CLINICAL STUDY PROTOCOL

Imaging the Effects of rTMS On Chronic Pain

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Introductory statement:

Neuropathic pain is estimated to affect 3%-4.5% of the worldwide population and is associated with significant loss of productivity and the development of mood and substance use disorders (Russo et al. Neurosurg Focus. 2015 Jun;38(6):E11, 2015). Chronic neuropathic pain is difficult to treat with medication and deep brain stimulation (DBS) targeting subcortical structures (periaqueductal gray or thalamic nuclei) has been investigated for refractory neuropathic pain. However, recent work indicates that stimulation of the dorsal anterior cingulate cortex (dACC) may be a new potential neuromodulatory target, given its role in affective processing of pain.

This is a feasibility study, aiming to investigate the use of repetitive transcranial magnetic stimulation (rTMS) directed at the medial prefrontal cortex and anterior cingulate as a potential treatment for neuropathic pain. Previous studies using rTMS for pain have shown some indicators of success (Tzabazis et al, Molecular Pain 2013, 9:33 2013), and we are investigating the effect of the H7 coil, which reaches the medial prefrontal cortex and the anterior cingulate, on chronic pain syndromes. Using the H7 coil (Brainsway LTD, Jerusalem Israel), which was developed to reach deeper structures in the prefrontal cortex including the anterior cingulate, we will investigate active vs sham treatment in chronic pain subjects.

Protocol: Imaging the Effects of rTMS on Chronic Pain

Specific Aim 1: Investigate the feasibility and tolerability of using rTMS on chronic pain in patients with opioid use disorder currently on methadone maintenance therapy and to investigate the effect of rTMS on chronic pain relief and substance use use in an exploratory manner. Previous studies indicate that deep brain stimulation of the prefrontal cortex/anterior cingulate induces pain relief. Our hypothesis is that active rTMS, compared to sham, will improve pain after five weeks of treatment, thereby improving functional capacity and reducing opioid and other substance use.

Specific Aim 2: Investigation of the effect of rTMS using imaging. We will investigate target engagement with brain imaging. Magnetic resonance spectroscopy (MRS) will be used to measure changes in glutamate and vMRI to gauge changes in volume. Our hypothesis is that active rTMS will decrease glutamate levels and increase brain volume of the mPFC and ACC compared to sham.

Specific Aim 3: Investigation of the effect of rTMS on cognitive (i.e. executive) functioning in patients with chronic pain and opioid use disorder on methadone maintenance therapy. Previous studies have implicated a broad range of cognitive deficits in patients with substance use disorders, both during intoxication and withdrawal and after prolonged abstinence. Neuropsychological testing completed before and after rTMS treatment will be completed to determine if rTMS improves cognitive functioning, which may be a possible mechanism for improvement in chronic pain and/or opioid use disorder.

Background and Rational

Chronic pain affects approximately 100 million Americans each year and costs an estimated $560-$635 billion annually, inclusive of health care expenses and lost productivity (Institute of Medicine Report from the Committee on Advancing Pain Research, Care, and Education, 2011). Aside from the economic cost, chronic pain is also associated with significant psychological and social consequences including anxiety, fear, depression, decline in social functioning and dependence on opioid analgesic (Institute of Medicine (US) Committee on Advancing Pain Research, Care, and Education, 2011). Furthermore, the lack of effective treatments for chronic pain is one factor that has contributed to the increase in opioid prescribing, and thus diversion, addiction, and overdoses in the U.S. Despite ongoing efforts to reduce opioid prescribing for chronic pain, an estimated 35% of all opioid prescriptions are for chronic pain, resulting in around 10 million American adults (3-4% of the population) receiving opioid treatment for this indication despite limited evidence of its effectiveness (Volkow, McLellan, et al, 2009; Boudreau , Von Korff, et al, 2009). In 2016, an estimated 11.8 million people in the U.S. (4.4% of the population) misused opioids, and 1.8 million (0.7% of the population) met DSM5 diagnostic criteria for an opioid use disorder (NSDUH 2017).

