PROTOCOL TITLE:

REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION FOR SMOKING CESSATION IN CANCER PATIENTS

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1.0 Objectives / Specific Aims

Specific aims: Smoking cessation and relapse prevention represent and important opportunity to improve cancer survival rates (1, 2), reduce the risk of cancer treatment complication (3), and improve the quality of life of patients with and survivors of cancer (4). Previous studies showed that repetitive TMS (rTMS) reduced cue craving to smoking and treat nicotine dependent smokers (5, 6). Recently one study completed by our team demonstrated that 10 sessions of rTMS over the left dorsolateral prefrontal cortex (DLPFC) reduced cigarette consumption and cue craving, and also increased quitting rate on target quit date in nicotine dependent smokers. Thus, we propose conducting a controlled, double-blind trial comparing the effect of treatments of active rTMS and sham rTMS on cigarette abstinence days, cigarette consumption and smoking craving during a 7-days of quit attempt period in 20 nicotine-dependent patients with cancer. Specific aims are: Aim 1: Assess a feasibility of the rTMS for smoking cessation in cancer patients. Aim 2: Obtain preliminary estimates of whether one-week active rTMS of left DLPFC tends to be more efficacious than sham rTMS during a 7-days of quit attempt laboratory model period increasing abstinence days, and also decreasing cigarette consumption and cue-elicited craving in cancer patients with smoking.

1.1. Primary objective

To assess a feasibility of the rTMS for smoking cessation in cancer patients: The primary feasibility measures are (1) whether or not we can enroll 20 cancer patients with smoking within 12 months? (2) Study attrition. How many subjects can complete 7-day quit attempt during rTMS treatment? How many subjects will complete one-month follow-up? (3) To measure the percent completion of assessment measures.

1.2 Secondary objectives

To obtain preliminary estimates of whether one-week active rTMS of left DLPFC tends to be more efficacious than sham rTMS during a 7-days of quit attempt laboratory model period increasing abstinence days, and also decreasing cigarette consumption and cue-elicited craving in cancer patients with smoking.

1.3 Exploratory objectives

Self-reported number of cigarettes smoked per day, cue-induced craving (QSU – Brief), visual analog scale for craving and side effect will be measured pre and post each rTMS session. Other assessment, Carbon Monoxide, Fagerstrom Test for Nicotine Dependence (FTND), and MNWS-R will be completed at baseline and the last TMS. Quitting attempt will verify daily CO < 5 ppm. FTND, Feasibility metrics will also be tracked, including numbers of complete TMS sessions and dropout rate.

2.0 Background

2.1. Smoking Cessation after Cancer

The benefits of smoking cessation after a cancer diagnosis are overlooked. In many high-income countries, cancer survival has improved over the last few decades (1). About half of patients with cancer are now expected to survive their cancer for at least 10 years after diagnosis (2). However, many people with cancer still continue to smoke despite smoking being a known and often reversible cause of premature death as a result of cancer, cardiovascular, respiratory, and several other diseases (4). In addition, continued smoking after a cancer diagnosis increases the risk of second primary tumors and cancer recurrence and it a cause of treatment complications (5). Smoking cessation after a diagnosis imparts significant survival benefits for people with cardiovascular disease,

diabetes, and multiple sclerosis (6). That is, all-cause mortality among cancer survivors who continue to smoke after a diagnosis is significantly worse than those who have never smoked (1).

2.2. Smoking Cessation for Cancer Patients

In 2008, when the US department of Health and Human Services treatment guidelines for tobacco cessation were last updated, 10 specific recommendations for treatment were formulated as a quick guide to the overall principles (7). While some patients may quit on their own or require minimal advice to quit, it is essential to keep in mind that the treatment of tobacco use in many patients with cancer may require a more intensive and comprehensive approach (2 5). Unfortunately, very few smoking cessation studies have been conducted in the cancer setting, and their focus is usually on the delivery of behavioral intervention rather than the effectiveness of a specific therapy or pharmacotherapy (8, 9). Likewise, patients with cancer are usually excluded from pharmacologic smoking cessation trials, mostly owing to concerns about the patients' ability to participate in and complete a trial and the difficulty of determining whether any emerging side effects are due to the cancer or cancer treatment or to a smoking cessation medication.

