role of the equipment or space in the intervention, e.g., primary intervention, or patient safety, or sub-hypothesis, or covariate (e.g., “metabolic cart is for nutrition status, a covariate”). If uncertain of these categories, then indicate briefly in “other” column.

In 4.d. indicate the amount expended. If contributed, enter 88888.

Check Equip.(E) or Space (S)	4.a.			4.b.	4.c.			4.d.			
	Date (mm/dd/yyyy)			Item	Purpose			Dollar Amount			
				Brief description or model #	Role of item in the intervention, e.g., <u>primary intervention</u> , or <u>patient safety</u> , or <u>sub-hypothesis</u> , or <u>covariate</u> – or explain.			(no decimals, please)			
#	E?	S?	mm	dd	yyyy	Model # or Room #	PI	PS	SH	C	Other?
I											
II											
III											
IV											
V											
VI											
VII											
VII I											
IX											
X											

5. Please list all Materials or Supplies required for the Intervention purchased or encumbered since last report. Please indicate the number of patients to be served – approximately; (e.g., 1,000 4X4 bandages should serve ?? patients).

In 5.a. please indicate date of purchase (or date of encumbrance).

In 5.b. please describe the equipment item by order or supply number.

In 5.c. please describe the role of the item in the intervention, e.g., primary intervention, or patient safety, or sub-hypothesis, or covariate (e.g., “metabolic cart is for nutrition status, a covariate”). If uncertain of these categories, then indicate briefly in “other” column.

In 5.d. indicate the amount expended. If contributed, enter 88888.

Check <u>Everyone. (E)</u> <u>Or only</u> <u>Some (S)</u>	5.a.			5.b.	5.c.				5.d.	
	Date			Item	Purpose				Dollar Amount <i>(no decimals, please)</i>	
	(mm/dd/yyyy)			Brief description or model #	Role of item in the intervention, e.g., primary intervention, or patient safety, or sub-hypothesis, or covariate – or explain.					
#	Number of Patients to be served	mm	dd	yyyy	Order # or Supply #	PI	PS	SH	C	Other?
I										
II										
III										
IV										
V										
VI										
VII										
VIII										
IX										
X										

Please fax this form back to the Coordinating Center at 410 – XXX-XXXX.
File the original with your Study records so you can answer questions if we need to call you
about an item.

Thank you for your assistance.

Current VHA Target Population

The VHA's clinical management operational data system, the Decision Support System (DSS), indicates that in 2005 approximately 130,193 veterans had received inpatient or outpatient care where their primary or principal diagnosis was "Depression", and had other mental health comorbidities, including: Dementia (12%), Schizophrenia (24%), Bipolar Disorder (23%), Anxiety (56%), PTSD (49%), Substance Abuse (66%), or Brain Injury (3%). These patients' condition demand considerable resources from the VHA, with all being hospitalized at least once per year, 9,744 (7%) being admitted three or more times annually, and 11,464 (11%) visiting the VHA ER three or more times per year. The combination of services provided to this population results in 9,676 (7%) of this comorbid Depression population receiving care valued above \$75,000 per year. The overall total expenditure from VHA for this population amounted to more than \$4.1 billion in 2005.

Potential Target Sampling Pool at Participating VHA Sites

Analysis of the DSS data for the entire patient caseload with Depression as a primary or principal diagnosis in either inpatient or outpatient care found that approximately 48,063 patients met this criterion in 2005. Of these, an estimated 21,663 were between the ages of 18 and 70, inclusively. As shown in Table ??, 228 also had Dementia and Brain Injury diagnoses during the year, with 8 having both. Since these secondary conditions would exclude them from recruitment to the trial's protocol, approximately 21,443 would be eligible for this protocol, nationally. This becomes the population to which the trial could generalize. This clinical population accounted for \$161.3 million in 2005 VHA expenditures for inpatient care and outpatient encounters and pharmacy.

