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A Single-Blind Randomized Clinical Trial to Evaluate the Efficacy of High Vector Electrokinetics (HiVE), A Form of Peripheral Magnetic Stimulation, In Treatment of Chronic Back Pain

NCT Number Pending

Background

Chronic back pain is a common disabling condition. Some 80-84% of US adults develop back pain sometime in their lifetime. While most cases of acute lower back pain resolve on their own, chronic pain that persists beyond 4 to 12 weeks is prevalent in about 7.31-9.10% of the adult population [1,2]. Back pain broadly falls into three categories from most common to least: 1) musculoskeletal injury, 2) neurologic conditions, and 3) non-neurologic conditions such as rheumatologic disease, malignancies, or infections. It is often unclear what category an individual suffers from as presenting symptoms are typically nonspecific, overlap among categories, require expensive diagnostic tests to differentiate, and may also be caused by multiple etiologies occurring simultaneously [21].

Despite unclear specific diagnoses in most cases of chronic back pain, patients generally respond in part or wholly to combinations of treatments such as medications, physical therapy, nerve stimulation, and other manipulations [3]. The most efficacious of these has been identified as exercise, which only shows a moderate effect on fully resolving chronic back pain. Lower-quality evidence exists for other modalities, including yoga, acupuncture, medications, heat or cold treatments, stretching techniques, cognitive behavioral therapy, mobilization treatments, manipulation, and nerve stimulators [3,4].

Patients may experience difficulty accomplishing activities of daily living, lifting light objects, achieving regular restful sleep, and even lose the capacity to hold down typically non-physically demanding jobs (5). Treatment duration has also been a barrier, with most treatment modalities taking significant time away from work and requiring personal effort each day to accomplish. Studies utilizing physical therapy suggest a mean dropout rate of 18.81% with a standard deviation of 13.59%, with some studies reporting as high as a 54.5% dropout rate [66].

Current Treatments for Back Pain and limitations

Conventional treatment for back pain has become a very wide field. It has typically depended on a combination of short-term treatments, such as non-steroidal medications [3], with the addition of physical therapy. Longer-term treatments maintain the medications and therapy but start to add a host of adjunct treatments that range from cognitive behavioral therapy to electrical or magnetic stimulation and even surgery in some etiologies. To understand the proposed clinical trial, we will focus the review on the adjunct electrical and magnetic stimulation techniques commonly used.

Transcutaneous Electrical Nerve Stimulation (TENS) has been widely used to treat musculoskeletal pain syndromes. This technique delivers small electrical impulses to sites of pain using small electrodes connected to a patient's skin. The mechanism of action is believed to be caused by the activation of a broad range of sensory afferent nerves between the electrodes. These impulses operate in the 2-150 Hz range. A subset of electrical stimulation is called interferential current, which uses 4 electro-conductive pads that conduct two waves that are out of phase with each other. When these waves collide, it generates an interference that stimulates neurons and can help reduce pain. The mechanism of action for electrical stimulation is not precisely clear but it is believed to either crowd out pain signals using non-noxious stimuli that are generated from the electrical nerve activations or through increased release of endorphins through heat generation at the site of stimulation [15, 25, 33,70].

A meta-analysis of seven randomized clinical trials totaling 700 patients using continuous TENS showed significant variability in methods between studies, such as employment of nonstandard intensities and frequencies. These factors have generated overall weak evidence of effectiveness. Overall, the data suggested that TENS had more effect on improving short-term functional disability but failed to consistently improve pain scores relative to other nerve stimulation techniques [25]. Research on interferential current therapy suffers from the same low volume and non-standardized treatment modalities. It is thought to be similar in

effectiveness to traditional TENS but may not be significantly better than conventional physical therapy [16,38].

A deeper dive into TENS research suggests that patients may build up a tolerance to the treatment unless the frequency of the currents applied is changed during the procedure [71]. The electrode placements also seem to make a significant difference, as stimulation over typical acupuncture sites seems to perform significantly better at reducing opiate intake than those at non-acupuncture sites [72].

Lastly, there also appears only to be low-quality evidence with pulsed electromagnetic therapy (PEMT) for chronic lower back or neck pain. PEMT has been approved by the FDA for treatment of fracture non-unions and enhancement of bone formation after lumbar cervical spine fusion surgery. It involves applying electromagnetic wave energy at usually 10-27 MHz and is applied peripherally at the site of injury using applicator pads attached to the skin. The proposed mechanism of action is that the magnetic fields activate voltage-gated calcium channels in the underlying muscles and soft tissue that release nitric oxide, which promotes blood flow and tissue growth in the area. Clinical evidence for treatment of neck pain is also limited in this technology as there has been no standardization of therapy between trials with various magnetic field strengths and frequencies or waveforms being tried. To date, 6 relatively high-quality clinical trials have evaluated the use of this device for the treatment of back pain and found generally decreased intensity and improved functionality in patients. [7]. More recently, in 2018, studies with PEMT started experimenting with much lower frequencies, from MHz ranges to 50 Hz, and a much lower power of 20 Gauss (0.002 tesla). This pilot study demonstrated good effects on pain alone but did not necessarily show the same effects on bone healing as in traditional PEMT [92].

Transcranial magnetic stimulation (TMS), or rTMS for repetitive TMS, is a noninvasive method that causes depolarization or hyperpolarization in the brain's neurons. It creates electromagnetic energy by passing an alternating current through a metal coil over the patient’s head to induce alternating magnetic fields that pass through the skull and target the brain cells directly. These fields induce an electrical current that can cause the axons of neurons to depolarize. By changing the field strength and frequency of stimulation, specific deep structures within the brain can be selectively stimulated. The magnetic field generated is comparable to a standard magnetic resonance imaging device of 1.5 to 3 Tesla but focused on the area beneath the coil only and typically operated at frequencies of 4-150 Hz. At these frequency ranges, it is much more selective in targeting neuronal tissue which shares these harmonic frequency bands. This contrasts with PEMT, which operates with much higher frequencies in the MHz range (107 Hz) bands and predominantly targets muscle and bone tissue [39, 40, 68, 69].

The mechanism of action of TMS is believed to be similar to electroconvulsive therapy in that it directly modulates the function of neurons, leading to changes in both brain chemistry and neuronal connections. TMS can target cortical and subcortical brain structures that are related to pain modulation or processing such as the orbitofrontal cortices, medial thalamus, anterior cingulate, and periaqueductal gray matter [42]. Recent studies in nerve stimulation also point to a measurable decrease in inflammatory cytokines which could also help explain the clinical observations [93].

A variety of TMS protocols have been tested, and systematic reviews of over 1,030 articles have shown significant variations between clinical trials for various pain conditions. Stimulation frequencies with higher frequencies >5 Hz are typically excitatory and lower frequencies <1 Hz are inhibitory to neural cortex activity and measurable circulatory changes. One hypothesis on how TMS functions in the brain is that repetitive excitatory stimulation with higher frequencies could be triggering inhibitory neural pathways at the dorsal-horn level, leading to suppressed pain perception [41, 42]. In short, the brain appears to change the way it perceives pain after TMS by either changing the way it codes information or by activating more neurons that suppress pain.