Recent imaging and neurophysiological evidence suggest that the dorsal anterior cingulate (dACC) plays an important role in the perception of pain (Russo et al, 2015, for review). Not only is the dACC involved in the cognition of pain but also the affective perception of pain, that is, the emotional valuation of pain. PET and fMRI studies have also demonstrated the dACC is involved in cognitive and affective pain perception. Morphometric magnetic resonance imaging has shown decreases in the dACC in chronic pain patients (Russo et al, 2015, for review). Additionally, dACC dysfunction has been implicated in various substance use disorders, including opioid dependence (Yucel, Lubman, et al, 2007). Protocol Summary Form 7208 Martinez, Diana Page 7 of 21 Advancements in the techniques of non-invasive brain stimulation such as repetitive transcranial magnetic stimulation (rTMS) have potential therapeutic effects for chronic pain and substance use disorder

treatment. rTMS could be an alternative to opioid medications since it can directly modulate brain activity in specific neuronal networks as opposed to medication which likely affects not only neuronal structures responsible for pain but also other brain regions that result in other side effects or make treatment less effective. Additionally, for chronic pain patients whose reduction in opioid use is limited by functional brain changes that result from and contribute to opioid misuse, directly targeting these dysfunctional brain circuits may have an additive effect with the reduction in pain, mediating a further reduction and possibly discontinuation of opioid use or misuse. One limitation of rTMS is that deeper brain structures that have been shown to be involved in pain perception were difficult to target. However, recent advances in the coil offers the ability to target the deeply located brain structure, the dorsolateral cingulate cortex (dACC), shown to play an important role in pain perception.

Subject population

Subjects will have chronic pain and opioid use disorder on methadone maintenance therapy. We expect that most subjects will have back pain or osteoarthritis. We will accept pain caused by these conditions, in addition to neuropathic pain (complex regional pain syndrome, phantom limb pain, thalamic pain, pain related to injury of nerve plexus/plexi, and neuropathic facial pain).

Inclusion and Exclusion criteria:

Inclusion:

Criteria	**Method of Assessment**
1. Chronic pain (back pain, osteoarthritis, complex regional pain syndrome, phantom limb pain, thalamic pain, pain related to injury of nerve plexus/plexi, or neuropathic facial pain)	1. Medical Assessment; Physical Exam, Interview with physician
2. Age 21-60	2. Identification
3. Able to give informed consent, and comply with study procedures	3. Interview with physician
4. Opioid use disorder, moderate or severe	4. Interview with physician and meet diagnostic criteria (4 or more criteria) based on Diagnostic and Statistical Manual (DSM) 5. (American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (5th ed.). Washington, DC: Author.)
5. Enrolled in methadone maintenance treatment program for at least 2 months and at least 1 month on a stable dose of methadone (up to 300mg/day)	5. Interview with physician; Urine toxicology

Exclusion:

Criteria	**Method of Assessment**

1. Medical conditions that preclude rTMS: including vasodepressor syncopy, glaucoma, increased intracranial pressure, cardiac disease, migraine disorder, cerebral vascular events (cerebral vascular accident. Transient ischemic attack), any brain lesions (such multiple sclerorsis), or seizure disorder of any type.	1. Medical Assessment; Interview with physician.
2. Meet DSM-V criteria for major psychiatric illness, such as bipolar disorder, major depression, or psychosis, that would interfere with participation or pose a risk for rTMS. Subjects with a current or past history of suicide attempt or suicidal ideation will be excluded from this trial.	2. SCID, Interview with physician; Hamilton depression rating scale < 17. Score of > 10 on the Young Mania Rating Scale or any answer od "yes" on the Columbia Suicide Severity Rating Scale (CSSRS) will be exclusionary.
3. Cognitive Disorder	3. Assessment by a study physician and score less than 25 on Mini Mental Status Exam (MMSE)
4. Currently pregnant	4. Medical history, urine HCG. A urine HCG on scan days will be performed on women of childbearing potential.
5 Metal implants or paramagnetic objects contained within the body which may interfere with the MRI scan, as determined in consultation with a neuroradiologist and according to the guidelines set forth in the following reference book commonly used by neuroradiologists: "Guide to MR procedures and metallic objects" Shellock, PhD, Lippincott-Raven press, NY 1998.14. This includes metal or shrapnel or bullet in the head or body, including metal shavings.	5. Medical history, self-report.
6. Subjects with positive responses to the Transcranial Magnetic Stimulation Adult safety screen (TASS, enclosed)	6. Responses to TASS
7. Currently taking the following medications that are a strong potential hazard for TMS (per Rossi et al): imipramine, amitriptyline, doxepine, nortriptyline, maprotiline, chlorpromazine, clozapine, foscarnet, ganciclovir, ritonavir, amphetamines, cocaine, MDMA, phencyclidine, PCP,ketamine, gamma-hydroxybutyrate (GHB), theophylline or	7. Medical history, self-report.