2.3. Transcranial Magnetic Stimulation for Smoking Cessation

To date, several human studies have begun to evaluate the effects of rTMS applied to the lateral or medial prefrontal cortex on cue-induced craving and cigarette consumption (5, 10-12). In one previous study, experimenters (10) administered high frequency rTMS to the left DLPFC of treatment-seeking smokers. Subjects received 20 trains of either real or sham rTMS (20Hz, 90% motor threshold, 2.5 secs-on, 42.5 sec intertrain intervals for a total of 1000 pulses) over the left prefrontal cortex. These investigators found that while real rTMS was associated with significant reduction in terms of the number of cigarettes smoked in comparison with sham stimulation ($p < .01$), levels of craving did not differ significantly between the groups. In contrast, Amiaz and colleagues reported that rTMS (100% rMT, 10Hz, 20 train/day, total 1000 pulses) of the DLPFC reduced both cigarette craving and consumption (5). One study has recently completed a preliminary parallel-groups sham-controlled trial of rTMS in combination with the nicotine patch to treat tobacco addiction in heavily-dependent patients with schizophrenia (13). They found that rTMS did not increase abstinence rates, but did significantly reduce tobacco cravings induced by short-term (30-60 minutes) abstinence, which was assessed before application of the nicotine patch. Recently Dinur-Klein and colleagues reported that deep rTMS of the prefrontal and insular cortices reduced cigarette consumption and nicotine dependence (14). A recently completed exploratory study led by the PI used a controlled, double-blind method to compare the impact of daily treatments of active rTMS (delivered to DLPFC) vs sham rTMS on cue craving and cigarette consumption in nicotine-dependent cigarette smokers. We found that 10-sessions of rTMS significantly reduced cigarette consumption and cue craving compared to sham stimulation. These studies suggest that high frequency rTMS delivered over the left DLPFC can be able to attenuate nicotine consumption and craving. However, to date, no study has been reported to use rTMS smoking cessation for cancer patients. **As such, TMS research of smoking cessation for cancer patients are greatly needed in future.**

2.4. The 7 Days of a Auit Attempt Laboratory Based Model

Recent medication screening paradigms have focused on the first 7 days of a quit attempt to evaluate treatment efficacy, because the early abstinence is a vulnerable time for most smokers (15, 16). Each year, 40% of smokers try to quit, but 50% to 75% relapse within the first week of a quit attempt (17). Furthermore, withdrawal symptoms peak during the first few days of abstinence (18, 19), and these symptoms, in turn, predict relapse (20). These laboratory-based models of medication screening provide smokers with medication and assess the number of days of abstinence during a 7-day simulated quit attempt as the primary end point. As such, we will perform the 7 days of abstinence attempt laboratory model for the rTMS study in smokers. Furthermore, Perkins and colleagues have reported that crossover design with laboratory model of 7 day abstinence attempt has improved the efficacy of initial tests in smoking cessation for efficacy in smoking cessation drug discovery (15, 16, 21-23).

3.0 Intervention to be studied

Transcranial magnetic stimulation (TMS) is a noninvasive (and relatively painless) brain stimulation technology that can focally stimulate the brain of an awake individual (24, 25). A localized pulsed magnetic field transmitted through a TMS coil is able to focally stimulate the cortex by depolarizing superficial neurons (26, 27) inducing electrical currents in the brain (28). If TMS pulses are delivered repetitively and rhythmically, the process is called repetitive TMS (rTMS). rTMS for the treatment of depression was approved for one manufacturer by the U.S. Food and Drug Administration (FDA) in October, 2008 (29, 30) and for a different device in January 2013. Researchers are investigating rTMS potential treatment effects in other neuropsychiatric disorders (schizophrenia, pain, alcohol, cocaine, stroke) (31)Treatment parameters and grouping – The time in the chair and the number of pulses on the head will be the same for all subjects. Active or sham TMS will be the only difference. The sham group only receives sham at all treatments. Stimulation frequency for all active subjects: 10 Hertz – Pulse train duration (on time) 5 seconds, Inter-train interval (off time) 10 seconds (15 second cycle time), Power (intensity) level 100% rMT, Total 60 trains, 15 minutes, Total pulses 3000 per day, 3000 x 10 = 30000 pulses for 10 sessions.