TMS has shown effectiveness in a variety of specific pain syndromes, such as neuropathic pain [48], fibromyalgia [47], central pain syndromes [49,50], and even phantom limb pain [43]. The latest 2020

European consensus guideline on rTMS found grade A evidence (highest confidence in evidence) that rTMS was effective for the treatment of neuropathic pain [62]. There has, however, only been one randomized clinical trial using rTMS to treat undifferentiated lower back pain [45] with 2 other case reports [44, 46]. While the body of evidence has been small, all the lower back pain data so far showed favorable outcomes using a stimulation technique over the M1 Primary motor cortex, Brodmann area 4. The lower back pain treatment group used 20Hz frequency using 10 pulse trains of 10 sec each (2000 pulses per session) with a figure 8 coil targeting 95% resting membrane threshold for a total of 5 sessions.

Yang's [42] meta-analysis data showed that most successful treatments used 10-20Hz frequency for around 10-20 sessions of 30 minutes each utilizing around 1600-3000 pulses per session targeting approximately 80-100% resting motor threshold. Targeting was generally achieved by utilizing either a 5 or 6 cm rule for general placement or the international 10-20 system utilizing measuring tape and marking pens to identify scalp location corresponding with the left prefrontal cortex or by marking the location that produces twitches in a hand muscle which corresponds to the M1 first dorsal interosseous region [56, 57, 58]. The efficacy was measured by the Visual Analog Scale (VAS) or Numerical Rating Scale (NRS). While a minority of studies (10%) showed no benefit, they contained more single treatment courses (43% of failure reports) instead of using a series of treatments [42]. Additional dose therapies have been associated with increased efficacy by 68%, though patient tolerance becomes more of a factor with 11% increased dropout rates when going from a standard dose of 3000 cycles to 6800 cycles [51]. To date, there has never been a randomized clinical trial done to evaluate TMS effects on undifferentiated neck pain or recommending a standardized treatment strategy [42].

Repetitive Peripheral Magnetic Stimulation (rPMS)

The final variation to be discussed here is repetitive Peripheral Magnetic Stimulation (rPMS). This process takes the neuron specific targeting of TMS and uses it in a way similar to a TENS or PEMT system by stimulating peripheral afferent (sending signals to the brain) nerves at sites of pain. This technique differs from those other modalities as the frequencies and power used are less likely to activate other structures like muscles or bones and can be more specific to neuron activation. There have been only 25 clinical trials to date that have tried to use the rPMS technique on pain management though most have seemed promising [73, 74]. More commonly, research for this tool is in stroke rehab settings to stimulate areas that have lost function. A meta-analysis of rPMS generally showed positive results in regard to pain control, motor dynamics, and reduction in muscle spasticity [54].

One proposed mechanism for rPMS is that the magnetic field directly depolarizes the axons of peripheral nerves that deliver signals from the body up to the brain. The larger and faster conducting Aβ (alpha beta) spinal nerves are directly stimulated, which crowds out the smaller Ad (alpha delta) and C type nerve fibers that usually process cutaneous pain signals similar to how a TENS unit is theorized to function [33]. However, magnetic fields in the usual rPMS treatment frequencies of around 20 Hz tend to directly activate proprioception nerves type Ia, Ib, and II. These proprioceptive nerves are responsible for sending messages of body position to the brain, so they do not necessarily share the same pathways theorized in TENS. There have not been any studies that found rPMS directly activating any pain inhibitory pathways in the brain or peripherally.

One other hypothesis is that the peripheral activation of neurons stimulates changes directly in the brain. The large amount of proprioception signals from peripheral stimulation seems to cause the frontoparietal networks of the motor cortex to change their activation patterns. PET scans performed on stroke patients receiving rPMS also showed increased regional blood flow to the premotor cortex, parietal lobe, and motor cingulum. These findings suggest that rPMS could directly influence how the brain perceives incoming signals; this might explain how this treatment can continue to have effects following therapy, whereas TENS ceases to have effects when not actively stimulating. Despite its inception 40 years ago, there is still no clear consensus on how this system functions in the body or brain [74, 55, 52].

A relatively recent study by Lim et al in 2018 [55] warrants closer examination as it is close in study design to our proposal. Lim's study focused on acute undifferentiated lower back pain using rPMS. Their study took 26 patients with 12 patients receiving 10 sessions of peripheral stimulation at a frequency of 20 Hz for 5 seconds followed by 25 seconds of rest for 20 minutes or 4000 total pulses delivered per session. The power setting selected was enough to trigger the motor potential along the paraspinal muscles of each subject. These settings mimic prior pilot studies done by Smania et al in 2003 and 2005 (75, 76). The target locations were over the area where patients described the most pain in their lower back. All patients tolerated the sessions extremely well with no reported side effects. Oswerty Disability Index (ODI) and a Visual Analog pain Scale (VAS) were used to measure the effects of treatment.

Patients in their real treatment group showed a statistical reduction in pain after every treatment with the most significant difference following the second session with overall lower total pain scores after 10 sessions compared with the sham treatment group. The treatment group also achieved statistically significant improvement to the ODI after 5 sessions which persisted to the end after all 10 sessions were performed. The study concluded that with early treatment, pain was improved and led to earlier functional recovery. Interestingly, Lim also confirmed that the analgesic effects of rPMS appeared to also persist following each treatment. This may suggest that the brain's perception of pain was also modulated from peripheral nerve stimulation and the pain relief was not only from spinal effects which would have stopped once the treatment session ended. There was however insufficient testing or evidence to draw a specific conclusion on why this occurred from their study.

Though few studies have evaluated rPMS, the procedures have been universally well tolerated. There have not been any significant side effects reported in any of the studies since the technology was invented in 1982 [54]. The most up-to-date literature in 2021 points to possible concerns with excessive heating of the magnetic coil with prolonged use, which may get as high as 43 degrees Celsius if not monitored. More treatment sessions also seemed to show improved response rates, though no longevity data have currently been published [74].

While there does not appear to be a significant concern with safety and implanted devices, there is still a theoretical complication with the use of this device with any ferromagnetic implants. Experiments on brain aneurysm clips using TMS have resulted in less than 0.0003 mm of movement. The induced voltage from magnetic fields may also theoretically disrupt implanted electronic devices such as pacemakers if applied directly over the area, so care must be taken around anyone with such a device [53].

The only other noted concerns have been mild muscle discomfort reported in studies that used very high frequency or impulse intensities. Still, no long-term side effects or life-threatening conditions were ever recorded. While traditional brain TMS has a seizure risk, this has never been reported in rPMS and is not theoretically possible since it does not stimulate the brain directly. The technology is likely safe for children but this has not been well studied. Similarly, no safety information has been established for pregnancy, but it has been suggested that pregnant women not receive lumbar spine stimulation due to theoretical risk of uterine contractions [74].