neuroleptics., or taking any other medications known to incrase the risk of seizure	
8. Subjects with claustrophobia making them unable to tolerate the fMRI scanning.	8. Self-report
9. Subjects involved in litigation regarding injury or worker's compensation benefits.	9. History, self-report
10. Subjects with a diagnosis of vasculitis, peripheral vascular disease, peripheral neuropathy, small-fiber neuropathy, or fibromyalgia.	10. Medical history, self-report.

Subject Screening:

Subjects will be referred to the study from the Addiction Institute Opioid Treatment Program.Subjects will also be recruited by word of mouth, fliers, newspaper advertisements, and postings on relevant websites. Contact information will be provided so that potential subjects may speak with a research coordinator/research assistant to learn more about the opportunity to participate in the study. Potential participants will take part in a brief phone interview to establish pre-eligibility. Pre-eligible participants will be given an appointment for a screening visit.

They will then undergo additional screening for the study, including a SCID, review of metal implants, pregnancy test (if indicated), medical history, physical exam, vital signs (HR, BP, temp), TASS, and consent for study procedures. For all females of child-bearing potential, a pregnancy test will be repeated prior to beginning rTMS sessions. Daily medication use will be assessed for the 4 weeks prior to study entry using the time-line follow back procedure.

Following screening, the subjects will undergo the following procedures:

1) Pregnancy tests will be performed weekly during rTMS and before each MRI. Before the rTMS begins, we will perform an initial determination of motor threshold. Subjects with a motor threshold of 85% (of maximal stimulator output) at the initial determination of motor threshold will be removed from the study. The rationale for this is that, in our experience, high motor thresholds of this level result in discomfort and anxiety when the actual rTMS sessions are delivered.
2) Volumetric MRI and MRS scans.
3) Baseline neuropsychological testing, including pain scales.
4) Five weeks of rTMS, Monday – Friday, on an outpatient basis. The pain scales will be performed during the weeks of rTMS, up to daily.
5) Repeat volumetric MRI and MRS scans after the rTMS.
6) Repeat neuropsychological tests after the rTMS.

Neuropsychological scales and tests: Subjects will be asked to complete the following tests and scales before and after the sessions of rTMS (at baseline and after the completion of the rTMS).

Scales (expected to take 60 minutes total):

1. Brief Pain Inventory (at baseline and daily before each rTMS session)
2. PEG scale (at baseline and weekly before each rTMS session)
3. PROMIS-29 pain intensity and pain interference items (at baseline and weekly before each rTMS session)
4. Hamilton Depression Rating Scale (at baseline and weekly)
5. Barratt Impulsiveness Scale (BIS -11) (at baseline)
6. Columbia Suicide Severity Rating Scale (at baseline and weekly)
7. Young Mania Rating Scales (at baseline and weekly)
8. Patient-rated clinical global impression (CGI) scale (at baseline and weekly)
9. Clinician-rated CGI scale (at baseline and weekly)
10. Clinician-rated CGI-opioid scale (at baseline and weekly)
11. Clinical Opiate Withdrawal Scale (COWS) (at baseline and weekly)
12. Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) (at baseline and weekly)

Medication use: Subjects will be asked to provide to us the number of medications they took as follows: 1) at baseline (in the week prior to starting sessions); and 2) at each session, where we will ask about opioid and other medication use since the previous session. The amount of opioids used will be converted to oral morphine equivalents and tallied for each day.