For the ten sites being considered, approximately 4,140 unique patients would be both eligible and within the age range of 18 to 70. Portions of this patient population have been seen for mental health comorbidities during the same year: Substance Abuse (19 %), PTSD (24 %), Anxiety (14 %), Bipolar Disorder (8 %) and Schizophrenia (6 %). These clinical incidence rates are consistent with those found in the overall population of 21,443: Substance Abuse (21 %), PTSD (22 %), Anxiety (14 %), Bipolar Disorder (9 %) and Schizophrenia (7 %), suggesting that these potential CSP 556 sites could render generalizable findings.

Total Unique SSNs			Other Diagnosis and Co Morbidity List						
VISN	MONTHS	All VHA Depression Past 4 QTRS	Dementia	Schizophrenia	Bi Polar	Anxiety, Personality Disorder	PTSD	Substance Abuse	Mental Disorder due to Brain Damage
NATION	12	130,193	15,336	31,789	30,150	73,270	63,539	85,701	3,531
1	12	6,395	839	1,614	1,842	3,808	3,842	4,381	226
2	12	3,988	505	1,072	1,055	2,555	2,368	2,814	114
3	12	4,878	568	1,654	1,317	2,855	2,821	3,324	92
4	12	7,002	709	1,743	1,941	4,153	3,683	4,817	174
5	12	4,744	610	1,395	1,306	2,851	2,827	3,350	136
6	12	8,322	835	1,827	1,652	4,789	4,141	5,398	197
7	12	8,502	905	2,488	1,835	5,103	4,469	5,731	232
8	12	12,542	1,651	3,183	3,296	7,096	5,729	7,751	350
9	12	8,577	920	1,793	2,004	5,006	3,960	5,515	162
10	12	6,534	789	1,837	1,783	3,990	3,450	4,735	148
11	12	6,036	603	1,487	1,371	3,388	2,822	4,230	135
12	12	6,267	734	1,744	1,665	3,779	3,090	4,545	161
15	12	6,684	831	1,661	1,644	4,001	3,095	4,527	197
16	12	13,176	1,348	3,222	2,507	7,222	5,867	8,853	347
17	12	7,699	898	1,907	1,698	4,055	3,805	4,928	139
18	12	7,280	920	1,686	1,746	4,174	3,738	4,679	334
19	12	4,778	453	1,010	1,313	2,685	2,369	2,994	137
20	12	7,166	795	1,538	1,624	4,016	3,969	4,803	182
21	12	6,106	843	1,517	1,522	3,315	3,223	3,897	222
22	12	7,149	753	1,931	1,898	3,924	3,322	4,581	170
23	12	7,621	987	1,547	1,772	4,267	3,484	5,068	343

Total Unique SSNs			High Risk And High Cost Unique SSNs									
VISN	MONTHS	All VHA Depression Past 4 QTRS	3 Or More ED Visits	3 Or More Inpat Admits	Combo 3 Or More ED Visits And Inpat Admits	Total 3 Or More ED Visits And 3 Or More Inpat Admits	Total Actual Cost Of Care \$75,000 Or Greater	Patients with 1 or more Discharges in Past 4 QTRS	Re-Admit Within 30 Days	Total Direct Cost Of Care For Patients With At Least 1 Co-Morbid Condition	Total Actual Cost Of Care For Patients With At Least 1 Co-Morbid Condition	
NATION	12	130,193	11,464	9,744	15,246	7,435	9,676	130,193	21,522	2,546,324,129	4,152,226,250	
1	12	6,395	286	687	419	245	688	6,395	1,297	147,598,947	243,629,275	
2	12	3,988	634	375	645	413	331	3,988	804	79,538,114	137,350,214	
3	12	4,878	330	552	495	322	866	4,878	926	132,236,801	233,156,299	
4	12	7,002	426	706	717	354	625	7,002	1,227	144,422,564	251,104,922	
5	12	4,744	339	533	550	398	475	4,744	895	101,816,016	173,558,642	
6	12	8,322	1,099	571	1,342	711	465	8,322	1,376	150,741,866	244,973,705	
7	12	8,502	540	539	896	424	544	8,502	1,255	159,195,565	261,898,897	
8	12	12,542	1,280	881	1,979	1,017	819	12,542	2,216	239,657,231	380,702,979	
9	12	8,577	1,444	507	1,704	932	484	8,577	1,475	150,871,606	241,739,792	
10	12	6,534	110	857	182	129	587	6,534	1,573	134,389,222	227,089,462	
11	12	6,036	478	488	611	234	405	6,036	940	116,099,765	189,630,665	
12	12	6,267	712	542	819	642	638	6,267	1,257	142,299,536	231,046,112	
15	12	6,684	736	558	1,150	633	365	6,684	1,100	117,307,903	191,701,371	
16	12	13,176	1,804	826	2,020	991	800	13,176	2,138	237,709,289	379,907,803	
17	12	7,699	603	659	1,017	436	506	7,699	1,514	144,758,344	226,520,975	
18	12	7,280	607	537	694	373	338	7,280	1,172	122,816,706	195,432,493	
19	12	4,778	457	349	378	203	351	4,778	739	94,589,301	152,560,215	
20	12	7,166	194	517	292	165	446	7,166	1,036	137,177,570	219,482,459	
21	12	6,106	610	515	709	372	769	6,106	1,089	154,810,596	253,891,661	
22	12	7,149	872	405	1,150	604	739	7,149	1,105	158,345,375	268,138,450	
23	12	7,621	139	743	224	148	648	7,621	1,278	170,874,112	263,604,565	