Mechanisms and Rationale of this Study

Chronic back pain likely involves two components: 1) the initial injury and 2) continuous compensatory muscle contraction. The positive feedback in this natural protection process forms a vicious cycle that contributes to developing chronic pain. The goal of this study is to test a treatment protocol that is designed to break this loop by masking the nerve pulses that carry both sensory information for pain going up to the brain (afferent) and the muscle contraction signals going down from the brain (efferent).

Over the past 3 years, the Langley AFB Optimizing the Human Weapon Systems team has been using a 510K Food and Drug Authority (FDA) approved TMS device for stimulating nerves in the brain in an off-

label manner as a peripheral magnetic treatment procedure to stimulate peripheral nerves instead of cranial nerves to treat fighter pilots' back and neck pains. The clinical team used an averaged 80Hz frequency range band in a similar stimulation cycle as in the 2018 Lim study but utilized a variable band stimulation frequency instead of the typical single 20Hz frequency as in traditional rPMS.

By avoiding a single discrete frequency, it is believed that more patients should be able to feel the pulse location in case their proprioception nerves do not operate on a single exact frequency and fail to achieve a resonance with the stimulation. This will aid the provider in applying stimulation to the exact location of their pain instead of just stimulating a general area. This technique also takes advantage of standard methods typically used in other treatment modalities like trigger point injections, where the exact location affects treatment outcome. While unpublished, the anecdotal response rate for lower back pain amongst fighter pilots treated with this procedure was around 60-70%, while neck pain seemed more resistant to this treatment with around 40% response.

The device we propose to test is the same as the modified TMS device used at Langley AFB. This TMS system has the same frequency control algorithm and utilizes the same electric pulse generator with internal temperature monitoring and an extended coil for magnetic stimulation. The coil is placed on the patient closest to sites of pain and steered by the patient's response to stimulation pulses. The pulse generator will generate trains of electromagnetic white noises to ensure the temporary blockage of both the neuromuscular transmission for both afferent and efferent signals.

We believe these pulses work through the application of signal-processing mechanics involving something called the Nyquist theorem. The Nyquist theorem states that a periodic analog signal must be sampled at more than twice the highest frequency component of the signal to reliably convert it discretely into a digital format; otherwise, aliasing may occur. Aliasing is the error phenomenon where a receiver source does not sample a signal fast enough to construct an accurate waveform record [79]. The reverse application of this theorem, therefore, is to flush twice as much discrete information in a given time to saturate the system.

An easier way to understand this is to apply a model of motion pictures or AC flickering to the human eye. Human visual processing is barely 10 frames per second. 24 slides/sec in movies or 60 Hz of flickering still images are more than twice as much as human eyes' maximal process rate. When watched, this reliably "fools" our senses, and we perceive the rapidly moving slide show of still images as if they123456 were in smooth continuous motion. In this case we are taking advantage of aliasing to perceive a movie. If you show slides at less than 10 frames/second, we would perceive each as discrete still images.

As in the Langley AFB off-label clinical treatment protocol, we have selected a variable pulse interval of 10 to 16 milliseconds. This results in the creation of a frequency range between 60 and 100 Hz with an average of 80 Hz. The pain sense nerves in the paraspinal region operate roughly between 8-30 Hz with variation between individuals. Supplying pulses at a rate that is more than twice the maximum rate may temporarily crowd out the normal pain contraction cycle. Providing randomization between pulses also ensures that we are not transmitting any perceptible information that could be constructed as discrete information packets, thus further improving the masking effect [72, 73, 77, 83]. Additionally, as proprioception nerves operate in this range, we utilize the patient to direct the treatment to the site of pain instead of just a specific anatomic area. This is also where we derive the term High Vector Electrokinetics (HiVE) for the title. "High Vector" because we are applying a sampling rate of more than twice the processing rate of the nerves we are targeting.

We would also have to supply enough power to cause axonal depolarization and mask both afferent and efferent signals. Our angulated figure of 8 magnetic coils consists of two 84x106 mm coils with a maximum power output of 1.65 tesla and with a maximal field depth of approximately 1.8 to 2.1 cm deep. In most cases, we would need to hold the figure 8 magnetic probe very close to or touching the skin to reach the spinal nerves. More specific to our test, we would be supplying roughly 0.3 tesla to 0.58 tesla of power (equating to approximately 20-35% maximum power on our machine) to the nerves under our probe.

As the tissue thickness between the skin and nerves is variable for each individual, which may weaken the signal that is delivered, we will start with the lower end of the theoretical threshold and titrate up based on patient tolerance. Patients can usually feel some tingling sensations with these stimulation levels, so they can generally direct the location and intensity [80,81]. Operating within these constraints on our study participants should offer a very targeted and safe treatment modality with high confidence of the effects.

Summary

Currently, available treatments for chronic back pain have been varied, with literature showing that a multimodal approach utilizing multiple therapies simultaneously has more impact than single treatment modalities. Additionally, a greater portion of fighter aircrew (37%) [67] experience chronic lower pains from increased G force loads when compared with incidence rates in the general population of around 9% at any particular point in time [1], which makes this study particularly interesting to the USAF.

The amount of pain not only affects typical disability-scoring mechanisms like household work in these pilots but also significantly reduces their combat lethality. Pain can distract pilot concentration, limit endurance in long flights, and reduce capabilities to endure prolonged wear of helmets. Due to tight flying schedules and some treatments or medications which may result in pilots temporarily losing their medical clearance to fly, or conflict with mission planning and flying, there is a tremendous need to find other non-invasive, non-pharmacological treatment modalities that can be applied quickly to alleviate their pain.

rPMS is known to be a well-tolerated procedure with few side effects. There is a growing body of evidence that suggests rPMS can be used to reduce pain burden in a variety of pain syndromes including undifferentiated lower back pain. The rPMS treatment protocol being evaluated here increases the stimulation frequency range to theoretically improve capture of individual nerve operating frequency and improve the masking effect.

This protocol would also offer significantly faster time to administer than most other adjunctive therapies, foster early functional recovery, and likely encourage return to combat duties faster than conventional treatments which makes it very attractive to use in an operational setting. We aim to compare the results of the visual analog pain scale and the Oswestry Disability Index after real rPMS compared to sham rPMS. It will also be interesting to compare our VAS results to the existing literature using traditional standard single-frequency rPMS.

Objectives/Specific Aims/Research Questions:

Purpose:
To evaluate the efficacy of the repetitive individualized Peripheral Magnetic Stimulation (rPMS) utilizing the High Vector Electrokinetics (HiVE) treatment protocol in comparison to sham rPMS in treating undifferentiated chronic low back pain (pain > 12 weeks).

Research Questions:

- Over the course of the study, is rPMS utilizing HiVE in conjunction with conventional treatment options (ie, home exercise program information) effective for treating chronic low back pain in adults as measured by Visual Analog Scale (VAS) scores?
- Over the course of the study, is rPMS utilizing HiVE in conjunction with conventional treatment options (ie, home exercise program information) effective for improving functional ability in chronic low back pain sufferers as measured by the Owestry Disability Index (ODI) scores?
- Does rPMS utilizing HiVE in conjunction with conventional treatment options (ie, home exercise program information) reduce pain severity in comparison to a sham rPMS in conjunction with conventional treatment options in chronic low back pain sufferers?