The sham TMS system will be connected to an electrical generator on a 9 V battery and electrodes will be placed over the prefrontal cortex. The regulator is triggered by the TMS machine to allow brief, microsecond, pulses of the electrical current through to the skin on the subjects' forehead. Electrical stimulation will be triggered by the TMS machine to correspond to the sham TMS pulses. To further assess the adequacy of the mask, TMS administrators, clinical raters, and patients will complete “best guess” questionnaires, assessing their best guess as to treatment condition, and their level of confidence in this guess.

4.0 Study Endpoints

4.1 Primary efficacy endpoint

Conducting feasibility includes: (1) how many cancer patients with smoking can be enrolled in 12 months. (2) Study attrition. How many subjects can complete 7-day quit attempt during rTMS treatment. How many subjects will complete one-month follow-up. (3) Measurement strategy- percent completion of assessment measures.

4.2 Secondary efficacy endpoints

Total number of smoke-free days during a 7-day quit attempt. Self-reported abstinence during the 7-day quit attempt will be assessed via timeline. The maximum number of consecutive days of abstinence will be recorded. Participants who does not report at least one 24-hour period of abstinence will be recorded as “0” days abstinent.

4.3. Exploratory endpoints

Self-reported number of cigarettes smoked per day, cue-induced craving (QSU – Brief), visual analog scale for craving and side effect will be measured pre and post each rTMS session. Other assessment, Carbon Monoxide, FTND, and MNWS-R will be completed at baseline and the last TMS. Quitting attempt will verify daily CO < 5 ppm. FTND, Feasibility metrics will also be tracked, including numbers of complete TMS sessions and dropout rate.

4.4. Follow-up

The treatment period of the study will conclude on the end of 5-treatment during 7-day quit attemp days. Participants will then enter the follow-up phase of the study. The one follow-up phone call will happen after 1 month of the last rTMS session. Cigarette consumption will be evaluated by asking: ‘how many cigarettes do you now smoke on an average day?’ Craving will be assessed by asking: ‘how much do you want to smoke a cigarette right now on a scale from 1 to 10?’ Nicotine dependence will be assessed by the FTND question.

5.0 Inclusion and Exclusion Criteria/ Study Population

Inclusion Criteria

To be eligible for this study, the patient must be all of the following criteria:
Ages Eligible for Study: 18 years and older (adult, Senior). the condition is rare in children as compared to adults.
Sexes Eligible for Study: All

1. Completed cancer treatment (e.g. surgery, chemotherapy and radiation) > 6 months. Patients with current endocrine therapy will be included for the study.
2. Have been diagnosed with noninvasive or invasive (Stage 1, 2, or 3A) lung cancer, head and neck cancer, breast cancer or prostate cancer.
3. Smoke 5 or more cigarettes per day and have a carbon monoxide (CO) level > 5 ppm indicative of recent smoking.
4. Not have received substance abuse treatment within the previous 30 days.
5. Meet criteria for low to moderate nicotine dependence as determined by the FTND ≥1.
6. Be willing to provide informed consent.
7. Be able to comply with protocol requirements and likely to complete all study procedures.
8. Is willing to consider trying to quit smoking.
9. Have no active cardiac, neurologic, or psychiatric illness.
10. 1 week -10 years post diagnosis of cancer at the time enrollment.

Exclusion Criteria

To be eligible for this study, the patient CANNOT meet any of the following criteria:

1. Current dependence, defined by DSM-V criteria, on any psychoactive substances other than nicotine or caffeine.
2. Contraindication to rTMS (history of neurological disorder or seizure, increased intracranial pressure, brain surgery, or head trauma with loss of consciousness for > 15 minutes, implanted electronic device, metal in the head, or pregnancy).
3. History of autoimmune, endocrine, viral, or vascular disorder affecting the brain.
4. History of neurological disorder that would lead to local or diffuse brain lesions or significant physical impairment.

6.0 Number of Subjects

The study will recruit 20 cancer patients who smoke 5 or more cigarettes per day.

7.0 Setting

1. The TMS treatment will be completed at Brain Stimulation Division in the Department of Psychiatry.
2. Screening and follow-up will be completed at Hollings Cancer Center (HCC).

Study Site

A single study site is at the Medical University of South Carolina.