Unique Patients with Prime or Principal Diagnosis as "Depression" in either Inpatient or Outpatient VHA Care							EXCLUSIONS:			for CSP 556	
VISN - FACILITY - Location	When Age is 18 to 70			Total	Brain Inj.	Dementia	D & B Inj	456			
	No	18 to 70	All Ages		Yes	Yes	BOTH				
7 - 509 - AUGUSTA	Unique Patients Using VHA	54	462	574	0	6	0	456			
	% within Station	9.40%	100.00%		0.00%	1.30%	0.00%				
	% within Age of 18 to 70	0.90%	2.10%		0.00%	3.30%	0.00%				
1 - 518 - BEDFORD	Unique Patients Using VHA	23	63	209	0	0	0	63			
	% within Station	11.00%	100.00%		0.00%	0.00%	0.00%				
	% within Age of 18 to 70	0.40%	0.30%		0.00%	0.00%	0.00%				
2 - 528 - BUFFALO	Unique Patients Using VHA	168	986	1,298	0	8	0	978			
	% within Station	12.90%	100.00%		0.00%	0.80%	0.00%				
	% within Age of 18 to 70	2.70%	4.60%		0.00%	4.40%	0.00%				
7 - 534 - CHARLESTON	Unique Patients Using VHA	15	162	192	0	0	0	162			
	% within Station	7.80%	100.00%		0.00%	0.00%	0.00%				
	% within Age of 18 to 70	0.20%	0.70%		0.00%	0.00%	0.00%				
10 - 539 - CINCINNATI	Unique Patients Using VHA	159	155	1,368	0	1	0	154			
	% within Station	11.60%	100.00%		0.00%	0.60%	0.00%				
	% within Age of 18 to 70	2.60%	0.70%		0.00%	0.50%	0.00%				
19 - 554 - DENVER	Unique Patients Using VHA	53	190	545	1	2	0	187			
	% within Station	9.70%	100.00%		0.50%	1.10%	0.00%				
	% within Age of 18 to 70	0.90%	0.90%		2.20%	1.10%	0.00%				
6 - 558 - DURHAM	Unique Patients Using VHA	404	510	4,047	1	7	0	502			
	% within Station	10.00%	100.00%		0.20%	1.40%	0.00%				
	% within Age of 18 to 70	6.60%	2.40%		2.20%	3.80%	0.00%				
12 - 578 - HINES	Unique Patients Using VHA	290	119	1,635	1	0	0	118			
	% within Station	17.70%	100.00%		0.80%	0.00%	0.00%				
	% within Age of 18 to 70	4.70%	0.50%		2.20%	0.00%	0.00%				
16 - 580BY - HOUSTON - BEAUMONT OUTPATIENT CLINIC	Unique Patients Using VHA	135	586	1,425	1	4	0	581			
	% within Station	9.50%	100.00%		0.20%	0.70%	0.00%				
	% within Age of 18 to 70	2.20%	2.70%		2.20%	2.20%	0.00%				
16 - 598 - LITTLE ROCK	Unique Patients Using VHA	66	133	465	0	0	0	133			
	% within Station	14.20%	100.00%		0.00%	0.00%	0.00%				
	% within Age of 18 to 70	1.10%	0.60%		0.00%	0.00%	0.00%				
21 - 640 - PALO ALTO	Unique Patients Using VHA	19	74	280	0	0	0	74			
	% within Station	6.80%	100.00%		0.00%	0.00%	0.00%				
	% within Age of 18 to 70	0.30%	0.30%		0.00%	0.00%	0.00%				
4 - 646 - PITTSBURGH(UD)	Unique Patients Using VHA	34	225	271	1	4	1	221			
	% within Station	12.50%	100.00%		0.40%	1.80%	0.40%				
	% within Age of 18 to 70	0.60%	1.00%		2.20%	2.20%	12.50%				
19 - 660 - SALT LAKE CITY	Unique Patients Using VHA	6	62	80	0	1	0	61			
	% within Station	7.50%	100.00%		0.00%	1.60%	0.00%				
	% within Age of 18 to 70	0.10%	0.30%		0.00%	0.50%	0.00%				
21 - 662 - SAN FRANCISCO	Unique Patients Using VHA	73	43	118	0	0	0	43			
	% within Station	61.90%	100.00%		0.00%	0.00%	0.00%				
	% within Age of 18 to 70	1.20%	0.20%		0.00%	0.00%	0.00%				
20 - 663 - SEATTLE	Unique Patients Using VHA	48	151	584	1	0	0	150			
	% within Station	8.20%	100.00%		0.70%	0.00%	0.00%				
	% within Age of 18 to 70	0.80%	0.70%		2.20%	0.00%	0.00%				
8 - 672 - SAN JUAN	Unique Patients Using VHA	12	98	117	0	0	0	98			
	% within Station	10.30%	100.00%		0.00%	0.00%	0.00%				
	% within Age of 18 to 70	0.20%	0.50%		0.00%	0.00%	0.00%				
1 - 689 - WEST HAVEN	Unique Patients Using VHA	209	161	412	0	2	0	159			
	% within Station	50.70%	100.00%		0.00%	1.20%	0.00%				
	% within Age of 18 to 70	3.40%	0.70%		0.00%	1.10%	0.00%				
CSP 556 POTENTIAL SITES				4,180	13,620				4,140		
ALL OTHER VHA SITES				Unique Patients Using VHA Care in 200	17,593	34,552	41	149	8	17,303	
				Total	6121	21,663	48,063	46	182	8	21,443
				% within Age of 18 to 70	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	
				% of Total	12.70%	100.00%	100.00%	0.20%	0.80%	0.00%	