Hypotheses:

- Five sessions of real rPMS treatment targeted over the correct nerve root area used in conjunction with conventional treatment options (ie, home exercise program information) will reduce pain severity in chronic back pain sufferers as measured by the VAS.
- Five sessions of real rPMS treatment targeted over the correct nerve root area used in conjunction with conventional treatment options (ie, home exercise program information) will improve functional ability in chronic back pain sufferers as measured by the ODI.
- There will be an improvement in Visual Analog Scale (VAS) and Oswerty Disability Index (ODI) scores in the real rPMS treatment group compared to the sham rPMS treatment group.

Study Design:

This clinical research is a prospective, single-blind, randomized, sham-controlled study designed to evaluate the efficacy of rPMS utilizing a new variable frequency hopping, low power, peripheral nerve stimulation modality in treatment of chronic low back pain.

Study Procedures, Data Management, and Privacy

PRESCREENING:
Participants will be recruited through poster advertisements, social media posts (i.e., Facebook), and briefings (i.e., Prostaff) to encourage patient referrals. Interested patients may contact their local site investigators for additional study information. Patient and referring providers will provide a full name, date of birth (DOB), and phone number to allow investigators to review medical history in the electronic medical record (EMR), Military Health System (MHS) Genesis to determine study eligibility using the Inclusion/Exclusion Checklist and contact the patient to inform them of their eligibility status. An IRB-approved HIPAA Waiver will be used to facilitate this process. Patients who are eligible will be contacted and scheduled for a consent visit and to obtain a pregnancy test for women capable of pregnancy. The consent visit will be approximately one hour. Prior to the consent visit, patients will be asked to provide their email address if they would like to be emailed study documents (i.e., consent documents, home exercise plan) or invited to come into the facility to pick up hard copies for pre-review to expedite the consent visit. All patients screened will be entered into the Pre-screen Log and assigned a pre-screen ID number.

CONSENT VISIT:
The investigator will review the consent form with the patient, answer any questions he/she may have, then document consent. After signing consent documents, women of childbearing age who are capable of pregnancy will complete a baseline pregnancy (HCG) test by urine or blood. Women with a negative result will continue in the study; those with a positive test will not (i.e., screen failed).

ENROLLMENT:
Patients who meet all study criteria will be assigned a subject ID, then randomized by equal distribution into study groups using randomizer.org. Participants will not know what study group they have been randomly assigned to; only the investigators will have this information. The Master Key will be pre-populated to identify the study group for each subject ID. The spreadsheet will be located on a shared Microsoft Teams site so all sites can see live updates and easily avoid using the same number.

Contact and demographic information will include email address (if not already obtained), AFSC (active duty), years of military service (active duty, retirees), age, sex, and current employment history for beneficiaries with and without prior military service (i.e., job title, years working in current job). Emergency contact information will be obtained and documented.

Participants will be advised to avoid starting any new clinical treatments (i.e., ultrasound, dry needling, trigger point injections and other holistic medicine treatments) or medication, and to use an effective form of birth control during the study. Participants that start a new treatment or medications during the test period will be withdrawn. Participants will be asked "Has there been any change to the medications you take within the last 30 days?" and "Have you started any new treatments such as ultrasound, dry needling, trigger point injection, or other holistic medicine treatments?" before each session.

All participants, including those who were not already doing some sort of home physical therapy routines, will be provided with information on a home exercise program with stretching and range of motion exercises. Participants will be given a printed set of exercises to do at home with pictures. It will include instructions on the frequency and number of sets to be done for each exercise and have an area to document this on the handout. Investigators will assess compliance with home exercises at the end of the treatment week by asking participants "How many days did you do the home exercises? How many sets did you do of each exercise? Participants will be instructed to perform exercises once a day with at least 1 set of each exercise for the week.

QUESTIONNAIRES:
Participants will be given a Visual Analog Scale (VAS) and Oswestry Disability Index (ODI) questionnaires to complete at various times. The VAS will be completed at baseline and at the beginning and end of each

treatment (ie, real rPMS or sham rPMS) session. The VAS is a commonly used clinical tool for assessing pain. It is usually a 100-mm long horizontal line with verbal descriptors at each end to express the extremes of the feeling. Participants will be instructed to verbalize the point on the line that best corresponds to their symptom severity. 0 would be no pain and 100 would be extreme pain. For those participants whose first treatment session is the same day as their consent visit, the same baseline VAS can be used for both baseline and before treatment.

The ODI will be completed at baseline and at the beginning of sessions 2 and 5. Subjects randomized to the sham group who opt to convert to the open label portion of the study will also complete it at sessions 7 and 10. The ODI assesses functionality and will be administered via hard copy printout. It is composed of 10 questions that help determine the amount of functional capability that patients have in their daily lives such as ability to lift, self-care, walking, or sitting function. The ODI has a long history of reliability and internal consistency since the 1990s [78]. It helps stratify pain quality, pain locations, other comorbidities, and functional disability. Many other studies also use either the ODI or a variation of it so this would also improve cross test comparisons. These data will be used to monitor for enduring treatment effects and help determine efficacy when compared to conventional treatments. It is free to use and download for physicians and clinical practices.

SESSIONS:
Participants will be scheduled for 5 sessions of real rPMS or sham rPMS based on their randomly assigned study group. The first session can be on the same day as the consent visit. Sessions will be performed daily during the work week by site investigators. In the case of family days, holidays, down days, scheduling conflicts, and weekends, no treatments will be provided. While it is likely that consecutive treatments without breaks may yield more beneficial results, this is unlikely to be a realistic scenario in real-life practice, and it is highly likely that the majority of the five sessions will not be consecutive. Thus, we will review the data for those participants who had treatment start and end date within 5 days of each other to do a secondary analysis.

At each session, prior to using the device, participants will be asked about possible adverse events that may have experienced since their last study session and to provide a VAS score of their current subjective pain levels. At the beginning of sessions 2 and 5, participants will be asked to fill out the Oswestry Disability Index (ODI). For those that continue on in the open label portion of the study, they will also fill out the ODI again at sessions 7 and 10. After each session, participants will be asked to provide another VAS subjective pain score and assessed for any immediate adverse events. Participants will be advised to continue with their current medications (if any) and physical therapy routines during the study. They will be asked to inform the research team of possible pregnancy, or any changes in medication or treatments to determine if it is appropriate for them to continue in the study.

The investigators will also state to all participants that they may or may not feel any sensation with the device but they will hear some computer-generated tones to indicate that the device is operating. The protocol here is single-blinded, as the participants cannot discern between TMS wands that are active versus TMS wands that are turned off without prior experience. The investigators administering the treatment will not be blinded as they will have to configure the device appropriately (ie, for real rPMS or sham rPMS) in each case. Patients who receive real rPMS will also be able to feel the nerve stimulation which is impossible to blind them to.