8.0 Recruitment Methods

1. Research staff member will recruit participants from Health Tobacco Treatment Program and HCC via flyers, internet and emails at MUSC.
2. **Methods** (1) We will recruit participants from Health Tobacco Treatment Program and HCC at MUSC (2) Initial assessment: An informed consent procedure will be completed prior to

conducting any research procedures. Study personnel will review the consent with the participants and assess participant's understanding of the study. Participants not able to understand the consent after help from the study personnel, and those either excluded or unwilling to participate after the informed consent procedure, will be provided with an appropriate referral for smoking cessation if they are interested. (3) After the informed consent procedure, participants will be assessed for study inclusion/exclusion criteria. Each potential subject will be asked about their current height and weight, past medical history focusing on chronic (and current) medical problems, seizure history, medications, psychiatric disorders, and substance use. The research procedures, risks and benefits will be explained.

9.0 Consent Process

Informed consent will be completed prior to conducting any research procedures. The patient will be given sufficient time to read the informed consent and the opportunity to ask questions. Study personnel will review the consent with the participants in a private setting and assess participant's understanding of the study. Patients will be informed that the participation is voluntary and that they may withdraw consent to participate at any time, they will be informed that choosing not participate will not affect the care that patient will receive for the treatment for his/her cancer. Participants not able to understand the consent after help from the study personnel, and those either excluded or unwilling to participate after the informed consent procedure, will be provided with an appropriate referral for smoking cessation if they are interested. After having obtained the consent, a copy of the informed consent form will be given to the patient.

10.0 Study Design / Methods

10.1 General Design of the Study

This is a randomized, double-blinded design of active rTMS and sham rTMS. The pilot will include a total of 20 nicotine-dependent patients with cancer. Subjects will be randomized to either sham rTMS or real rTMS over the left DLPFC. At the end of 7-day study, everyone can be referred to the Hollings Cancer Center (HCC) Tobacco Treatment Program for active treatment.

10.2 Baseline Evaluation

After the informed consent is obtained, participants will be assessed for study inclusion/exclusion criteria.

(1) Demographic Data: Basic demographic information including age, gender, race, and medical history will be collected. (2) Mini International Neuropsychiatric Interview (MINI) (32): This is a well-standardized structured instrument used to provide quick and accurate DSM-IV psychiatric diagnoses. The MINI will be used to confirm the inclusionary/exclusionary diagnoses in the participants. (3) Tobacco Use History: Detailed history of current and past tobacco use will be obtained, including cigarette smoking. The questions addressed will include the amount, frequency, duration of smoking, preferred brand, reasons for smoking, smokeless tobacco, family history, etc. (4) Fagerstrom Test for Nicotine Dependence (FTND)(33): This is a self-rating questionnaire for nicotine dependence. (5) Questionnaire of Smoking Urges- Brief (QSU-B) (34): This is a 10-item self-rating questionnaire for assessment of craving. (6) Minnesota Withdrawal Scale - Revised (MNWS-R) (35): MNWS-R is a DSM-IV based instrument to assess symptoms of nicotine withdrawal. (7) Biomarkers: We will also use carbon monoxide (CO) level in the expired air by a standard CO breathalyzer at each visit. (8) Tobacco diary: This is a daily diary of all tobacco products consumed in the period between visits,

including cigarettes. Participants will maintain a daily tobacco diary, which will be collected at each visit.