Unique Patients with Prime or Principal Diagnosis as "Depression"		for CSP 556	Eligible 18 to 70 Year Old Patient's Other Mental Health Comorbidities					SEX
VISN - FACILITY - Location			Subs Ab Yes	PTSD Yes	Anxiety Yes	BiPolar Yes	Schiz. Yes	
7 - 509 - AUGUSTA		456	114 24.70%	146 31.60%	73 15.80%	35 7.60%	44 9.50%	85 18.40%
			2.60% 28.60%	3.10% 28.60%	2.40% 15.90%	1.90% 17.50%	3.20% 4.80%	2.50% 9.50%
1 - 518 - BEDFORD		63	18 0.40%	18 0.40%	10 0.30%	11 0.60%	3 0.20%	6 0.20%
			0.40% 13.70%	0.40% 24.00%	0.30% 18.50%	0.60% 5.90%	0.20% 5.50%	0.20% 16.40%
2 - 528 - BUFFALO		978	135 3.10%	237 5.00%	182 6.00%	58 3.20%	54 4.00%	162 4.70%
			3.10% 29	5.00% 42	6.00% 27	3.20% 10	4.00% 8	4.70% 28
7 - 534 - CHARLESTON		162	29 17.90%	42 25.90%	27 16.70%	10 6.20%	8 4.90%	28 17.30%
			17.90% 0.70%	25.90% 0.90%	16.70% 0.90%	6.20% 0.50%	4.90% 0.60%	17.30% 0.80%
10 - 539 - CINCINNATI		154	41 26.50%	31 20.00%	17 11.00%	15 9.70%	7 4.50%	29 18.70%
			26.50% 0.90%	20.00% 0.70%	11.00% 0.60%	9.70% 0.80%	4.50% 0.50%	18.70% 0.80%
19 - 554 - DENVER		187	79 41.60%	59 31.10%	22 11.60%	35 18.40%	17 8.90%	19 10.00%
			41.60% 1.80%	31.10% 1.20%	11.60% 0.70%	18.40% 1.90%	8.90% 1.20%	10.00% 0.60%
6 - 558 - DURHAM		502	88 17.30%	135 26.50%	71 13.90%	39 7.60%	21 4.10%	101 19.80%
			17.30% 2.00%	26.50% 2.80%	13.90% 2.30%	7.60% 2.10%	4.10% 1.50%	19.80% 2.90%
12 - 578 - HINES		118	31 26.10%	26 21.80%	18 15.10%	15 12.60%	7 5.90%	15 12.60%
			26.10% 0.70%	21.80% 0.50%	15.10% 0.60%	12.60% 0.80%	5.90% 0.50%	12.60% 0.40%
16 - 580BY - HOUSTON - BEAUMONT OUTPATIENT CLINIC'		581	102 17.40%	88 15.00%	52 8.90%	26 4.40%	32 5.50%	85 14.50%