The standard of care/conventional treatment of home exercise regimens and stretches will be administered to both treatment and sham group. The sham group will only be different from the treatment group in that their five sessions with a TMS wand will not be powered. If the sham group elects to join the treatment group in the open portion of the experiment, they will also be able to feel the nerve stimulation difference.

Real rPMS treatment sessions: The investigator will:

1) Configure the rPMS device to deliver the treatment regimen (duration time of 2 minutes and 30 seconds), place the treatment wand over the participant's back pain area, then verbalize to the patient that they are activating the system.

2) Begin stimulation operation at 20% advancing in 5% increments to maximum of 35% machine power which in our case is approximately 0.3 tesla to 0.58 tesla of power (a typical outpatient MRI is 1.5 to 3 tesla). The power of the unit will be titrated up to the maximum 35% based on patient tolerance by asking participants to "Tell me if you feel a painful muscle contraction". Patients receiving active therapy would be able to feel the stimulus usually described as a vibration sensation. If patients report painful muscle contractions, stop and go back by 5%. Doing this helps ensure that we would not cause any potentially painful muscle contractions and avoid confounding our test data. The first treatment will start at 20% power then increase by 5% until the titrated power level is identified, subsequent treatments will start at the power level used in the last treatment session and decreased by 5% increments if the participant reports painful muscle contractions when stimulation is started. The power level that produces no painful muscle contractions will be used for the treatment. The power setting used for each treatment session will be annotated in the data sheet for that patient. Annotate the tolerated power setting in the data sheet for that patient on each visit. The titrated power setting will be used for all 5 sessions.

3) Adjust the stimulation over the area of pain to the patient's preference. If pain is bilateral, then ask the patient to pick the most painful spot to perform the treatment. The patient will generally be able to tell if the nerve is being stimulated and the treating investigator will adjust the probe based on patient response toward the most painful location.

4) Use a variable stimulation rate (i.e. the time between pulses will change between each pulse using a computer algorithm randomizer for each value). The center value will be 13ms between pulses with lower bounds of 11ms and high of 14 ms. This translates to estimated values of lower bounds of 71.43 Hz, central value of 83 Hz, and maximum value of 99 Hz for comparison with other studies though the word "frequencies" cannot be readily applied here due to the variable times between pulses but is used for ease of discussion. Each variable stimulation session will utilize all of the frequencies between 71.43 Hz to 99 Hz.

5) Once the treatment location and stimulation powers are determined under steps 3 and 4, the treatment stimulation session will begin. It will consist of 10 trains with 10 seconds between trains. Each train is 5 seconds or approximately 3500-5000 total pulses per session. Each session will last 150 seconds (2 minutes, 30 seconds). The magnetic coil will only be operated when coil temperature is below 23 degrees C. There is an internal temperature monitor built into the testing device that displays the temperature on the operator's screen. There is also a built-in automatic safety that cuts off machine function if it is over 25 degrees C.

6) The investigator will document the treatment session in the participant's electronic medical record using the same format and coding as for a routine appointment.

Sham treatment sessions: The investigator will:

1) Configure the rPMS device to not utilize any power, then place the treatment wand over the participant's back pain area and hit the start button as normal. When the power setting is set to zero, the magnetic wand will not generate any power but will still make the customary computer-generated tones as it does in normal operation. The device is set to play a completed tone once 2 minutes and 30 seconds have elapsed just as it does in the normal treatment. The investigator will then replace the wand back to the storage position and notify the patient that the session is completed.

Following completion of 5 sessions, the sham group will be offered to receive up to 5 sessions of real rPMS stimulation. The data from the sham treatment and real rPMS treatment for these patients will be tracked separately.

Data Collection:

Demographics information: AFSC (active duty), years of military service (active duty, retirees), age, sex, and current employment history for beneficiaries with and without prior military service (i.e., job title, years working in current job)

Location (left, right,upper back, lower back) of pain obtained from participants at the time of enrollment and at each study visit.

Compliance with home exercises will be obtained at the beginning of sessions 5 and 10. Data will be collected on the number of sets performed for each exercise and number of days exercised.

Changes to participant's normal drug regimen will be assessed at the beginning of each visit by asking, "Has there been any change to the medications you take within the last 30 days?" to determine continued study participation. A yes or no response will be recorded. Participants with a "yes" with be withdrawn from the study.

Changes to participant's clinical treatment regimen will be assessed at the beginning of each visit by asking, "Have you started any new treatments such as ultrasound, dry needling, trigger point injection, or other holistic medicine treatments?" to determine continued participation in the study. A yes or no response will be recorded. Participants with a "yes" with be withdrawn from the study.

Adverse Events will be assessed at the beginning and end of each session. At the beginning of the session, participants will be asked "Have you experienced any symptoms or been diagnosed with any new conditions since you enrolled into the study?" Immediately after the session they will be asked, "Are you having significantly more pain or burning in the area treated? A yes or no response will be documented. Additional information will be obtained for "yes" responses to determine if IRB reporting is appropriate.

Primary

VAS (self-reported) obtained at time of enrollment (baseline) and compared to the end of session 5. VAS will also be obtained before and after each session. For participants randomized to the sham group who opt to convert to the real PMS portion of the study, the VAS will also be obtained at the beginning and ends of sessions 6-10. Zero (0) indicates no pain and 100 indicates extreme pain. A response from 0-100 will be recorded. VAS recordings are done during each clinic visit to help assess for significantly increased pains which may indicate an adverse event but the end point of comparison will be for beginning of treatment and 5 sessions later.

Secondary

ODI: electronic or printed copies will be provided to participants to complete at the time of enrollment (baseline), and the beginning of sessions 2 and 5. For participants randomized to the sham group who opt to convert to the real PMS portion of the study, it will also be obtained at the beginning of sessions 7 and 10. A score of 0 – 5 will be obtained for each question. There are a total of 10 questions. The total score will be divided by 50 (total score possible) then multiplied by 100. The final score will be a percent ranging from 0 - 100. The percent will be recorded.

Managing Data (Data Management and/or Sharing Plan) and/or Human Biological Specimens for this Study:

Plan for acquiring data (electronic, hard copy): Data will be acquired through participant interview (demographic, medication history, location of pain, adverse events, home exercise compliance), pregnancy test results from the electronic medical record, and administering questionnaires (VAS, ODI).

Plan for accessing data during the study: Data collected will be documented in Excel spreadsheets maintained in a private, invite only Microsoft Teams folder with password encryption and participant's electronic medical record (by investigators) on a DOD CAC-enabled computer by authorized study investigators only. Access to the Microsoft Teams folder will be granted only to site investigators. All data will be accessible to study investigators throughout the duration of the study.

Plan for storage of data: Hard copy data will be kept in a locked filing cabinet. Those containing PII/PHI will be separated. Electronic documents will be stored on a DOD CAC-enabled computer, in encrypted and password-protected files accessible to each site investigator. The Screening Log and Enrollment Master Key will be kept separate from each other and in a separate folder from all other electronic study documents. These documents will not be printed at any time. These records will be accessible only to study investigators, the IRB, DGMC HRPP staff, and employees of authorized Federal departments and regulatory agencies.

