Example Protocol:

Title: A MIND-BODY TREATMENT FOR INSOMNIA: INVESTIGATION OF NEUROFEEDBACK TREATMENT OF INSOMNIA

ABSTRACT

Estimates of the prevalence of sleep problems range from 40 to 70 million Americans. Primary Insomnia is the most debilitating of these; it includes both nighttime sleep difficulties and their concomitant daytime problems. This, the Insomnia Syndrome, is estimated to occur in 10-20 percent of our population. The proposed project is a feasibility study which is part of an extensive research effort designed to identify new psychophysiological and complementary and alternative medicine (CAM) treatments for insomnia. To date, the only treatments in these areas that have been found to be efficacious are Cognitive Behavior Therapy (CBT), in many randomized controlled trials (RCT), and melatonin, in a considerably smaller number of studies. Our overall goal is to develop non-pharmaceutical, non-invasive, innovative and effective psychological and CAM treatments for insomnia. Our purpose in this pilot study is to evaluate the feasibility of conducting a trial of neurofeedback for the treatment of insomnia. We will assess participant recruitment, retention and compliance and implementation of a neurofeedback treatment protocol. We will also collect preliminary data on the relative effectiveness of two Neurofeedback (NFB) treatments (an individualized protocol and a standard protocol). The participants will be 10 volunteers with insomnia as judged by self report and questionnaires, and a clinical interview. High frequency brainwaves are associated with insomnia. At least one other study has demonstrated that by diminishing the proportion of high frequency brainwaves with a NFB training program, symptoms of insomnia can be improved. We will seek not only to replicate some of the findings of this earlier study, but to compare these with a Quantitative Electroencephalograph (qEEG)-guided NFB protocol. Our primary outcome measure is sleep efficiency as determined by Activity Counts on a 3-day (72 hour) Actigraph recording. The secondary measures will be the Pittsburg Sleep Quality Index, daily sleep logs, and changes between pre and post qEEG and Minnesota Multiphasic Personality Inventory-2 (MMPI-2).

A. SPECIFIC AIMS

According to the 2005 NIH Conference on Insomnia, one of the areas insufficiently understood is that of the physiological activation which accompanies insomnia. It is known that psychological disorders have the strongest association with all measures of insomnia: prevalence, incidence, and persistence. The high comorbidity of insomnia with psychological disorders makes it difficult to separate the two conditions. However, only one type of psychological treatment (Cognitive Behavioral Therapy) has been shown to be efficacious in the treatment of insomnia. Since it is suggested that heightened autonomic and/or central nervous system activity is also associated with insomnia, studies that combine both psychological and physiological conditions should be emphasized in further attempts to understand and treat this insidious problem. The primary means for studying psychophysiology is Biofeedback, the process of displaying physiological functioning in an operational display (visual, auditory, tactual) that allows for the psychological operant conditioning of the underlying psychophysiological system. One such process is called EEG Biofeedback, or neurofeedback (NFB), the operant conditioning of brainwaves. There is a growing body of evidence that NFB is effective in ameliorating insomnia, but there have been no full scale randomized controlled trials of this treatment to demonstrate its effectiveness (4). This pilot study seeks to investigate the potential benefits of operant conditioning of EEG brainwaves in the treatment of chronic insomnia. Two
different approaches to the use of NFB will be compared: a Standard Protocol Design and an Individualized Protocol Design based on a person's baseline brainwave pattern.

The immediate goal of this pilot study is to evaluate the feasibility of conducting a randomized controlled trial (RCT) of the efficacy of NFB for the treatment of chronic insomnia with participants remaining in their home for sleep monitoring and maintaining twice weekly treatment visits to the Helfgott Research Institute lab. An exploratory goal is to evaluate the use of quantitative EEG (qEEG) and the Minnesota Multiphasic Personality Inventory (MMPI-2) as potential outcome measures for a future NFB trial.

Specific Aim 1 To determine the feasibility of conducting a clinical trial of neurofeedback to treat insomnia. We will evaluate participant recruitment, retention, compliance and the implementation of our experimental protocol.

Specific Aim 2 To examine the relative effectiveness of two different neurofeedback treatment protocols (Standard vs. Individualized) for treating insomnia using the following outcome measures.

- Actigraph recordings for sleep efficiency from pre-post
- PSQI change from pre to post treatment
- qEEG changes from pre-post
- QOLI changes from pre to post treatment

Specific Aim 3 To explore the use of qEEG, and MMPI-2 as outcome measures for evaluating the effects of neurofeedback in the treatment for insomnia.

If we find an indication of effectiveness and the above mentioned outcome measures are useful and appropriate, we will proceed to a NIH/NCCAM grant application.

B. BACKGROUND and SIGNIFICANCE

B.1. Insomnia is a serious health issue The 2005 NIH Conference on Insomnia referred to the prevalence and severity of insomnia as an epidemic. The most recent National epidemiological estimate is that the multi-symptom syndrome of Insomnia affects between 10 and 20 percent of adults, a larger percentage of seniors, and possibly even up to 40 percent of children, especially those already burdened with neurodevelopmental and mental health disorders, or social/economic vulnerabilities. This syndrome, also called insomnia disorder, is defined as symptoms that are complaints about sleep (falling asleep, frequent or prolonged awakenings, or poor quality sleep, despite adequate opportunity) in the presence of a significant impairment of daytime function (fatigue, mood disturbance, impaired cognitive function).

Psychological disorders have the strongest association with the prevalence, incidence, and persistence of insomnia in all age groups. Yet, there has been little effort to study psychological treatments for insomnia, other than the research on Cognitive Behavioral Therapy (1). CBT has demonstrated efficacy in many random controlled trials and it is generally accepted that this is a very effective treatment modality. That it is the only reported psychological treatment with demonstrated efficacy in the treatment of insomnia may result primarily from the lack of research on other forms of psychological treatment for this problem. There is a large body of evidence demonstrating that various types of psychotherapies (in addition to CBT) obtain measurable improvement in 50% of patients by 8 sessions, and approximately 75% by 26 sessions. (2) These also need to be evaluated with respect to Insomnia. The positive findings for psychotherapy are higher than those observed for psychotropic medications, which nonetheless continue to be prescribed more often than CBT or other forms of psychotherapy for both psychological disorders and insomnia. Unfortunately, psychotropic medications also have common side-effects that are known to cause further
psychological problems, as well as sleep problems. The present study is the beginning of a research program that will seek to fill some of the gaps in research on psychological, psychophysiological and CAM treatments for insomnia.