			17.40% 2.30%	15.00% 1.90%	8.90% 1.70%	4.40% 1.40%	5.50% 2.30%	14.50% 2.50%
16 - 598 - LITTLE ROCK		133	39 29.30%	46 34.60%	22 16.50%	10 7.50%	9 6.80%	17 12.80%
			29.30% 0.90%	34.60% 1.00%	16.50% 0.70%	7.50% 0.50%	6.80% 0.70%	12.80% 0.50%
21 - 640 - PALO ALTO		74	30 40.50%	26 35.10%	19 25.70%	9 12.20%	2 2.70%	10 13.50%
			40.50% 0.70%	35.10% 0.50%	25.70% 0.60%	12.20% 0.50%	2.70% 0.10%	13.50% 0.30%
4 - 646 - PITTSBURGH(UD)		221	24 10.70%	25 11.10%	16 7.10%	23 10.20%	6 2.70%	42 18.70%
			10.70% 0.50%	11.10% 0.50%	7.10% 0.50%	10.20% 1.30%	2.70% 0.40%	18.70% 1.20%
19 - 660 - SALT LAKE CITY		61	12 19.40%	19 30.60%	14 22.60%	11 17.70%	7 11.30%	11 17.70%
			19.40% 0.30%	30.60% 0.40%	22.60% 0.50%	17.70% 0.60%	11.30% 0.50%	17.70% 0.30%
21 - 662 - SAN FRANCISCO		43	2 4.70%	3 7.00%	0 0.00%	1 2.30%	1 2.30%	1 2.30%
			4.70% 0.00%	7.00% 0.10%	0.00% 0.00%	2.30% 0.10%	2.30% 0.10%	2.30% 0.00%
20 - 663 - SEATTLE		150	25 16.60%	43 28.50%	14 9.30%	11 7.30%	9 6.00%	21 13.90%
			16.60% 0.60%	28.50% 0.90%	9.30% 0.50%	7.30% 0.60%	6.00% 0.70%	13.90% 0.60%
8 - 672 - SAN JUAN		98	4 4.10%	15 15.30%	13 13.30%	3 3.10%	5 5.10%	12 12.20%
			4.10% 0.10%	15.30% 0.30%	13.30% 0.40%	3.10% 0.20%	5.10% 0.40%	12.20% 0.30%
1 - 689 - WEST HAVEN		159	18 11.20%	36 22.40%	23 14.30%	16 9.90%	10 6.20%	21 13.00%
			11.20% 0.40%	22.40% 0.80%	14.30% 0.80%	9.90% 0.90%	6.20% 0.70%	13.00% 0.60%
CSP 556 POTENTIAL SITES		4,140	791 19%	995 24%	593 14%	328 8%	242 6%	665 16%
ALL OTHER VHA SITES		17,303	3,612 21%	3,771 22%	2,479 14%	1,514 9%	1,131 7%	2,793 16%
		21,443	4,380 100.00%	4,742 20.20%	3,056 21.90%	1,832 14.10%	1,366 8.50%	3,441 6.30%
								100.00% 15.90%