10.3. TMS Procedures

(1). All TMS procedures will be performed by a highly trained faculty or staff member of the Brain Stimulation Laboratory at MUSC under the supervision of a licensed M.D. with specialized training in TMS delivery. (2). Treatment parameters and grouping – The time in the chair and the number of pulses on the head will be the same for all subjects. Active or sham TMS will be the only difference. The sham group only receives sham at all treatments. Stimulation frequency for all active subjects: 10 Hertz – Pulse train duration (on time) 5 seconds, Inter-train interval (off time) 10 seconds (15 second cycle time), Power (intensity) level 100% rMT, Total 60 trains, 15 minutes, Total pulses 3000 per day, 3000 x 5 = 15000 pulses for 5 sessions. If patients can not complete 5 sessions, they can complete 5 sessions within 7-day quit attempt (3). Subject Preparation for TMS delivery - The subject will be asked to remove and store any glasses or earrings, and to remove wallets from their pockets if they contain magnetic media (e.g., credit cards). They will be asked to empty their bladder to avoid treatment interruption. Ear protection will be provided. (4). Resting Motor Threshold (rMT): At entry, we will determine each subject's rMT and all rTMS dosing will be given relative to this value. The coil will be positioned over the area of the skull roughly corresponding to the motor cortex and then systematically moved and adjusted until each pulse results in isolated movement of the right thumb. Once we completed "threshold hunting", we will use a modified PEST algorithm attached EMG to determine rMT. (5). Localizing the TMS Coil over DLPFC: At a visit after providing informed consent, participants will be fitted with a white lycra swim cap. This cap will be worn during all TMS sessions in order to insure proper placement of the TMS coil across visits. Localization of the stimulation site in the prefrontal cortex will be performed using Bean Method developed by our team (36). (6). Treatment administration: The Neuronetics TMS will be used for the study. (7). Active Sham rTMS: Successful patient and operator masking is key to the success of this trial. In one of our previous studies, we have successfully developed an active sham system (37). To further assess the adequacy of the mask, TMS administrators, clinical raters, and patients will complete "best guess" questionnaires, assessing their best guess as to treatment condition, and their level of confidence in this guess.

10.4. The 7 days of a quit attempt: Participants will be asked to start a quit attempt after the first TMS session.

During the abstinence attempts, subjects will be told that you "go as long as you can without smoking". We will compare the numbers of cigarettes smoked and days of abstinence between active rTMS week the sham rTMS week.

10.5 Study Calendar

Timepoints	**Baseline**	**TMS 1**	**TMS 2**	**TMS 3**	**TMS 4**	**TMS 5**	**Follow-up**
Assessments							
Informed Consent	X						
Demographic	X						
Medical history	X						
Tobacco Use History	X						
Fagerstrom Test for Nicotine Dependence (FTND)	X						
Questionnaire of Smoking Urges- Brief (QSU-B)	X						

Minnesota Withdrawal Scale - Revised (MNWS-R)	X						
carbon monoxide (CO)	X						
Tobacco diary	X						
Primary Outcome – number of abstinence days	X	X	X	X	X	X	
Secondary Outcome – cigarette per day	X	X	X	X	X	X	
Visual analog scale of craving for cigarette	X	Pre and post X	Pre and post X	Pre and post X	Pre and post X	Pre and post X	
Adverse Events		X	X	X	X	X	
Best guess		X				X	
Phone call							X

11.0 Specimen Collection and Banking

Not applicable.

12.0 Data Management

12.1. Data collection

Data analyses will include the use of descriptive statistics for feasibility metrics and outcome measures. Graphical displays will be used to illustrate the effect of rTMS vs. sham TMS on the outcomes over time. General linear mixed models, ideal for modeling repeated longitudinal outcome data, will be used to estimate the potential treatment benefit of rTMS on numbers of cigarettes smoked per day. Poisson (or negative binomial) regression models will be used to estimate the potential treatment benefit of rTMS on numbers of days abstinent from cigarette smoking during their 7-days following their quit attempt. The regression models will allow us to estimate rTMS treatment benefit along with 95% confidence intervals. All analyses will be conducted in collaboration with the SCTR BERD biostatisticians.

The data from follow-up will be used to measure the durability of one week rTMS treatments. We hypothesized that the number of quit day would predict a long-term effect for smoking cessation.

Electronic and hard copy CRF's will be provided for the recording of data. With the exception of hard copy case report forms utilized for expedited reporting requirements, such as the reporting of SAE's, the remainder of patient data will be collected and submitted via electronic CRFs. All data should be substantiated by clinical source documents organized within a patient research record. ICH Good Clinical Practices are to be followed.

Electronic data for on study and follow-up patient data is submitted via REDCap. REDCap is managed from the Medical University of South Carolina as a consortium partner under their CTSA. REDCap CRF is a secure, Web-based application designed to capture and manage research study data.

The system has been reviewed for 21CFR Part 11 compliance and has been deemed "21CFR 11 Capable." Users of the REDCap system are limited to members of the IRB approved research team

who are delegated data management responsibilities, typically the study coordinator and data manager.