B.1.1. Insomnia impacts daily functioning. Since insomnia includes not only sleep dysfunctions, but significant problems during waking hours as well, it creates an enormous burden for the individual. Dysphoria is significantly related to insomnia, as is also decreased quality of life to an extent even greater than that in patients with congestive heart failure or depression. Furthermore, insomnia patients have more physical problems than patients with depression. Indeed, recent studies (3) have linked insomnia to obesity, in itself a major health risk factor.

Recent studies of work show numerous troubling correlates of insomnia including significantly more errors, more accidents, and poorer efficiency, more fatigue and irritation with one’s children, and more health care consequences on a number of dimensions. The numerous physiological changes reported in patients with primary insomnia suggest an important physiological basis that is consistent with nervous system activation and may be related to the increased risk for depression, hypertension, cardiac disorders, or possibly mortality over time. According to the 2005 NIH Conference report, this implies that many current treatment studies may not address the underlying disorder or ameliorate long-term risks. The data suggest there is a need for “(1) increased attention to treatment of physiological activation in short-term studies followed by (2) controlled, long-term studies that confirm increased risk for depression and/or cardiovascular disease in placebo groups with decreased risk in treated groups.” (1, p. 59)

B.2. Current pharmaceutical treatments for insomnia have limitations At the 2005 NIH Conference (p 92), it was reported that though there is evidence that benzodiazepines and nonbenzodiazepines and antidepressants are all effective treatments, it was concluded that these drugs also: “...pose a risk of harm and that benzodiazepines have a higher risk of harm than nonbenzodiazepines. Additional studies are needed to determine the efficacy of combined, safe treatments for chronic insomnia.” Based on a small number of studies, there is some evidence that melatonin is effective in the management of chronic insomnia, and there is no evidence that it poses a risk of harm. Cognitive Behavior Therapy is the only psychological treatment that has demonstrated efficacy in the treatment of insomnia. In fact, it is as effective as hypnotics in the short term and the effects are longer lasting than those of the hypnotics.

Reynolds (21) in his review of the literature in 2000, opines that the lack of scientific and clinical evidence to support the prevalent clinical practice of chronic sedative hypnotic prescription for patients with chronic insomnia is a scandalous public health issue. “Not only is there a lack of controlled data to support this practice, there is also reason to think that it may be ultimately harmful...” He argues that what is most needed are RCTs comparing zolpidem (narcotic), paroxetine (SSRI anti-depressant), and 8 weeks of CBT. He predicts that these would show that all three treatments are equally effective over a 1-year period and that CBT and paroxetine would be superior to zolpidem in measures of daytime well-being, mood, alertness and psychomotor performance. He also predicts that 8 weeks of CBT would be more cost effective than either of the medications over a 1-year maintenance period. Such studies have not been published as of the date of this research proposal.

B.3. Costs associated with Insomnia Beyond the individual burden resulting from insomnia, the burden on society is huge, in terms of direct treatment costs, indirect costs, workplace productivity, quality of life, and personal relationships. The additional cost for health care services sought by people with insomnia is estimated to be $3-$14 billion annually. The indirect costs to the economy in terms of lost productivity and higher accident rates is estimated at $80 billion annually. Given that the prevalence is about the same as most common medical conditions, there is a great need for public education of the sequelae, long and short term, of insomnia for the individual and for society at large. With these costs personally and nationally, economically, physically and mentally, it would be wise for us to initiate a national campaign, similar to that regarding smoking, to heighten public awareness and encourage responsible self care. Such an effort
should educate the public about the hazards of untreated insomnia, the hazards of self-medication with over-the-counter (OTC) drugs, the known hazards of pharmaceutical drug treatments, and the availability of other previously demonstrated, safe and efficacious treatments.

**B.4. Neurofeedback is a potentially effective and non-invasive therapy** In 1998, the American Academy of Sleep Medicine recommended Biofeedback and progressive muscle relaxation for insomnia, after reviewing the quality of research, using American Psychological Association research criteria. Biofeedback was rated “probably efficacious” along with sleep restriction and cognitive-behavioral therapy (Morin et al., 1998). However, to date there have been no RCT studies comparing the effectiveness of Biofeedback alone or in comparison with either drugs (hypnotic or psychotropic) or CBT. Clearly, there is an urgent need to find additional efficacious and effective nonpharmacological, non-invasive, safe alternative treatments that address the psychological issues as well as other complementary/alternative medicine treatments, in combinations or sequentially. These treatments need to be effective on the various states of disturbed sleep as well as with different individual personality and population variables. It is little more than 50 years since brain scientists have been able to study, and have only begun to understand, the correlations between neuronal activity in the brain and its resulting behavioral manifestations. Though the electrical activity of the brain was discovered many years earlier, only in the late 1950’s did psychologists begin to use that information to study how the brain’s electrical activity is related to behavior. Today, researchers are able to demonstrate, through brain imaging techniques, the unconscious brain activities that are in fact the antecedents of conscious, observable, measureable, human behavior. All this has been made possible by the technological advancements in brain imaging that allow us to make conscious (via visual displays) the unconscious (physiological).

The two greatest pioneers in the study of human behavior—Freud and Skinner—both argued, from diametrically opposed viewpoints, that the ability to do this was necessary in order to allow for the control of human behavior (of self or other). This process of imaging physiological activity (chemical and electrical) to allow for conscious human control, referred to as Biofeedback, has been an important impetus for the explosion of brain/behavior research in the past 15 years. EEG Biofeedback has, in this period, gone from primarily a research tool for use mainly in well funded laboratory settings, to one that is available in any type of practitioner setting, from university offices to independent private practice to clinic practice (privately or publicly funded). Thus, it can become a mainstream tool for the healing of brain/behavior trauma spectrum problems, from addiction, anxiety and depression, ADD/HD and PTSD to epilepsy, stroke, pain control, and brain trauma from any source. Psychological healing is now possible in many of those conditions previously thought to be treatable only with medication, surgery or electric shock therapy, all of which have unwelcomed and often deleterious side effects.