Plan for storage at the conclusion of the study and final disposition: All hard copy study documents will be maintained by the principal investigator for 6 years after the last use of the HIPAA authorization (DoDM 6025.18, Section 7.3.d.(2) in locked file cabinets. Six years after the last use of the HIPAA authorization these documents will be shredded or placed into government authorized shredding bins for later shredding. Electronic documents will be de-identified at time of study closure to destroy links of data to individual study participants then stored on a DOD CAC-enabled computer, in password-protected files. Electronic documents will be deleted 6 years after last use. and Excel spreadsheets in Microsoft Teams will be deleted from cloud based shared drives and local disk drives. DGMC HRPP staff will have access to all documents (hard copy, electronic).

Statistical/Data Analysis Plan

Data Analysis Plan

All data collected will be entered as coded or raw data and tabulated into Excel spreadsheets. The data will be verified for accuracy by the principal investigator and/or at participating sites by a designated 711 HPW auditor to ensure compliance with research grant requirements. An initial audit will occur after the first enrollment at each site, then at random intervals. After all data has been collected and de-identified it will be securely forwarded to the biostatistician for analyses.

Statistical Considerations

Descriptive statistics (eg, mean, median, standard deviation, range, frequency, and percentage) will be calculated for AFSC, years of military service, current employment history (dependents, retirees), age, and sex to provide a demographic of the enrolled population.

Descriptive statistics will also be calculated for location and level of pain (ie, VAS).

Descriptive statistics will also be calculated for compliance with standardized back pain home exercise plan.

Primary Outcomes: to measure the effects of rPMS on chronic low back pain by comparing VAS scores in rPMS treatment versus sham treatment. We will also evaluate the change in VAS pain scores before and after each treatment session.

The primary efficacy outcome measure will consist of the change in VAS score from baseline to the end of session 5. Treatment efficacy may also be defined as a greater reduction in mean VAS score in the rPMS treatment group compared to the sham treatment group. VAS change scores will also be assessed to determine if they are greater than the previously reported Minimal Clinically Important Difference of 1.4 cm on the 10cm-VAS [79]. Clinical improvement will be calculated as percentage change using the following formula:

Change Score (%) = Baseline VAS – end of 5 sessions of rPMS VAS x 100

Secondary Outcomes: to measure the effect of rPMS on disability and functional capabilities.

The secondary efficacy outcome will include the comparison of ODI scores. Symptom measures will consist of the change in ODI total scores from baseline until the end of 2 and 5 sessions of treatment or sessions 7 and 10 for the sham group that later opts to receive open label (ie, real rPMS) treatment.

The following formulas will be used for calculating the percentage change in symptoms:

Completed Treatment Change Score (%) = Baseline ODI scores – end of 5 sessions of treatment
ODI scores x 100

The data will be plotted to assess normality and equality of variance and determine whether parametric or nonparametric tests are appropriate; critical alpha level will be .05. If the appropriate assumptions are met, analysis of variance (ANOVA) using time as a repeated measures factor will be used to determine if there is a statistically significant change in VAS and ODI scores as a function of time in the real rPMS group and the sham rPMS group; if assumptions are not met then the appropriate nonparametric technique (eg, Friedman's test or Skilling's Mack test) will be used instead. The appropriate parametric or nonparametric technique (eg, Student's t test or Wilcoxon Mann Whitney test) may be used to compare change scores between real rPMS

and sham treatment groups at different points in the study; the Bonferroni correction procedure will be used in cases of multiple pairwise comparisons.

Our data may also be numerically compared with data from historical (published) single frequency rPMS although statistical tests will not be performed due to variability in study designs.

Data from participants in the sham group who later wish to participate in the open label/ real rPMS portion of the study will have their VAS and ODI data analyzed separately from those initially allocated to the rPMS group since they will not be blinded; they will be designated "rPMS-a" for ease of reference.

Data collected on any participant that withdraws from the study will still be analyzed. Outlying data will be analyzed and participants with missing data will be analyzed using the pairwise deletion method to maximize available data.

Sensitivity analyses may also be performed as necessary to check the robustness of the primary findings.

Sample Size:

88 total participants will be recruited into the study; 44 participants will be randomized into the rPMS treatment group and 44 participants will be randomized into the sham treatment group. The assignment to group will be determined by consulting a pre-generated randomized list. We anticipate up to 20 participants will be lost to attrition.

Please provide a justification for your sample size

G-Power 3.1.9.7 determined that a sample size of 34 per group (68 total) would detect a relatively large effect size of 0.7 using an independent samples t test with a two-tailed alpha of .05 and 80% power.
We plan to enroll 88 participants to allow for up to 20 dropouts.

If there are more than 10 dropouts in the sham group and/or the treatment group, we may only have the power to detect an effect larger than 0.7; this will be acknowledged in our results and the actual effect size detectable may be calculated *post hoc.*

Ref:
Faul, F., Erdfelder, E., Buchner, A., & Lang, A.-G. (2009). Statistical power analyses using G*Power 3.1: Tests for correlation and regression analyses. *Behavior Research Methods*, *41*, 1149-1160.

https://www.psychologie.hhu.de/arbeitsgruppen/allgemeine-psychologie-und-arbeitspsychologie/gpower

Participant Information

Subject Population:

Active duty and other members eligible for care at the participating military treatment facilities (MTFs) who are between the ages of 18-64 years with a diagnosis of unspecified chronic low back pain for greater than 12 weeks.

Age Range:

Check all the boxes that apply. if the age range of potential subjects (specimens, records) does not match the range(s) selected, please specify in the text box.

☒ 18-24

☒ 25-34

☒ 35-44

☒ 45-54

☒ 55-64

Gender:

☒ Male

☒ Female

☐ Other

Inclusion Criteria:

- Diagnosed with chronic low back pain (greater than or equal to 12 weeks) with or without concurrent neck pain.
- Low back pain in the paraspinal region (L1-S2) by asking the patient to point to their area of pain.
- 18 - 64 years old (on the day of informed consent)
- Willing and able to attend all study visits.
- No medication changes for at least 30 days before study enrollment (self-report)
- Eligible for care at military treatment facilities located at Edwards AFB, Luke AFB, or Langley AFB
- Able to read and understand English.
- Negative pregnancy test for women capable of pregnancy.