12.2 Data analysis

General considerations: All data will be analyzed in consultation (Dr. Paul Nietert) with the electronic system called REDCap (Research Electronic Data Capture). Statistical analyses will be performed using SPSS 22.0 (IBM Inc.). Baseline demographic and baseline characteristics, together with safety analyses will be performed on all enrolled subjects. Baseline values are defined as the measures on screening visit. The standard summary statistics for continuous variables are: mean, standard deviation, median, minimum and maximum. The standard summary statistics for categorical variables are: count and percentage. All statistical tests will be two-sided. For comparison of means (continuous variables), the two-sample t-test or the Wilcoxon rank sum test will be used as appropriate. For comparison of proportions (discrete data), the Chi-squared test will be used as appropriate. All test performed at significance $\alpha = 0.05$.

To assess a feasibility of the rTMS for smoking cessation in cancer patients: The numbers of subjects who were randomized and who entered and completed each visit of the study will be provided, as well as the reasons for all post-randomization discontinuations, grouped by treatment and by major reason. The discontinued subjects, protocol deviations, and subjects excluded will be proved as well.

To obtain the secondary estimates: The abstinence days, and cigarette consumption and cue-elicited craving will be compared between the active TMS and sham groups with a t-test or a repeated measures analysis of covariance model. Baseline daily number of cigarettes smoked, sex and center will be used as covariates.

To analyze the exploratory measures: cue-induced craving (QSU – Brief) and visual analog scale for craving will be measured pre and post each rTMS session. Other assessment, Carbon Monoxide, FTND, and MNWS-R will be compared between two groups.

12.3Safety analysis

Following standard procedures, frequency and severity measures of side effects will be constructed from the clinical measures. Descriptive statistics as well as changes from baseline will be presented by study group at each scheduled visit.

13.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

1. *Trial Management:* The study will be managed from the Brain Stimulation Lab within the Department of Psychiatry and Behavioral Sciences at the Medical University of South Carolina.
2. *Data Management and Analysis:* Data will be entered by research assistants directly into a computer using standard database software. The data analysis plan is outlined in the Data Analysis Plan section.
3. *Quality Assurance:* The PI will have weekly meetings with the research assistants to discuss qualitative comments received during data collection and any problems in data collection. The statistician will periodically examine the database to look for irregularities. Initial data analyses will examine distributions of variable scores, and comparability of baseline characteristics across conditions in case analyses need to be adjusted for these. Confidentiality protections are outlined above.
4. *Regulatory Issues:* All unexpected Adverse Events (AEs) will be reported to the MUSC IRB and Committee on Human Research within 48-business hours. Serious AEs will be reported within 24-business hours. Follow-up of all unexpected and serious AEs will also be reported to these agencies.

5. *Definition of AE and SAE:* An AE is defined as any untoward medical occurrence in a study subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment (ICH GCP). Any unwanted change, physically, psychologically or behaviorally, that occurs in a study participant during the course of the trial is an adverse event. A Serious Adverse Event (SAE) is defined as an adverse event that has one of the following outcomes: death, life-threatening, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability/incapacity, a congenital anomaly/birth defect.
6. *Documentation and Reporting:* AEs/SAEs are documented and reported as per IRB requirements. Research staff will identify adverse events and obtain all available information to assess severity, seriousness, study relatedness, expectedness, outcome and the need for change or discontinuation in the study intervention. Adverse events are generally documented on AE Logs and AE Case Report Forms (CRFs). Additional relevant AE information if available will be documented in a progress note in the research record as appropriate to allow monitoring and evaluating of the AE. If the AE meets the definition for serious, appropriate SAE protocol specific reporting forms are completed and disseminated to the appropriate persons and within the designated timeframes as indicated above. For each AE/SAE recorded, the research staff will follow the AE/SAE until resolution, stabilization or until the participant is no longer in the study as stated in the protocol. We will report adverse events to the Medical MUSC IRB online per the IRB's guidelines.
7. *Study endpoints proposed:* The study is considered completed with the last visit of the last subject undergoing the study. Safety concerns, including a high rate of seizures (5%) can cause early study termination.