**B.5. Physiological rationale for testing effectiveness of neurofeedback treatment** A recent literature review of Cortoos, et al., regarding use of the latest technology in neuroimaging and neurofeedback “…suggests that a state of hyperarousal with a biological basis is the underlying cause of insomnia…. and a focus on cortical or central nervous system (CNS) arousal should be pursued. As such, the use of EEG neurofeedback, a self-regulation method based on the paradigm of operant conditioning, might be a promising treatment modality.” A study by Pavlova (25) tested one aspect of that hypothesis: that hyperarousal traits among insomnia patients (on self-report measures) would be higher than normals as well as persons with other sleep disorders. They found significant differences between the groups, with insomnia subjects scoring significantly higher on Hyperarousal, as well as on the React subscale and on the Introspectiveness subscale. In fact, all sleep disorder groups had increased total Hyperarousal scores, although these increases were accounted for by different scale items.

Cervena et al (4) studied the effects of CBT on sleep EEG power spectra in insomnia and found that CNS hyperarousal may be characteristic of primary insomnia, though the very high frequency gamma waves were not analyzed. In addition, there was a reduction of high frequency beta activity during NREM sleep after...
CBT. The slow brain wave activity (SWA) was increased both in absolute and relative power indicating that CBT is able to reinforce cortical synchronization. Furthermore the dynamic of SWA throughout the night was also modified. Perlis et al (7) have shown that increased beta activity is associated with sleep state misperception, a common symptom within the syndrome of insomnia, and this did not change with CBT, despite objective and subjective improvement in sleep continuity. Perlis et al (7) also found that high frequency activity (HFA) brainwave activity was inversely associated with Delta wave activity.

Perlis (26) found, in addition, that patients with primary insomnia exhibited more average NREM activity for Beta-1 (14-20Hz), Beta-2 (20-35Hz) and Gamma activity (35-45Hz) than the other two groups (p.<.01), and that this is negatively associated with the perception of sleep. These findings of higher amplitudes of high frequency EEG waves during sleep suggest very strongly that operant conditioning in the awake state designed to lower these amplitudes should lead to both their lessening during sleep and also increased sleep time. This is what was discovered in cats by Sterman (17) almost 40 years ago, which then led to the development of the techniques of EEG Biofeedback in humans.

In 1970, the pioneer of Neurofeedback (the operant conditioning of brainwaves), M. B. Sterman (17), found that EEG operant conditioning of the Sensorimotor Rhythm (12-14 Hz) in awake cats led to a selective and sustained increase in SMR activity during sleep. It also enhanced the length of their sleep periods. While it is almost 40 years since this early research on cats, it is only recently that a similar study of human brainwave operant conditioning in the waking state has been conducted. This study by Cortoos (8), as yet unpublished, followed up on these data, using a particular sensorimotor rhythm (SMR) NFB training protocol for the treatment of insomnia. Though a pilot study, with an n=17, It demonstrated the successful application of NFB training in the treatment of insomnia in humans. The authors used operant conditioning to lower high frequency brain waves. They compared this SMR NFB treatment with a Relaxation Training protocol of frontal EMG. They found significant improvement in Total Sleep Time (TST) after SMR training, but not after the EMG training. Other measures of Sleep Efficiency yielded a significant main effect for SMR treatment group as well. There were no drop outs during the 12-week study and no significant side-effects were reported. The SMR protocol had significantly greater positive effects on total sleep time in comparison with EMG biofeedback (relaxation training). Sleep latency was positively influenced by both training protocols.

The present proposed study will build on this research to compare the efficacy of the standard (SMR) protocol used in the Cortoos study with a protocol individually derived from participant’s baseline qEEG designed to reduce high frequency waves. The latter (individualized) protocol follows the current “gold standard” of procedures for designing NFB protocols (9).

C. PERSONNEL AND PRELIMINARY DATA

Co- Principle investigators Barbara Hammer, PhD and Agatha Colbert, MD have complementary expertise in Neurofeedback and CAM research. Dr. Hammer is a clinical psychologist with extensive hands on experience in EEG Biofeedback (NFB), Psychometrics, Psychotherapy, and Cognitive Behavior Therapy. She has studied Neurofeedback in depth using quantitative electroencephalogram (qEEG) to map an individual client’s brainwave pattern and then train that person to positively change the brainwave pattern.

To obtain the qEEG’s used in her practice, Dr. Hammer uses a normative database developed by Applied Neuroscience, Inc and approved by the FDA. It has demonstrated high reliability and validity and is able to obtain accurate quantification of the EEG signal (19). The resulting analysis yields raw and transformed (Z score) data as well as visual mapping of the brainwave frequency distribution. These data will be used as the basis of protocol design and evaluation, as well as to document pre and post qEEG changes associated with NFB treatment.
Figures 1 and 2 are examples of brain mapping of a patient with brainwave dysregulation. The illustrations are from a patient diagnosed with Primary Insomnia (DSM IV 307.42). In Figure 1, the 9 Hz frequency pattern occurs within the normal range in most areas of the brain (represented by green shading), but the 9Hz frequency is extremely high in the red shaded area of the brain and low in the blue shaded area. In Figure 2, the red areas indicate a disproportionately high amplitude of the 41 Hz frequency signals, and the blue areas indicate a disproportionately low amplitude of that frequency. Different areas of the brain correlate with different functions and behaviors. The entire map will show these types of pictures for all frequencies from 1 Hz through 50 Hz. A map mostly green is indicative of a normal pattern of brainwaves.

Dr. Hammer will also serve as the clinical investigator in this study. She will conduct the initial screening interviews and psychological tests on the participants. She will design and administer (with help from Drew Litchy, Tineke Malus, Shannyn Fowl, Elisa Minerich, Elena Ilioi, and Sean Griffith) the individualized treatment protocols based on qEEG findings of the participants.