Exclusion Criteria:

- Diagnosed with low back pain of less than 12 weeks duration
- History of back fractures or surgical repair of the back
- History of depression with vagus nerve stimulation
- Any type of transcranial magnetic stimulation (TMS), or rPMS treatment prior to study enrollment.
- Currently using any other adjunctive treatments for chronic back pain such as low-level laser treatment, ultrasound, dry needling, chiropractor manipulations, cervical collars, TENS units, or other stimulation, eastern medicine regimens including Qi Gong or Tai Chi. (**Exception:** strength building physical therapy, non-neuropathic pain modifiers, and non-anticonvulsant routine pain medicine regimens such as NSAIDS and Acetaminophen are allowed).Scheduled for nerve ablation, dry needling, trigger point injections, nerve block, therapeutic ultrasound, other stimulation, or similar adjunct treatments during the study period.
- Diagnosed with a specific low back pain: osteoarthritis, rheumatoid arthritis, phantom limb pain, central pain syndrome, spinal cord damage, myofascial pain syndrome, or other more specific diagnosis (at investigators discretion).
- Unstable or poorly controlled mental health diagnosis (e.g., current changes in medication or medical management).
- Dermal or subdermal implants (e.g., aneurysm clips, shunts, stimulators, ferro magnetic implants, stents, or electrodes, or pacemakers) or any other metal object within or near the site of stimulation which cannot be safely removed.
- Clinically significant abnormality or clinically significant unstable medical condition that, in the investigator's judgment, might pose a potential safety risk to the subject or limit interpretation of the trial results.
- Any condition which, in the judgment of the investigator, would prevent the patient from completing study procedures.
- Pregnancy
- Younger than 18 years old (on the day of informed consent)
- Older than 64 years old (on the day of informed consent)
- NOT willing or able to attend all study visits.
- Medication changes for back pain less than 30 days prior to study enrollment (self-report)
- NOT eligible for care at MTFs
- NOT able to read and understand English.

Recruitment and Consent

Participants will be recruited through poster/flyer advertisements, social media posts (i.e., Facebook), and briefings to healthcare personnel (i.e., Prostaff) to encourage them to refer patients with chronic back pain. Interested patients may contact their local site investigators for additional study information. Patient and referring providers will provide a full name, date of birth (DOB), phone number, and email address (optional) to allow investigators to review medical history in the electronic medical record (EMR), Military Health System (MHS) Genesis, to determine study eligibility using the Inclusion/Exclusion Checklist, and to later contact the patient to inform him/her of their eligibility status. An IRB-approved HIPAA Waiver will be used to facilitate this process. Patients who are eligible, will be contacted and scheduled a consent visit to obtain a pregnancy test (women capable of pregnancy), review and sign consent documents. Women with a negative pregnancy test will be enrolled into the study.

Pre-screening process.

Interested patients and referring providers will provide a full name, date of birth (DOB), and phone number to allow investigators to review medical history in the electronic medical record (EMR), Military Health System (MHS) Genesis to determine study eligibility using the Inclusion/Exclusion Checklist, and to later contact the patient to inform him/her of their eligibility status. An IRB-approved HIPAA Waiver will be used to facilitate this process. Patients who are eligible, will be contacted and scheduled a consent visit to obtain a pregnancy test (women capable of pregnancy), review and sign consent documents. All patients who are screened will be given a pre-screen ID. Patient who require a pregnancy test will be consented prior to ordering and completing the HCG (sample of urine or blood). Women with a negative pregnancy test will be enrolled into the study.

Consent Process:

After an investigator confirms study eligibility by reviewing the patient's medical history in the EMR, he/she will contact the patient to schedule a consent visit to review and sign consent documents and order a pregnancy test (women capable of pregnancy). At this time, the investigator will offer to email (or provide access to a hard copy) consent documents, and home exercise plan to allow the patient to review them prior to the visit. If the patient desires to review the documents, the investigator will obtain his/her email address or arrange for them to be obtained in person at the MTF. When the patient returns for the consent visit, it will be conducted in a private room. The investigator will review the consent documents with the patient. Patients who desire to participate in the study will sign the consent document.

Withdrawal from Study Participation:

Members can withdraw from the study at any time. Investigators may also withdraw participants if they start new treatments (per study exclusion criteria), initiate changes to their medication regimen, fail to attend and complete one or more treatment sessions, or are diagnosed with or develop a condition of exclusion during the study. Investigators will attempt to enroll replacements for each participant withdrawn. All data collected prior to withdrawal will still be analyzed. Site investigators will defer to the PI to make a determination if there are any concerns about a participant's continued participation in the study.

Risks and Benefits

Risks include: sham treatment group not receiving any potential benefit if it is found that the rPMS treatment is effective in decreasing pain, risk of being assigned to the sham group, no significant improvement in symptoms, increased pain during or after rPMS treatment, skin burns if the probe is too hot, injury from the probe if it is accidentally dropped on the participant, breach of confidentiality, potential harm to an unborn child if pregnant occurs during study participation, or financial burden from lost work hours to attend study visits.

Measures to Minimize Risks of Harm (Precautions, safeguards):

Sham treatment group participants will be given the option to convert to the open label after session five. The device has an automatic temperature cut-off feature built into it which cuts off use at 23 degrees C to prevent skin burns. All investigators are trained on device use and safe handling. When documenting in the participant's electronic medical record, the documentation will have the same format and coding as a routine appointment. Use of CAC-enabled computers, private network folders available only to the investigators, password encryption, and maintaining study binders in locked cabinets/drawers will minimize breach of confidentiality. Participants are given standard of care patient education material which is still one of the cornerstones of conventional back pain treatments. Such individuals are not worsened by participating in this trial as conventional therapy utilizes a similar trial and error strategy utilizing many alternative treatment methods and they may still pursue other treatment modalities. Increased pain is mitigated by having the patient titrate maximum power to tolerated and setting a maximum of 35% machine power. This level has been deemed to be safe from anecdotal experience derived from off-label use at Langley AFB. Instruction given to female participants capable of pregnancy to use an effective form of birth control during study participation.

Confidentiality Protections (for research records, data and/or specimens):

Use of subject ID instead of identifiers, coding data, file encryption, and CAC-enabled government computers and networks. Hard copy records will be secured in locked cabinets only accessible to the study team. Nerve stimulation treatments will be documented in the electronic medical record using the same format and coding as a routine appointment. Original signed hard copy ICD/HIPAAs will be stored separately from other study documents. Electronic records are secured via DoD Microsoft Teams pages locked and only accessible to study personnel by invitation. At the conclusion of the study, all documents (hard, electronic) will be maintained for at least six years then destroyed by shredding, deleting file/folder from a secure drive and/or the cloud.

Potential Benefits:

Participants may benefit with reduced pain symptoms. The treatment may be an additional modality that does not require medications. Subjects may also help advance scientific research, satisfy curiosity about developments in medicine, or learn about the latest in clinical treatments available. You may gain improvements to daily function and get education on common exercises used for treatment of lower back pain. Aircrew as a population may further benefit from a validated non-invasive treatment modality that can be added to available treatments to address their chronic pains. No one participating in the study would be denied conventional treatment modalities so should not suffer any undue harm from lack of treatment.

Benefit to DoD

Currently available treatments for chronic back pains have been varied with literature showing that a multimodal approach utilizing multiple therapies simultaneously have more impact than single treatment modalities. Additionally, a greater portion of fighter aircrew of 37% [67] experience chronic lower pains from increased G force loads when compared with incidence rates in the general population of around 9% at any particular point in time [1]. The amount of pain not only affects typical disability scoring mechanisms like household work in these pilots but also significantly reduces their combat lethality. Pain can be

distracting to pilot concentration, limit endurance in long flights, and reduce capabilities to endure prolonged wear of helmets. Due to tight flying schedules and some treatments or medications which may result in pilots temporarily losing their medical clearance to fly, or conflict with mission planning and flying, there is a tremendous need to find other non-invasive, non-pharmacological, treatment modalities that can be applied quickly to alleviate their pain.