APPENDIX N

LIST OF POTENTIAL PARTICIPATING SITES AND LIKELY PATIENT POPULATIONS

APPENDIX N: LIST OF POTENTIAL PARTICIPATING SITES

SITE NAME
Palo Alto, CA
Charleston, SC
Salt Lake City, UT
Philadelphia, PA
Cincinnati, OH
Pittsburgh, PA
Temple, TX
San Francisco, CA
White River Junction, VT

APPENDIX O

TMS TRAINING AND CERTIFICATION

Proper training and supervision and oversight of TMS operators are very important for both safety and probably efficacy. We will institute, without question, the most rigorous training and certification process of any TMS multi-site trial ever. This is an important aspect of this trial as we will be having registered nurses, nurse practitioners, or physician assistants performing the large majority of treatments, under the close supervision of licensed and trained psychiatrists or neurologists who are also trained in rTMS. These physicians have experience caring for patients with major depressive disorder, and most have experience conducting rTMS clinical trials. The daily treatments take about an hour in terms to prepare the patient, answer questions about safety and their condition, and conduct the actual treatment. Having MDs perform these treatments would make TMS prohibitively expensive for most patients, and for the VA medical system.

Thus, during this study we will develop training and quality methods not only for the MDs who will be doing the treatments, but also for the registered nurses, nurse practitioners, and physician assistants administrating the treatment. The training curriculum and certification will be developed and overseen by Mark George, M.D and David Avery, M.D., leading TMS experts and researchers. The TMS training and certification process used in this trial will take advantage of the knowledge gained from the conduct of the recent NIH Optimization of Transcranial Magnetic Stimulation for Depression (OPT-TMS) trial, the Neuronetics-sponsored multisite trial of TMS in depression, knowledge gained with the recent FDA approval of TMS and the need to train psychiatrists across the country regarding proper TMS technique, and workshops and seminars on TMS use conducted over the past few years at the annual meeting of the American Psychiatric Association.

The physicians who will be supervising and prescribing TMS are all VA psychiatrists or neurologists, licensed and credentialed in their respective states and with VA clinical privileges. An important concept of the trial is that these physicians will be responsible for each TMS session. In the OPT-TMS trial, most sites had more than one TMS certified physician, in order to cover TMS delivery when a physician was out of town, sick, or on vacation.

The certification process for the MDs, RNs, RNPs, and PAs will start before the kickoff meeting, and there will be ongoing recertification as well as the potential for new certification of MDs throughout the trial, as personnel change and move away from a VA. Prior to the first kickoff meeting, candidate study staff will receive pre-reading materials. The training will involve pre-reading materials including the safety paper (Rossi, Hallett et al. 2009) and the curriculum from the APA TMS course. There will be lectures at the kickoff meeting and a written test which will include testing on how to handle safety issues including what to do if there is a TMS induced seizure. This will be followed by hands-on testing of how to operate the TMS machines, find the motor area, determine the motor threshold, find the treatment area, and deliver the treatment. The TMS device manufacturer will be available at the meeting and at the time of device set-up at the site to provide a cursory overview of the