Co PI, Agatha Colbert completed an NCCAM sponsored post doctoral research fellowship in 2004 and is a faculty member of NCNM and an Investigator at the Helfgott Research Institute. She is currently the recipient of two NCCAM funded studies (R21AT003293 Static Magnetic Therapy for Carpal Tunnel Syndrome and R43AT004134 Multichannel System for Measuring Skin Impedance at Acupuncture Points). Dr. Colbert established the Helfgott Psychophysiology Laboratory with the goal of quantifying physiologic responses to CAM interventions. In conjunction with three NCNM students she is developing a series of pilot projects to collect preliminary data on heart rate variability, respiratory rate, skin temperature and skin conductance response to CAM interventions such as acupuncture, meditation and Energetic healing. She has experience in collecting sleep data using the actigraph and correlating activity counts with skin impedance measurements. An actigraph recording (Figure 3) is obtained with a small, lightweight, activity monitoring device, the Actiwatch (Figure 4). The Actiwatch measures long-term gross motor activity according to the degree and speed of motion. Time epochs are scored as asleep or awake depending on the level of movement during that epoch. Activity counts recorded with the Actiwatch serve as a surrogate

![Figure 1.](image1.png)

![Figure 2.](image2.png)

![Figure 3.](image3.png)
sleep measure for the more complicated and expensive polysomnography (Sleep EEG) that is used in Sleep laboratories. Internal memory and programming allows the Actiwatch to keep data for up to one week. The main advantage of actigraphy is that it can provide objective and naturalistic measures of sleep-wake behavior in the home environment on multiple occasions. In addition automatic computer scoring can be utilized in the analysis of actigraph data.

**Figure 4. Actiwatch**

**Co investigators** William L. Gregory, PhD, biostatistician will serve as the biostatistician for this trial. Dr. Gregory is a Senior investigator with NCCM. Dr. Gregory has more than 30 years of interdisciplinary research experience in a variety of health and social science areas and recently has focused his considerable expertise in CAM research. Dr. Gregory has extensive expertise in trial data analysis and program evaluation with emphasis on multivariate analysis, outcome evaluation, measurement and interpretation of psychosocial constructs including, satisfaction, expectancy, patient perceptions, QOL, pain, functioning, other areas of focus include psychoneuroendocrinology. He has received funding from both the National Science Foundation and the NIH.

Andrew Litchy is a graduate student at the National College of Natural Medicine (NCNM) and possesses the necessary skill set to be an investigator for the study. Mr. Litchy has been involved with the Helfgott Research Institute ongoing research on physiological responses associated with meditation. He clearly understands biofeedback and neurofeedback equipment set up, software, and data interpretation necessary for the study.

Tineke Malus is a graduate student at the National College of Natural Medicine (NCNM) and possesses the necessary skill set to be an investigator for the study. Ms. Malus has been involved with the Helfgott Research Institute ongoing research on physiological responses associated with meditation. She clearly understands biofeedback and neurofeedback equipment set up, software, and data interpretation necessary for the study.

Sean Griffith is a postbaccalaureate student in Psychology at Portland State University who will serve as a research assistant for the study.

**D. RESEARCH DESIGN AND METHODS**

**STUDY FLOW**
D.1. Overview

We will use a pre-post study design enrolling 10 otherwise healthy participants between 18-60 years of age, who have Chronic Insomnia. Participants will be randomized to receive either individualized or standard neurofeedback treatments. Potential participants will be recruited from the NCNM community (students, staff, faculty and NCNM clinics) and the general population. Participants will initially be screened by telephone to determine general eligibility. Those who meet the telephone screening eligibility criteria will be invited to a screening visit. At the screening visit they will complete five baseline questionnaires: a health history, a sleep questionnaire (the Pittsburgh Sleep Quality Index (PSQI), a psychological test (the Minnesota Multiphasic Personality Inventory (MMPI-2), a structured clinical interview (the Psychiatric Diagnostic Screening Questionnaire (PDSQ), Quality of Life Inventory (QOLI), and a sleep log documenting the individual’s general sleep pattern. Potential participants who are eligible for randomization and are willing, will have a quantitative EEG (qEEG) performed by Dr. Hammer. The baseline qEEG serves two purposes. It will define an individualized NFB protocol for half of the participants and serve as a secondary outcome measure for all participants. Once randomized to either the individualized or standard treatment protocols, participants will come to the Helfgott Research Institute for a total of 15 treatment sessions over 8 weeks. Our primary outcome measure is sleep efficiency as recorded on an actigraph. The actigraph data will be collected on an Actiwatch that will be worn for 72 hours prior to starting NFB training and for 72 hours after completing the NFB training course. Secondary outcomes include the participant’s self report of insomnia symptoms on the Pittsburgh Sleep Quality Index (PSQI), daily sleep logs, changes in the MMPI-2 and in the qEEG.

D.1. Recruitment

Potential participants with Chronic Insomnia will be recruited from the NCNM faculty, staff and students, the NCNM clinics and the general population. Advertisements will be posted on the school and clinic bulletin boards and on bulletin boards in apartment complexes and local businesses in the neighborhood. Electronic postings will include Craig’s list and the NCNM web page. Oral announcements about the study will be made during NCNM class sessions, staff meetings and faculty meetings.

D.2. Description of participants with Insomnia

The definition of insomnia will be that of Roth (12) which is elaborated in the Inclusion criteria.

D.2.1. Inclusion criteria All potential participants must meet these inclusion criteria:
- Both genders
- Age ≥ 18 to 65 years
- Meet all of Roth et al (12) diagnostic criteria for Insomnia including:
  - difficulty falling asleep, staying asleep or nonrestorative sleep
  - this difficulty is present despite adequate opportunity and circumstance to sleep
  - this impairment in sleep is associated with daytime impairment or distress
  - this sleep difficulty occurs at least 3 times per week and has lasted at least 1 month
- Be willing to discontinue use of sleep aids (both prescription and over-the-counter) for two weeks prior to randomization and during the remaining weeks of the study.
- Be willing and able to sign Informed consent form
- Not planning on moving away from the area for the subsequent 12 weeks.