The rPMS procedure is known to be a well-tolerated procedure with few side effects. There is a growing body of evidence that suggests rPMS can be used to reduce pain burden in a variety of pain syndromes including undifferentiated lower back pain. The rPMS treatment protocol would offer significantly faster time to administer than most other adjunctive therapies, foster early functional recovery, and likely encourage return to combat duties faster than conventional treatments which makes it very attractive to use in an operational setting.

If this method of treatment is found to also be efficacious, it would serve to improve quality of life, help with readiness, retention, productivity, and improve operational mission success of service members currently suffering from chronic back pain.

Aircrew are not worldwide qualified or deployable while undergoing medication trials and especially if they are still having distracting symptoms. Additionally active-duty members often remain on duty and/or mobility limiting profiles that either temporarily hinder the commander's mission or lead to need for medical board evaluation and eventual permanent duty limitation or medical separation versus normal retirement. Obtaining a new successful modality for enhancing treatment of chronic back pains could limit this burden and support mission readiness and success.

Privacy for Subjects:

Use of subject ID instead of identifiers, coding data, file encryption, and CAC-enabled government computers and networks. Hard copy records will be secured in locked cabinets only accessible to the study team. Nerve stimulation treatments will be documented in the electronic medical record using the same format and coding as a routine appointment. Original signed hard copy ICD/HIPAAs will be stored separately from other study documents. Electronic records are secured via DoD Microsoft Teams pages locked and only accessible to study personnel by invitation. At the conclusion of the study, all documents (hard, electronic) will be maintained for at least six years then destroyed by shredding, deleting file/folder from a secure drive and/or the cloud.

Incidental or Unexpected Findings:

Incidental findings will be reported to the participant and their primary care provider by the site investigators and documented in their medical record. Pregnancy discovered in this study may be an incidental finding and participants found with this condition will be withdrawn from the study and referred to their primary care providers for prenatal care.

Reportable Events

Expected adverse events include burning the skin if the probe is too hot, increased pain and discomfort with high intensity peripheral stimulation. If a participant experiences an adverse response from rPMS, the treatment will pause and the site investigator will assist in coordinating care by the participant's primary care provider for evaluation or transfer to the emergency department. After the event resolves, the principal investigator will determine if it is safe for the participant to continue in the study.

Participants will be assessed for adverse events at each visit by site investigators. Adverse events (AE) will be summarized using Medical Dictionary for Regulatory Activities (MedDRA) terms. They will be listed and summarized by body system, incidence, severity and duration. Serious adverse events and Unanticipated Problems Involving Risk to Subjects or Others (UPIRSO) will be reported by the principal investigator to the IRB by completing and submitting an EIRB Reportable Event Form. After submission, the form will be routed to the DGMC C&T Board. DGMC HRPP staff regularly monitor C&T Board notification; they will notify the institution's HRPO of the reportable event by email or telephone until it has been received and acknowledged. All other AEs will be reported at the time of the continuing review.

Equipment/non-FDA Regulated Devices

Does the study involve the use of any unique non-medical devices/equipment:

No

FDA Regulated Products

Will any drugs, dietary supplements, biologics, or devices be utilized in this study?

Yes

device name – cloud TMS

cost – approximately $96,000 per unit

FDA approval – 510K approval letter 2018

IDE appropriate - control software for HiVE frequency distribution developed by Noether Tech

possible untoward effects – probe may get hot with use and is heavy. Dropped probe may cause injury. Nerve irritation may result from inappropriate frequency use. Seizures can occur with direct brain stimulation utilizing incorrect pulse strength and frequencies.

investigators authorized to use – all PI and Ais have received device training from vendor with certificate of training completion.

References and Glossary

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Abbreviations and Acronyms:

AE – Adverse Events
AFB – Air Force Base
AHLTA – Armed Forces Health Longitudinal Technology Application
AI – Associate Investigator
BP – Blood Pressure
CBC – Complete Blood Count
CMP – Comprehensive Metabolic Profile
COVID – novel coronavirus-19 and its variants
EEG – Electroencephalograph
EMBP – Electromagnetic Brain Pulse
FDA – Food and Drug Administration
HCG – Human Chorionic Gonadotropin
HIPAA – Health Insurance Portability and Accountability Act
HiVE – High Vector Electokinetics
HR – Heart Rate
ICD – International Classification of Disease
IRB – Institutional Review Board
MCID – Minimal Clinically Important Differences
MedDRA - Medical Dictionary for Regulatory Activities
MDD – Major Depressive Disorder
MDG – Medical Group
MHS – Military Health System
MTF – Military Treatment Facility
NDI – Neck Disability Index
NRS - Numerical Rating Scale
ODI - Oswerty Disability Index
PEMT - Pulsed Electromagnetic Therapy
PI – Principle Investigator
PII – Personal Identifiable Information
RR – Respiratory Rate
rPMS – repetitive Peripheral Magnetic Stimulation
rTMS – repetitive Transcranial Magnetic Stimulation
RA – Research Associate
TENS – Transcutaneous Electrical Nerve Stimulation
UPIRSO - Unanticipated Problems Involving Risk to Subjects or Others
VAS - Visual Analog Scale (VAS)
VpPMS - Variable Pulse Peripheral Magnetic Stimulation
VpTMS – Variable Pulse Transcranial Magnetic Stimulation

Protocol Abstract/Summary:

This is single blind sham controlled clinical trial evaluating the effects of utilizing a magnetic device that stimulates the nerves of the lower back in an effort to help treat pain. The mechanism of action of this type of treatment is not entirely clear but is believed to be similar to crowding out of pain signals through stimulation of other non-pain receptor nerves. Multiple studies have shown an overall positive effect for patients utilizing similar non-invasive nerve stimulation techniques, but this will be the first study to utilize a frequency range that more specifically targets the peripheral proprioception nerves and avoids a lot of the historical compounding variables such as heat generation. Peripheral magnetic stimulation may offer a non-invasive, safe, and quick technique that may be added to the collective armamentarium.

The target population will include 88 adult male and female DoD beneficiaries with existing chronic lower back pain without a specific etiology from Edwards AFB, Luke AFB and Langley AFB. After confirming eligibility, participants will be consented then randomized equally to the repetitive peripheral magnetic simulation (rPMS) treatment or sham treatment group. Participants will receive five treatments sessions in addition to continuing conventional treatments and current prescribed medications. Additionally, they will be given standardized home exercises to perform, and compliance will be assessed at follow-up visits. Pain will be assessed at baseline and every session using the visual analog scale (VAS). Function will be assess at baseline and at sessions two and five using the Oswerty Disability Index (ODI). The primary outcome is to determine overall effectiveness of the treatment by comparing VAS and ODI scores over time and in each group.