device. The curriculum for the MD training has been adopted from a course prepared by Dr. George and Dr. Ziad Nahas which has been given each year at the American Psychiatric Association, and which will also be given this year at the annual meeting of the Association for Convulsive Therapy (see course outline below). Each certified MD, RN, RNP, and PA will have to pass the written test and a hands-on skill course at this meeting in order for the site to launch. We will also be offering this series periodically through the life of the trial either at the Ralph H. Johnson VA Medical Center in Charleston or online or at other venues in order to train and certify secondary MDs, and to handle personnel changes at sites. TMS training and certification for the CSP 556 study will be conducted at the site, using a combination of written materials, PowerPoint slides, videos, hands-on by currently study-certified staff, a written exam, and a video conference with Dr. Mark George. Importantly, all TMS treatments in this study will be supervised by these TMS-certified MDs and administered by the TMS-certified RNs, RNPs, and PAs. This approach is entirely consistent with the recent safety consensus paper and with clinical delivery of TMS in the US community. Because the MDs will be responsible for determining the initial motor threshold and finding the treatment scalp location, the training will focus more on correctly monitoring patients during treatment sessions, safety issues in terms of seizures or syncopes, and how to safely interrupt treatments. There will also be vignettes of different patient emergencies and how to handle them (e.g. fire alarm, patient discomfort, power interruption, device malfunction, etc.). This initial series of training, certification and constant monitoring was developed by Dr. George and Dr. Nahas and was used in the industry sponsored trial and the recently completed NIH sponsored TMS depression trial.

In addition to this rigorous initial training, we will have periodic re-assessments of skills at the annual investigators meetings, and will have on-site testing by Dr. George or other members of the certifying and quality assessment group. Dr. George has designed a phantom head with a small pickup coil inside it that can be used to test the skill level of TMS operators. The TMS vendor has built this phantom and it will be beta-tested before the annual meeting and then potentially used as a mannequin or dummy for certification and recertification. This phantom can be used at yearly meetings or carried to sites to make sure that operators can reliably and accurately determine the proper motor area and motor threshold.

If an MD, RN, RNP, or PA fail the initial written test they will be allowed to retake it only two more times, and then will be deemed ineligible and the site will have to put forward other candidates. The same will apply for the hands-on skill testing.

Should this CSP study find evidence of TMS efficacy and safety in the depressed VA population, the lessons learned in this study regarding proper training and certification, and the curriculum and methods developed, will likely serve as the building block for how the VA might adopt the technology as a treatment and insure safe and qualified use of TMS.

Rossi, S., M. Hallett, et al. (2009). "Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research." Clin Neurophysiol 120(12): 2008-2039.

Certificate course on TMS

Table of contents

1. How TMS works- Mechanisms of action of TMS
2. Safety in TMS: Potential side effects and their management
3. Regulations and policies concerning TMS
4. TMS efficacy in major depressive disorder
5. Practical topics in clinical TMS management
6. How to set up and staff a TMS service
7. Use of the MagPro30 device and components
8. Obtaining motor threshold
9. Administrating TMS
10. Practicum sessions and testing
11. Written exam

See next page

Cooperative Studies Program #556
Certificate of completion

The Executive Committee of CSP #556 certifies that on (date)

(Name)

*Attended the certificate course in Transcranial Magnetic Stimulation and
successfully passed the course examination. This didactic and practicum
course included review of selection and preparation, TMS technique,
management of complications, TMS treatment management and
medicolegal issues. A one hour written examination tested the theoretical
and practical knowledge learned in the course*

*Jerome Yesavage, MD
Chairman, CSP #556*

Mark George, MD

SAFETY PLAN: VA VERSION

Step 1: Warning signs:

1. _____
2. _____
3. _____

Step 2: Internal coping strategies - Things I can do to take my mind off my problems without contacting another person:

1. _____
2. _____
3. _____

Step 3: People and social settings that provide distraction:

1. Name _____ Phone _____
2. Name _____ Phone _____
3. Place _____ 4. Place _____

Step 4: People whom I can ask for help:

1. Name _____ Phone _____
2. Name _____ Phone _____
3. Name _____ Phone _____

Step 5: Professionals or agencies I can contact during a crisis:

1. Clinician Name _____ Phone _____
Clinician Pager or Emergency Contact # _____
2. Clinician Name _____ Phone _____
Clinician Pager or Emergency Contact # _____
3. Local Urgent Care Services _____
Urgent Care Services Address _____
Urgent Care Services Phone _____
4. VA Suicide Prevention Resource Coordinator Name _____
VA Suicide Prevention Resource Coordinator Phone _____
5. VA Suicide Prevention Hotline Phone: 1-800-273-TALK (8255), push 1 to reach a
VA mental health clinician

Step 6: Making the environment safe:

1. _____
2. _____

CSP #556 - PATIENT STUDY ID CARD
(Printing on Both sides of card)

FRONT SIDE OF CARD

CSP #556 PATIENT IDENTIFICATION CARD

Patient's Name _____
Address _____ Phone # _____
Subject ID #: _____ Subject Treatment #: _____

I am participating in a clinical trial being conducted at the _____ During this trial I will have repetitive transcranial magnetic stimulation (rTMS) or sham treatment that may decrease my depression symptoms. Please contact the physician or nurse listed on the backside of this card if I require medical attention that might be affected by my participation in this trial or if you have questions regarding the trial.

BACK SIDE OF CARD

IN CASE OF EMERGENCY, Please Notify:

Site Investigator:	Name	Work number
Nurse:	Name	Work number

National Clinical Trial Chairs: Jerome Yesavage, M.D. 650-852-3287
Mark George, M.D. 843-876-5142
J. Kaci Fairchild, Ph.D. 650-493-5000 x63432
Pharmacy Coordinating Center: 505-248-3203 (24 hrs/7days per week)
Study Biostatistician: (410) 642-2411 ext 5283

*This card should be shown to any health care professional
treating you for any reason.*

Card Size – 2 inches high x 3 1/2

Dark Salmon



Department of Veterans Affairs

[Insert Site Specific Information Here]

Dear Veteran:

Version April 2014

You recently signed an Informed Consent Form indicating:

You will be paid for your time and inconvenience in each of the three study phases as follows:

- Screening Phase: \$18
- Intervention Phase: \$30
- Follow-up Phase: \$27

Additional reimbursement funds are now available. The new reimbursement structure is as follows:

You will be paid for your time and inconvenience in each of the three study phases as follows:

- Screening Phase: \$40
- Intervention Phase: \$300
- Follow-up Phase: \$60

If you withdraw or stop early in any of the three phases, you will be paid according to what phase you are in. For example, if you withdraw at any time during the Intervention Phase you would receive payment of \$40 for the screening phase and \$300 for the Intervention Phase, but not \$60 for the follow-up phase. If you complete all three phases you would receive a total of \$400.

Your signature below confirms that you have read this memo, or it has been read to you. You will receive a copy of this memo after you sign it. A copy of this signed memo will be included in the research record.

Signature

Date



Department of Veterans Affairs

[Insert Site Specific Information Here]

Version February 2016

Dear Veteran:

You recently signed an Informed Consent Form for the CSP #556 Study indicating:

There is a possible risk of hearing loss due to the sounds made by the device. You will wear earphones during your rTMS sessions. This should greatly reduce the possibility of hearing loss. Your hearing will be tested at screening, after the intervention phase, and after follow-up to see if any hearing loss has occurred.

Due to recent findings, the study protocol has been changed:

- You will wear **earplugs** and **headphones** during your rTMS sessions.
- Your hearing will be **not be** tested at screening, after the intervention phase, and after follow-up to see if any hearing loss has occurred.
- If you think your hearing is getting worse during the study, tell the study team right away.
- After your last study treatment, you may keep the headphones if you choose.

Your signature below confirms that you have read this memo, or it has been read to you. You will receive a copy of this memo after you sign it. A copy of this signed memo will be included in the research record.

Signature

Date

Page 1