D.2.1.2. Exclusion criteria: Participants who answer “yes” to any of the below criteria will be excluded:
- Females who are lactating or who are pregnant
- Night shift workers, and individuals who nap 3 or more times per week over the preceding month
- Consumption of caffeine beverages (i.e. tea, coffee, or cola) comprising usually more than 5 cups or glasses per day
- Participation in another trial for insomnia
- Persons unable to complete the study questionnaires and psychological tests
• Persons who are unable to participate for the entire duration of the study, or in the opinion of the investigators, are likely to be non-compliant with the obligations inherent in the trial participation
• Persons diagnosed with a mental disorder at the time of the study as evaluated by screening with the MMPI-2, the PDSQ and Dr. Hammer’s clinical evaluation.
• Persons with a history of epilepsy, seizures, or dementia
• Any significant, severe or unstable, acute or chronically progressive medical or surgical condition
• Serious head injury or stroke within the past year
• Persons who are taking sleep medications, anti-depressants, anti-anxiety and other mind or mood-altering drugs, herbal preparations such as melatonin, valerian root and tryptophan.

D.3. Screening for eligibility
Eligibility will be determined through a stepwise screening process including a telephone screening (TS) and an in-person interview with Dr. Hammer. The Telephone screen is included in the Appendix.

D.4. Screening Visit
D.4.1. Procedures at the screening visit
During the first visit we will review and sign the informed consent form with the participant and the participant will complete the following written and/or verbal questionnaires

D.4.1.1 Questionnaires (all questionnaires are included in the Appendix)
- Health History questionnaire
- **Minnesota Multiphasic Personality Inventory (MMPI-2)** The most frequently used validated measure of psychopathology, the MMPI-2 will be used to verify that participants do not have a comorbid mental disorder and to confirm Dr. Hammer’s clinical impression of mental status. The MMPI-2 has ten clinical scales and four validity scales which can detect subject response biases. It is suitable for ages 18-60. Interpretations are based on the overall pattern of subscale scores; T scores for each of the scales range from +or- 50-70+. Scores over 65 are considered elevated. A score of 65 will be used as the cut-off score to determine exclusion on the basis of psychopathology (22). This process will be conducted in two steps: a) any participant with only one subscale score over 65 will be further evaluated by Dr. Hammer through the Psychiatric Diagnostic Screening Questionnaire (PDSQ) and a clinical interview to determine the presence of mental disorder and b) any participant with two or more subscale scores over 65 will be automatically excluded. This will ensure that we will be studying individuals with insomnia as the primary diagnosis. The MMPI-2 questionnaire is untimed but usually takes between 60-90 minutes to complete.

- **The Pittsburgh Sleep Quality Index (PSQI)** will be used to assess overall sleep quality and verify Insomnia diagnosis. (~10 minutes) It is a questionnaire which assesses sleep quality and disturbances over a 1-month time interval. Nineteen individual items generate seven “component” scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The sum of scores for these seven components yields one global score.

- **Psychiatric Diagnostic Screening Questionnaire (PDSQ) and clinical interview:** All potential participants will have an in-person interview with Dr. Hammer who will administer the PDSQ, a brief self-report validated instrument. The PDSQ screens for DSM-IV Axis I disorders that are commonly encountered among individuals 18 years of age and older who are routinely seen in medical and outpatient mental health settings. The PDSQ will be used to rule out mental disorders and confirm the diagnosis of Chronic Insomnia. The PDSQ and clinical interview will take between 20-30 minutes. If Dr. Hammer determines that a potential participant is suicidal or severely depressed she will ask that potential participant for permission to contact his or her primary care physician. Dr. Hammer will
discuss her findings with the primary care physician (PCP) and help to facilitate a visit for the patient with his/her PCP as soon as possible.

- **Quality of Life Inventory (QOLI):** All potential participants will complete the QOLI, a brief self-report validated instrument. The QOLI is a measure that assesses different aspects of a participant's life. Topics include: health, goal setting, money, self-esteem, learning, recreational interest, community, and overall quality of these entities. The QOLI is a validated scale for the condition of insomnia and is relevant to the study because of its usefulness in assessing quality of life with insomnia, as well as comparing our results with our studies concerning insomnia. The QOLI and will take between 15-20 minutes.

- **Sleep log** A sleep log is a record of an individual's sleeping and waking times, usually over a period of several weeks. It will be used to diagnose Chronic Insomnia and to monitor at the end of the FNFB sessions, whether NFB is successful. The sleep log will be given to participants to report the previous month’s sleep activity. Completion takes approximately 5 minutes)

**D.4.1.2. Quantitative electroencephalogram (qEEG)**

Those potential participants who meet the final eligibility criteria of the screening visit will be invited to participate in the treatment phase of the study. As a baseline measure and to guide selection of the NFB protocol for participants in the Individualized treatment protocol group, participants will be instrumented for a qEEG evaluation at the second visit. The qEEG is used to study a person's brainwaves via an analytic procedure called “brain mapping”. The qEEG is derived by digitally analyzing the EEG to measure the amount of various EEG frequencies at different scalp locations (power analysis) and the connections between different areas (coherence analysis). Quantitative EEG frequencies will be measured at 19 sites on the head. The data obtained at 19 standard sites on the head is compared with data from normal individuals in the Applied Neuroscience, Inc database. qEEG data will be analyzed by Dr. Hammer in the manner described in Section C. to obtain brain maps and Z Scores for each person. For those participants randomized to the individualized treatment protocol, this qEEG will define the individualized treatment protocol to be used. These qEEG analyses will provide a baseline for before/after treatment comparison in both the Individualized treatment group and the Standard treatment group.

The electro-cap (Figure 5) that contains the 19 electrodes used to obtain the EEG signal is somewhat tight fitting in order to obtain a good connection between the electrodes and the scalp. However, it causes little discomfort and does not remain in place more than a half-hour generally. The electrodes measure the electrical patterns coming from the brain. On the day of his or her brain mapping, and every subsequent day when s/he comes for a treatment) his or her hair must be thoroughly cleaned and shampooed. S/he will not be able to apply any styling aids (hairspray, conditioner, styling lotions, etc) on that day. We will apply a gel to the electrodes to help keep them electrodes in place. We may use a wooden blunt tipped Q-tip to slightly abrade the scalp underneath the electrodes. During the brain mapping the participant will be required to rest quietly in a seated position.

**D.4.1.3. Actiwatch** At Visit 2, after having their qEEG performed, participants will be instrumented with the Actiwatch and instructed in its use. The Actiwatch will be worn for 72 hours. Participants will return the Actiwatch at the time of their next visit when they will receive their first NFB treatment.