Repetitive Transcranial Magentic Stimulation (rTMS): The participants will be randomized into 2 groups: 1) high frequency rTMS (20 Hz), 2) and sham treatment. The rTMS will be administered using the TMS system provided by Brainsway (Brainsway, LTD, Jerusalem, Israel). The rTMS system is equipped with a positioning and cooling system. The positioning system includes a helmet that comprises the coils (which will be either the sham or the H coil), an adjustable arm connected to the helmet, and a device enabling rotation of the helmet around three orthogonal rotation axes. The positioning device enables the accurate and comfortable placement of the coil over the patient's head. The cooling system is designed to maintain ambient temperature in the coils during repetitive operation by allowing streamed the cooled air into the helmet and maintains the coils at ambient temperature.

Motor threshold determination: In order to determine the resting motor threshold (RMT), subjects will be seated in a recliner with hands in a comfortable resting position and wearing the helmet which holds the H coil tangentially to the skull surface. TMS pulses will be applied over the leg motor area to induce activation of the tibialis. The optimal site for stimulation of the right tibialis muscle will be determined. The optimal stimulation site is defined as the position from which the largest motor-evoked potentials (MEPs) were consistently obtained. RMT is identified as the lowest stimulus intensity (in percentage of maximum stimulator output) that elicited at least five small MEPs (greater than 50 μV) out of 10 consecutive stimulations. The first determination of the RMT can take up to 15-30 minutes. To help decrease risk of seizure, subjects will have their motor threshold determined once at the start of each week of rTMS and 100 - 110% of that stimulus intensity will be used for treatment of the anterior cingulate cortex, by positioning the coil over the midline, 5cm anterior to the optimal site for stimulation of the tibialis. We will begin with an intensity of 80% and increase to 110% over 2-3 days.

Sham method: A sham coil is placed in the helmet along with the active coil. The determination of the operating mode (active or sham) is done using magnetic cards. The sham coil setting is designed to mimic the auditory artifact and the scalp sensations evoked by the real coil, and to produce activation of facial muscles similar to the effect of a real H coil, without stimulating the brain itself.

Stimulation procedure: A pre-selected treatment protocol will be programmed into the rTMS stimulator. The stimulator sends electrical pulses to the coil positioned (within the helmet) on the subject's scalp at the intended site of stimulation (approximately 5cm downward from positioning at motor threshold determination, along the midline). Magnetic field intensity is set at 110% of that subject's observed RMT. rTMS will be delivered as shown:

Active rTMS (H coil)

Amplitude (% motor threshold)	80-110%
Frequency (pulses per second, Hz)	20 Hz
Train Duration (seconds)	2 s
# pulses / train	40
Time between trains (seconds)	20 s
Number of trains/session	50
Total number of pulses/session	2000

The rTMS will be administered at the STARS outpatient research clinic.

The staff members who will administer the rTMS will be required to meet all of the following:

- Practical demonstration of ability to perform several determinations (at least 5) of the resting motor threshold, under the direct supervision of a physician investigator experienced in rTMS.
- Performing at least the first two rTMS study sessions under the direct supervision of a physician investigator experienced in rTMS.
- Working knowledge of the principles and practices of rTMS and the rTMS device being used in the study, including common side-effects and how to recognize them. Knowledge will be based on completed tutorial sessions with the investigators or rTMS consultant experienced in rTMS.
- Knowledge how to contact the covering physician available in the building.
- Knowledge of seizure first aid, the location of the emergency equipment and medication, how to engage the emergency response system.
- Bachelor's degree or higher.

In addition, a physician with the following qualifications will be readily available in the vicinity if the need arises (in the institute, and immediately available).