14.0 Withdrawal of Subjects *A subject will be withdrawn from the study for any of the following reasons:*

1. Withdrawal of consent
2. Subject is not compliant with requirements of the study, including inclusion criteria and exclusion criteria
3. The study is prematurely stopped
4. The investigator believes that for safety reasons it is in the best interest of the subject to stop treatment.
5. Subject motor threshold cannot be located.
6. Subject voluntarily withdraws from the study without reasons.
7. When a subject withdraws before completing the study, the reason for withdrawal will be documented on the CRF.

15.0 Risks to Subjects

Potential Risks. Investigational Device Exemption: Transcranial Magnetic Stimulation is FDA approval device for depression treatment. It is an investigational device for smoking cessation The IRB at MUSC (in cooperation with the FDA) has determined repetitive TMS to be a non-significant risk intervention.

Potential Risks of TMS:

Potential risk of a seizure:
The most serious side effect associated with rTMS is the accidental induction of a seizure. Although accidental seizures occur at a frequency of <0.1%, there are factors that may increase the risk of rTMS triggering a seizure such as family history of seizures, alcohol use and previous neurological condition. The risk of seizure induction is also related to the intensity, duration, frequency and rest interval of stimulation as well coil type. To date, 2 outpatients have been reported with seizures at

MUSC since 1997. Both patients received therapeutic treatment with Brainsway H coil. To our knowledge, neuronetic stimulator with the parameters and settings we propose to use does NOT cause seizures.

Potential for scalp discomfort and headaches:
Some people report some mild discomfort when the magnetic pulses are applied over the scalp, and a small number of people (~5%) report headache following rTMS. However, the headaches are temporary and manageable with common over-the-counter pain remedies.

Potential hearing loss:
The discharge of the TMS coil generates a high-energy click that may cause damage to the inner ear. Humans exposed to TMS have shown temporary increases in auditory threshold (especially at high frequencies) lasting at least 5 minutes and less than 4 hours. Foam earplugs can protect against these changes and will be worn during TMS sessions.

Potential changes in cognitive function:
There have been no reports of long-term changes (more than a minute) in cognitive function (memory, attention, etc) in TMS studies. Safety studies specifically looking for these changes did not find any effects of TMS with the exception of one open study in which healthy volunteers were exposed to 150 sequences of TMS at different site of stimulation in a procedure that lasted more than 3 hours. There was a significant decrease in scores on a logical memory test. The stimulation parameters exceeded the recommended safety range and there was no control for patient fatigue or other non-specific effects.

Other potential effects of TMS on brain tissue:
TMS is thought to be safe, with no brain damage, despite extensive use in humans and other animals. We have reported a safety study looking at the MRI scans before and after 2 weeks of daily left prefrontal TMS for depression. No structural changes were found in left prefrontal lobe of patients who received active TMS compared to those who received sham TMS. We have also performed an MRI diffusion imaging study before and after TMS/fMRI study and found no harmful effects of TMS on brain tissue at the site of stimulation.

Safety in case of pregnancy:
This protocol will exclude pregnant women. The risks of using TMS with pregnant women are currently unknown. If you are pregnant, or think you might be pregnant at any point during this study, please inform the investigators and the TMS will be discontinued immediately.

Unknown Risks:
TMS is an experimental procedure that has not been approved by the FDA as a treatment for nicotine craving and it may have unknown side effects. The researchers will let you know if they learn anything that might make you change your mind about participating in the study.

<u>Potential Risks of Nicotine Craving Laboratory Procedures:</u>

Risk of emotional distress:
The procedures proposed in these studies are widely used in research and clinical evaluation procedures and have been shown to be safe.

Risks regarding Confidentiality:
Despite efforts to maintain subjects' anonymity and confidentiality, there is always some minimal risk of people other than the study investigators gaining access to your health information. Every effort will

be made to ensure that your health information will be collected and stored in a manner that ensures the highest level of protection of confidentiality.

16.0 Potential Benefits to Subjects or Others

There will be no direct benefit to the subject. However, it is hoped that the information gained from the study will help in smoking cessation in cancer patients. Smokers may be able to stop smoking from this study trial.

17.0 Sharing of Results with Subjects

If we have significant new findings during the course of the study, we will notify the patient.

18.0 Drugs or Devices (if applicable)

Neuronetics TMS is a treatment device for depression. We will use the TMS device for smoking cessation in cancer patients. TMS device is a claim of a non-significant risk device.

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