**D.5. Randomization**

Potential participants who meet all eligibility criteria and continue to be willing to participate will be randomized to receive either an individualized or standard NFB treatment protocol. Randomization will be performed by the biostatistician who will use a computer algorithm to output a random sequence of 10 statements, half stating “Group 1 (HAS4)” and the other half indicating “Group 2 (SMR).” The randomly
D6. Neurofeedback Intervention (Visits 4-16)

D6.1. Participants will continue in their group assignment for the duration of the study. All participants will be given 4-15 (fifteen) treatment sessions, on a semiweekly schedule. At each session medical grade EEG paste holding electrodes will be placed on the participant’s head at 2-5 different places. The electrodes will be held in place by medical grade EEG paste or Velcro headbands using a medical conductive liquid made for EEG recording. During the session, the participant will be coached to control the images s/he sees on the computer screen. Images include: the EEG waveform, the individual’s color-coded Z test score numbers, and some computer games which indicate correct responses by the advance of an animal on a race track or filling of marbles in a jar. Participant instructions and a screen shot of these images is shown on the next page in Figure 6. The individualized treatment group will have 4 filtered EEG waves and 4 sets of numbers of Z scores whereas the standard protocol group will have only one EEG wave and one set of Z scores. With this coaching, and practice, participants will learn to control their brainwave patterns. Each individual session will last a total of approximately 30-45 minutes which will include initial check-in, a brief discussion to clarify details of sleep logs, an opportunity to ask and answer questions about procedures, and to verify the absence of negative side effects, followed by a 20-minute NFB treatment. The 20 minute duration of treatment is the usual and customary length of an NFB session and was chosen to be comparable to a study by Cortoos (5) which yielded significant effects of NFB in a patient population with a diagnosis of Chronic Insomnia. All training will be conducted using the Atlantis Neurofeedback system EEG equipment manufactured by BrainMaster, Inc. The NFB treatment will be designed and supervised in person by the PI, Barbara Hammer. Drew Litchy or Sean Griffith will assist at the NFB sessions as needed.

The following picture, Figure 6, shows a typical Training Screen that will be seen by the participant. Both Treatment groups will see a similar picture, but that for Treatment Group 1 will have all the numbers shown below, while the picture for Treatment Group 2 will have only a small portion of the numbers, since it has only one active electrode while the other group has 4.
Figure 6. Typical computer screen that will be seen by participant

The participant will be given these instructions:

“The electrodes that we’ve attached to your scalp will be measuring your brainwaves. You will be controlling the pictures on the screen with your brain waves by playing a game in which you’ll try to get the most blue balls into the jar (on the right top of the screen). In addition, or if you prefer, you can look at the numbers in the bottom two-thirds of the screen that will tell you how well you’re doing in the game. When the numbers are white, you will get another ball in the jar; if the numbers change colors you will either not get a ball or one will be taken away (indicated by a red fading ball in the jar). I will be varying the amount of white numbers that are required for you to get a ball into the jar, so that you will be continually improving your skill. Now, please relax and let me know when you’re ready to start the brain-game. Do you have any questions about the game before we start?”

As the training progresses and the participant receives points, Dr. Hammer will offer encouragement such as commenting: “Good Job!” to increase the reinforcement value of the visual feedback on the computer screen.

The training under each treatment condition will be programmed on the computer using a Z score guided system. The goal of all NFB training is to bring the distribution of brainwave frequencies over the cortex into a normal pattern using operant conditioning. This describes the process referred to as “normalizing dysregulated brainwave patterns.” The specialized Z Score training system to be used in this study provides the most advanced and innovative, state-of-the-art signal processing, using the Applied Neuroscience normative database analysis, and new computational methods to accomplish that goal. It will provide 248 real-time, simultaneous values for 4 scalp sites computed on a continuous basis by the software. These calculations are performed more than 30 times per second. The resulting Z Scores provide an
An instantaneous measure of how the trainee’s EEG compares with a normal population, so that over- or under-training cannot occur. These are then used to determine the outcome or consequence (e.g. reward or non-response) to be provided by the EEG equipment in order to train the desired response. The Z scores are based upon the EEG signal, the sensor locations, the age of the trainee, and whether eyes are open or closed (20).

**D.6.2. Experimental Groups**

**Group 1-(HAS4)- Individualized protocol.** The individualized treatment protocol will be based on selection of the Highest Amplitude Site/s (HAS) from the qEEG analysis. This statistical analysis of each individual qEEG recording will be provided by the proprietary software from Applied Neuroscience, Inc.. It will yield standardized amplitude data for all frequency bands as compared with a general population normative data base. The training protocol will be designed to lower the amplitude of high frequency brainwaves at the four sites (HAS4) with the highest amplitudes that have been identified by the qEEG .This is the standard procedure for using this normative data base and software combination; this methodology is the “gold standard” (9) for designing NFB protocols. Training will proceed through the sets of four highest amplitude sites, as the timing of the 15 session design allows, until normalization (Z scores +or- 0.5) occurs or the 15 sessions have concluded or the participant feels the insomnia has been successfully treated, whichever occurs first.

**Group 2 (SMR) Standard protocol** The standard treatment protocol will consist of placing one active electrode at site Cz, referenced at A1 (left ear). An operant conditioning paradigm will provide reinforcement for EEG wave frequencies 12-15 Hz (LoBeta), and the inhibition of 4-8 Hz (Theta) and 25-30 Hz (HiBeta). Training will continue until 15 sessions have concluded or the participant feels the insomnia has abated sufficiently to discontinue treatments.

**Table 1. Schedule of visits and procedures**

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<tr>
<th>Visit number</th>
<th>Week 1</th>
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<th>Week 5</th>
<th>Week 6</th>
<th>Week 7</th>
<th>Week 8</th>
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Once per week participants will return the Sleep Logs completed over that week.

**Final Visit (18).** At the final study visit participants will be interviewed and debriefed by Dr. Hammer, asked to complete 5 questionnaires and have a repeat qEEG performed.

**D7. Outcome measures.** Several outcome measures will be used. The primary outcome measure will be sleep efficiency derived from actigraphy. Sleep efficiency is calculated by determining the total time an individual spends in bed (lights out until out of bed) and dividing that value into the amount of time an individual has actually slept.