Post-treatment Follow-up

Participants will return at 2 weeks and 4 weeks after completion of rTMS for the following measures:

1. Self-reported methadone dose adjustments/changes and other substance use

2. Brief Pain Inventory
3. PEG scale
4. PROMIS-29 pain intensity and pain interference items
5. Hamilton Depression Rating Scale
6. Hamilton Anxiety Rating Scale
7. Patient-rated clinical global impression (CGI) scale
8. Clinician-rated CGI scale
9. Clinician-rated CGI-opioid scale
10. Quality of Life Enjoyment and Satisfaction Questionnaire
11. Visual Analogue Scale (VAS) for Opioid Craving

Statistical Analysis:

The primary effectiveness outcome measure will be proportion of subjects who achieve ≥ 50% reduction in average pain score as measured by VAS and no significant increase in opioid medication use [defined as greater than 25% increase in morphine equivalent dose].

The effect of rTMS on chronic pain will be performed with a repeated measure ANOVA. Post-hoc contrasts between the groups will be assessed with t tests with correction for multiple comparisons. Groups will be prospectively matched for variables suspected to influence the outcome measures (age, gender, ethnicity). The effect of these variables on each dependent variable will be assessed by ANOVA. In case of significant or near significant effect ($p < 0.10$), these variables will be included in the model (ANCOVA). For all analyses described above, a two tailed probability value of $p < 0.05$ will be selected as significance threshold and correction for multiple comparisons will be applied. In case of nonnormality or inhomogeneity of variance, we will first evaluate data transformation techniques (log or square root) to address these issues. If this cannot be achieved, we will use nonparametric tests, or bootstrap analysis.

Criteria for Early Discontinuation

Subjects will be assessed at least weekly by a study psychiatrist. Subjects will be removed from the study if they experience a worsening of depressive symptoms or an HRSD > 17. Any answer of "yes" on the Columbia Suicide Severity Rating Scale or a score of >10 on the Young Mania Scale will require a psychiatric evaluation to determine if continuation in the study is appropriate.

A Clinical Global Impression-improvement score and CGI opioid improvement score will be obtained weekly by a study physician. Subjects will be assessed, by a study physician, for continuation in the study if they score 6 or 7.

Risks associated with the study:

1. MRI scans.

The scan may be dangerous if combined wih magnetic objects in the body. While there have been no reports of any harmful long-term effects caused by the MRI scanner, including magnets of high strength, the long-term effects of being placed in a magnet of the strength used in this study is unknown. Subjects with metallic objects in their body which would exclude them from receiving an MRI for clinical purposes are excluded from the

study. Also, although there are no known risks associated with pregnancy, subjects will not be included if pregnant.

2. Reduction in opioid use.

Participants may reduce or stop using opioids through the duration of the study. Reduced opioid use may result in reduced tolerance to opioids, which increases the risk of opioid overdose if a participant resumes opioid use at the same or greater quantity and/or frequency. Participants will be informed that reduced or discontinued opioid use will result in reduced tolerance and increased risk of overdose if opioids are resumed at the same or greater quantity and/or frequency. In addition to this counseling, participants will be offered an overdose reversal kit with intranasal naloxone (which are provided by the New York City Department of Health and Mental Hygiene and stored at our outpatient research clinic STARS and offered to any participant using illicit opioids and/or participating in an opioid treatment research study). However, since we do not anticipate reductions in their methadone dose, and participants will continue to engage in normal methadone program treatment, including drug counseling, participants will be at lower risk for overdose than patients with OUD who are not on agonist replacement therapy in the community.

3. rTMS.

The main risks of rTMS are as follows:

a. Seizure: This is the greatest concern with rTMS treatment. The incidence of rTMS-induced seizures worldwide is low and roughly comparable to the estimated incidence of spontaneous seizures with antidepressant therapy (0.1– 0.6 %). In addition, rTMS-induced seizures are likely occur during or just after the rTMS treatment session (rather than after a delay) while our subjects will be under observation. In addition, there have been no reports of epilepsy or repeated spontaneous seizures occurring due to after rTMS. Since the advent of the 1998 safety guidelines, we are aware of only 8 reports of rTMS-associated seizures, and six involved either stimulus parameters exceeding the safety guidelines, or included concomitant medication or sleep deprivation, which lower the seizure threshold.

b. Lowering the Seizure Threshold: The use of concurrent medication has been implicated as a risk factor in some of the seizures reported with rTMS. These medications include tricyclic antidepressants and neuroleptics, which are not used in this study.