Several secondary outcome measures are also derived from actigraphy: (1) total sleep time, (2) total wake time in bed, and (3) latency to onset of sleep. These three measures plus the sleep efficiency measures are also derivable from the sleep questionnaires that participants complete and are used for convergent validation.

Additional secondary measures include the subscales of the MMPI-2, subjective reporting of sleep quality and experience from the clinical interviews, QOLI, and qEEG measures, and the Daily Sleep Logs. In addition, changes in the participants’ daily living arrangements (e.g. visitors, illness, significant relationship losses or changes, work changes) that could have a clinically significant impact on sleep will be reported to Dr. Hammer for effects on outcome.

**D8. Data analysis.** The primary outcome measure, sleep efficiency, will be analyzed using a paired t-test. Participant’s baseline values will be compared to their post-treatment values. This will allow a determination of whether significant changes in sleep efficiency have occurred or if any trends toward significant changes in sleep efficiency have occurred. This will be performed for each treatment group separately.

Additionally, the sleep efficiency data for both groups will be analyzed using a 2 (between participants factor: treatment type) by 2 (within participants factor: baseline vs. post-treatment) mixed analysis of variance (ANOVA). The test of the between by within interaction will determine if there are significant differences between treatments in any changes in sleep efficiency, or if there are any trends toward significance.

All secondary outcome measures will be analyzed using these same two methods. As this is a pilot study, no attempt will be made to control for familywise alpha error by setting more stringent alpha levels to determine significance. Instead, the overall pattern of results will be examined to determine if either or both treatments have any effects on outcome measures.

**D9. Power analysis.** Means and standard deviations from two different insomnia treatment studies using actigraphy were used to calculate power for the sleep efficiency outcome measure (Edinger et al., 2007; Sivertsen et al., 2006). Based on these two studies, power for a paired t-test with 5 participants is estimated to be between .16 - .31 with a one-tailed alpha of .05. Any increase in sleep efficiency is considered beneficial for insomnia sufferers. To achieve customary power of .80, approximately 30 persons would need to be treated with one method.

**D10. Data management.** All data will be locked in secured cabinets located at the NCNM and on password protected computers of the study personnel. Only persons involved directly with the study will have access to the data.

**E. Human Subjects Research**
All research personnel at NCNM have completed Responsible Conduct in Research and HIPAA certification through the OHSU Office of Integrity.
E.1 Risks to Participants

E.1.1. Human Participant Involvement and Characteristics: We plan to enroll a total of 10 participants, female and male, between 18 and 60 years of age with a confirmed diagnosis of chronic insomnia. Participants must report non-restorative sleep that lasts for at least one month and score over 5 on the Pittsburg Sleep Quality Index scale. Potential participants who are on prescription or OTC medications or, any homeopathic remedies or dietary supplements being used to treat their symptoms of insomnia will be excluded from participating in the study.

We will also exclude individuals who are currently taking prescribed medications for mental or emotional conditions, even if they have not been seen by the physician or therapist in the past year. Since at the screening visit we will be excluding anyone who is diagnosed with depression or is suicidal, it is unlikely that any of our participants will become either depressed or suicidal. Anyone who is participating in a conflicting research study will be excluded. Individuals who are unable to read or verbally comprehend English will be excluded as will potential participants who the Principle investigators deem are unlikely to be compliant with the protocol. Participants must be: willing and able to come to the Helfgott Research Institute for in-person pre and post treatment assessment measures and 15 additional visits for neurofeedback treatment.

E.1.2 Sources of Materials:

Research Materials New data for research purposes will be obtained from every participant by self-report questionnaires, psychological tests, quantitative EEG measures, and interviews. All data used for this project will be obtained only after receiving patient consent.

Data recorded on human subjects. Baseline measures will also include a health history questionnaire, information about the participant’s insomnia symptoms and impact on his/her daily functioning; his/her general health status and medication and CAM use. Follow-up assessments will include changes in the outcome measures from the baseline questionnaires and psychological testing, daily sleep logs, and to assess compliance with the treatment. Participants will also be asked to keep a daily log throughout the 9-week study period to document adverse or unpleasant symptoms or experiences.

Linkages to participants and access to participant identities

Self-report questionnaires: The only identifier on a given data collection form is a unique patient identification number; no other personal identifiers are recorded on these forms. All NCNM study staff are trained in the confidentiality of patient data.

Data storage: Paper data collection forms will only include unique study ID numbers, will be accessible only by study personnel, and will be kept in locked filing cabinets. Computer files with patient names will be password protected with restricted access to project staff who will only use this information to recruit patients and obtain follow-up data. All analytic data files and tracking databases will be maintained on a secure, password-protected server at NCNM.

E.1.3 Potential Risks:

E.1.3.1. Risks associated with qEEG The quantitative electroencephalogram (qEEG) is used to measure the electrical activity of the brain, using sensors placed on the scalp. This procedure is painless and non-invasive. No electric current is put into the brain. No adverse events have been reported as a result of a qEEG.-The qEEG cap is tight fitting and may be a little uncomfortable. Skin preparation entails lightly abrading the scalp under the sensors.

E.1.3.2. Risks associated with neurofeedback (see below section E.2.2) Negative side effects of NFB very rarely occur. If and when they have occurred, they have been primarily in-session anxiety or fatigue, or out-of-session heightened anxiety or agitation.
E.1.3.3. Risks associated with breach of confidentiality Inadvertent disclosure of patient-specific or provider-specific data could be harmful or embarrassing to the individual involved.

E.2. ADEQUACY OF PROTECTION AGAINST RISKS

E.2.1. Recruitment and Informed Consent Recruitment Participants will be recruited from the NCNM community (staff, faculty and student body), the NCNM clinics and the general public:

The NCNM community Participants will be recruited through recruitment notices posted on bulletin boards throughout the college, through classroom announcements and word of mouth and through electronic postings on the NCNM website

The NCMM clinics: Participants will be recruited through individual patient referrals by NCNM Physicians and through recruitment notices posted at the clinics and on the NCNM Website.

The general population Potential participants in the community will be recruited via flyers will be posted in local businesses. Advertisements will also be placed in free community newspapers in ethnic neighborhoods to encourage participation by minority groups.

Consent Subjects will provide consent prior to enrollment in the study. The study coordinator will obtain verbal informed consent for the TS. The final informed consent form will include all required information on the risks and benefits of the study and will be approved by the NCNM IRB. Participants will be given a copy of the signed consent form. The original will be stored in the patient record in a locked file cabinet at NCNM.

E.2.2. Procedures to minimize risk
Every effort will be made during the planning phase to address potential risks. The protocols will be reviewed and approved by the NCNM IRB before recruiting any subjects. All study staff will be trained and certified in the HIPAA requirements for research involving human subjects. The PI’s and investigative team will monitor and review activity of the study in an ongoing activity of the study throughout the time frame of the study. The safety protocol detailed below will be used to minimize harm.

Risks associated with qEEG If participants are unable tolerate wearing the qEEG cap for the 20-30 minute testing, the cap will be removed and they will be withdrawn from the study.

Risks associated with neurofeedback. If anxiety, headache, dizziness or fatigue occur during the session, the participant will be helped to alleviate these conditions as clinically appropriate. If there is no amelioration in the session, the session will be terminated and the participant offered the remaining session time to discuss and work through anxiety or fear, or helped to relax (e.g. through discussion and relaxation techniques) or return home to rest until less fatigued and/or dizziness and/or headache subsides. This session will not count toward the 15 session plan. If heightened anxiety or agitation is reported out of the session and s/he calls Dr. Hammer, she will discuss the person’s discomfort or distress by phone and if not alleviated, participant will be invited to come in for clinical visit with Dr. Hammer. If these are not alleviated by that procedure or adjustments in the treatment protocol, the treatment will be discontinued. Such possible side effects are closely monitored during all treatment. Treatment will be adjusted (i.e. training will be slowed down or changed as allowed by experimental conditions) or terminated, and treatment for appropriate amelioration of symptoms will be recommended. In the extremely unlikely event that a study participant becomes severely depressed and/or suicidal during the study, we will refer the person to his/her PCP and/or take necessary steps to seek immediate medical attention.

Risk of Breach of Confidentiality All participant information, and even the fact that an individual is in the
study, is considered confidential. Confidentiality will be assured in this study through several mechanisms. During interviews and treatments, the investigators and study coordinator will ensure physical privacy by conducting interviews in a closed room. All data are stored in a secured area accessible only to study staff. Each participant will be assigned an anonymous study ID number, which will then be used on all study forms. All study forms, and paper records that contain participant information (e.g., address lists and phone lists) will be kept in secured, locked areas when not in use. In addition, such materials, when in use, will be kept away from public scrutiny. Access to all participant data and information, will be restricted to authorized personnel. In the case of computerized information, access to the study data on computers will be password protected. Staff members receive individualized account numbers and passwords that allow them access only to those elements of the data management system to which they are authorized. In addition, study personnel will be asked to sign a confidentiality statement affirming that they agree to abide by the policies on research confidentiality and ethics of the participating institutions. When the study database is made available to the project office, it will not include actual identities or contact information for participants. Finally, participants will not be identified by name in any reports or publications, nor will data presented in such a way that the identity of individual participants can be inferred. All staff are trained and annually re-certified regarding these procedures.

E.3. POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO THE SUBJECTS AND OTHERS
Potential benefits for study subjects include up to 15 (fifteen) neurofeedback treatment sessions at no cost to them and the possibility that their symptoms may improve as a result of the intervention. In addition, participants may receive feedback on their psychological test and interview results. An additional benefit for some participants may be the personal satisfaction of being part of a study that may further scientific knowledge concerning the application of neurofeedback therapy.

Incentives. No other financial incentives will be offered to participants

E.4. IMPORTANCE OF THE KNOWLEDGE TO BE GAINED
Based on the knowledge to be gained from this study we will decide whether to proceed to a full scale trial involving larger financial, personnel and participant resources. The risks to subjects are reasonable in relation to the importance of the scientific knowledge that may reasonably be expected to result.

E.5. DATA AND SAFETY MONITORING PLAN
Few if any AE are anticipated in this "moderate" risk study. The estimated risk classification of this study is "moderate" because it entails the evaluation of a generally healthy population (individuals with insomnia and no concomitant serious illness), student participants, low risk procedures (questionnaires) and intervention (neurofeedback)

Our overall monitoring plan includes the following
- Identification of adverse events (AEs). Any untoward experience will be identified through spontaneous reports from participants and assessment of participant log sheets.
- AE Reporting. Adverse events will be reported to the NCNM IRB
- AE Grading. Severity of events will be graded according to a generalized severity scale (0= No adverse experience, 1= mild AE -no treatment needed, 2= moderate AE- resolved with treatment, 3= severe AE- inability to carry on normal activities, asked professional medical attention, 4= life threatening or disabling AE, 5= Fatal AE.
- AE Attribution The OHSU IRB 3-point scale will be used by the PI to attribute relatedness of the experience to the study procedures/interventions: Related, Possibly related, Not related.
- Adverse Experience Reporting Schedule Grades 4 and 5 AEs will be reported to the NCNM IRB within 24 hours and to the NCCAM within 7 days. Grade 3 AEs will be reported to the NCNM IRB within 10 days. Grade 1 and 2 AEs will not be reported.
Safety will be reviewed by the PIs throughout the study. In addition, a safety/efficacy review will be performed every 4 months by an independent individual (Patricia Elmer, PhD) who will review enrollment, dropouts, AEs and protocol violations/ deviations.

E.6. INCLUSION OF WOMEN AND MINORITIES
Insomnia and Neurofeedback IRB #071508B
IRB Submission date: July 1, 2008
IRB document approval date: 5-28-09
• Women

Both genders are included in this study but we anticipate that about that 60% to 70% of our participants will be women because of the higher prevalence of insomnia observed in women.

• Minorities

All minorities are included in our recruitment pools listed above. We anticipate that recruitment from the community at large will reflect the minority population in the Portland metropolitan area (80% white, 6.6% African American, 6.8% Hispanic or Latino).

E.7. Inclusion of Children

Children will not be invited to participate in this study because of the small sample and the fact that neurofeedback is not generally used for children with insomnia.

F. Vertebrate Animals

Not applicable

G. Select Agent Research

Not applicable

REFERENCES:


Retrieved from:

http://www.ncnm.edu/images/Helfgott/IRB-Documents/protocol-example.doc