In the event of a seizure, the following procedures will be employed. An MD will be in the building and immediately available during all rTMS sessions. The staff member with the subject will make sure that the participant is on the floor (cannot fall) and will clear the area of all objects. Most seizures will end spontaneously at 1 to 2 minutes. In the event that the seizure has not ended in two minutes, the hospital emergency team will be called and Lorazepam (which is stored in the room) will be administered IM (4mg). If seizures continue or recur after a ten to twelve minute observation period, an additional intravenous dose of 4 mg may be administered until the acute care medical team arrives.

Brainsway has performed studies using the TMS H-coil device in control subjects and subjects in clinical conditions, including major depressive disorder, schizophrenia, bipolar disorder, obsessive compulsive disorder, addiction, blephorospasm, Parkinson's disease, and post-traumatic stress disorder (PTSD) (Brainsway, Ltd., unpublished data). High frequency (10-20 Hz) and high intensity (<120% of motor threshold [MT]) rTMS have been administered to 209 subjects, who were treated with for a total of 3314 sessions and 143,514 pulse trains. 98 of the 209 subjects received rTMS treatments (1296 sessions, 54,432 pulse trains) without concomitant psychotropic medications (which may lower the seizure threshold) and none experienced a seizure. The remaining 111 subjects received rTMS (2018 sessions, 89,082 pulse trains) in addition to concomitant

medications that could affect seizure threshold. Three of these subjects had a seizure. Of these three, one was taking antidepressant medications (venlafaxine, mianserine, mirtazapine), another was taking medications for schizophrenia (olanzepine, citalopram and lorazepam) and the third was taking lithium and clonazepam for bipolar disorder.

The primary safety outcome will be the absence of a serious adverse event or an unresolved non-serious adverse event. For each subject, we will inquire about potential non-serious adverse events after each sessions of rTMS. We will ask about headeache, hearing changes, jaw pain, and mood symptoms. If these events are reported by the subject, we will follow these daily until they remit.

The risk of pregnancy and rTMS are unknown therefore subjects who are pregnant will not be included in the study.

c. Headache: A mild headache, which responding readily to non-opioid analgesics is the most common side-effect reported in depression treatment trials. All volunteers will be treated with NSAIDs as needed for headache.

d. Hearing Impairment: Rapid excitation of the stimulation coil produces clicks that have resulted in transient increase in the auditory threshold, which does not occur if earplugs are used. A previous study assessed the auditory threshold before and after 30 sessions of rTMS (over 6 weeks) in subjects wore earplugs during stimulation and no significant mean changes were detected. All participants will wear earplugs during the delivery of stimulation.

e. Additional risks include scalp pain, dental pain, and rTMS-induced manic effect. Subjects will be evaluated for each of these and treated with over the counter pain medications if required for the scalp and dental pain. Subjects will also be evaluated for an rTMS-induced manic effect. If mania occurs, they will be removed from the protocol and monitored until these symptoms resolve.

f. Additional risks include scalp pain and rTMS-induced manic effect. Subjects will be evaluated for each of these and treated with over the counter pain medications if required for the scalp and dental pain. Subjects will also be evaluated for an rTMS-induced manic effect. If mania occurs, they will be removed from the protocol and monitored until these symptoms resolve. Convulsive 14 syncope has also been reported, and we will take the following measures to prevent this: participants will be asked to immediately report and symptoms of syncope (e.g. feeling dizzy, light headed, visual changes) and will be placed in the supine position with elevated legs if syncopal symptoms appear.

5. Risks associated with the psychological test battery include potential nervousness and frustration with the tasks. A member of the research team will carefully explain the tests before hand and will be available for questions during the tasks should they arise.

<u>Adverse Event Reporting</u>

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects and investigators, and are mandated by regulatory agencies worldwide.

1. Adverse Event Definitions and Classifications

• Adverse Event

An adverse event is any untoward medical occurrence in a clinical study subject. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product. (Definition per International Conference on Harmonization [ICH])

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

• Serious Adverse Event

A serious adverse event as defined by ICH is any untoward medical occurrence that meets any of the following conditions:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect

Note: Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in situations other than those listed above. For example, important medical events may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the outcomes listed in the definition above. Any adverse event is considered a serious adverse event if it is associated with clinical signs or symptoms judged by investigator to have a significant clinical impact.

• Unlisted (Unexpected) Adverse Event

An unlisted adverse event, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure for an unapproved investigational product or the package insert/summary of product characteristics for an approval product) (ICH)

2. Adverse Event Classification

• Mild:

Signs or symptoms, usually transient, requiring no special treatment and generally not interfering with usual activities.

• Moderate:

Signs or symptoms that may be ameliorated by simple therapeutic measures yet may interfere with usual activities.

• Severe:

Signs or symptoms that are intense or debilitating and that interfere with usual activities. Recovery is usually aided by therapeutic measures.

3. Relationship to Investigational Device

For all adverse events, the relationship to study device and / or procedure will be determined by the investigator, using the following terms:

- Probably related:

Follows a reasonable temporal sequence from study device delivery / retrieval, and cannot be reasonably explained by known characteristics of the patient's clinical data or the surgical procedure applied.

- Possibly related:

Follows a reasonable temporal sequence from study device delivery / retrieval but could have been produced by the patient's clinical state or by the surgical procedures regardless of the study device.

- Probably not related:

Temporal association is such that the study device is not likely to have had any reasonable association with the observed event.

- Not related:

No relationship to study device activation is perceived.

4. Adverse Event Reporting Procedures

All adverse events will be reported from the time a signed and dated informed consent form is obtained until completion of the last study-related procedure. Events meeting the definition of serious adverse events must be reported using the Serious Adverse Event Form, including serious adverse events spontaneously reported to the investigator within 30 days after the subject has completed the study (including post study follow up).

All events that meet the definition of a serious adverse event will be reported as serious adverse events, regardless of whether they are protocol-specific assessments. All adverse events, regardless of seriousness, severity, or presumed relationship to study treatment must be recorded using medical terminology in the source document and the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (e.g., cough, runny nose, sneezing, sore throat, and head congestion should be reported as "Upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the adverse event to study treatment. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions. In the case of a seizure, the investigators will provide to those patients experiencing a seizure a letter documenting that the seizure was experimentally produced.

The PI assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The investigator will report these events to the appropriate Institutional Review Board, which approved the protocol unless otherwise required and documented by the IRB.

5. Serious Adverse Event Reporting Procedures

All serious adverse events occurring during clinical studies must be reported to the PI by investigational staff within 24 hours of their knowledge of event. Information regarding serious adverse events will be recorded on the Serious Adverse Form, which must be signed by a member of the investigational staff.

All serious adverse events that have not resolved by the end of the study, or that have not been resolved upon discontinuation of the subject's participation in the study must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value is available
- The event can be attributed to agents other that the study treatment or to factors unrelated to study conduct

The cause of death of subject in a clinical study, whether or not the event is expected or associated with the investigational agent, is considered a serious adverse event. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a clinical study must be reported as a serious adverse event, except hospitalization for:

- Pre-planned hospitalizations, i.e. before enrollment into the study and which are not related to the disease itself
- Social reasons in absence of an adverse event
- Surgery or procedure planned before entry into the study (must be documented in the CRF)

6. Pregnancies

Pregnancies occurring during the study must be reported by the investigational staff within 1 working day of their knowledge of the event. Any subject who becomes pregnant during participation in a clinical study for which pregnancy is a standard exclusion criterion must be promptly withdrawn from the study.

Confidentiality

Participants divulge information, for example, regarding drug use, which is sensitive and may have adverse social consequences if released. We deal with issues of confidentiality by using coded records, storing signed consent forms in a locked safe, and try to the best of our ability to maintain confidentiality. Data are kept on a password protected computer, and if there is any electronic transmission concerning the study, it will use numeric identifiers rather that participant names. Brainsway, the company providing the H-coil, will not have access to participant records. We also point out to prospective participants that we cannot assure that their drug histories and other personal records might not become known. In addition, we inform volunteers that we must conform with NY State reporting requirements (e.g., child abuse). In addition to a discussion of this topic, the information is clearly stated in our consent forms.