

UB HRP-503 TEMPLATE: Protocol

PROTOCOL TITLE: Investigating the short-term effects of *Passiflora incarnata* and mobile audio-guided meditation on blood pressure and heart rate in naturopathic medical students

PROTOCOL DATE: 3/28/19

Template Revised: June 14, 2010

Protocol Title

Investigating the short-term effects of Passiflora incarnata and mobile audio-guided meditation on blood pressure and heart rate in naturopathic medical students

1) Investigator

Kimberly M. Sanders, ND

Mark Mattie, MD, PhD

2) Objectives*

This study is intended to study the effects of one-time acute dosing of a solid extract of *Passiflora incarnata*, also known as Passionflower, along with a 10 minute audio-guided mobile meditation on medical students after a didactic examination. Our hypothesis is that blood pressure levels and heart rates, as an assessment of sympathetic tone, will decrease significantly in response to both *Passiflora incarnata* and the meditation.

3) Background*

Elevated blood pressure is a risk factor for development of hypertension later in life, which is a major public health crisis currently, and long-term exposure to high blood pressure may increase the risk of cardiovascular disease (1,6). Hypertension can be caused by an increase in sympathetic tone and/or by an increased heart rate, vasoconstriction, and release of epinephrine and norepinephrine (2). Increased sympathetic output also stimulates the release of renin and, thus, angiotensin II. This ultimately stimulates ACTH release and the release of adrenal glucocorticoids (i.e. cortisol) and aldosterone (3-5).

Meditation is a form of mindfulness that focuses on positive, relaxing thoughts and deep breathing. Medical schools have begun implementing research on the effects of mindfulness on medical students with virtually no evidence of adverse events (7,8). These studies have looked at the effects of meditation and mindfulness over the course of many weeks, whereas our study aims to evaluate its effect for one session only. A 2018 study utilized the mobile application Headspace for 30 days for 10-20 minutes each and found significant improvements in general well-being (9). Literature also supports a positive effect of meditation on blood pressure. One study in pre-hypertensive adults found a significant reduction in systolic blood pressure numbers in those who received 6 months of meditation (10).

Passiflora incarnata, commonly known as Passionflower or passionfruit, is a botanical belonging to the *Passifloraceae* family that is traditionally used for anxiety (11). Research has found that it may reduce stress and

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anxiety (12-14) with mild and non-serious adverse effects, including headache, abdominal pain, and flatulence. Doses in these trials ranged from 260mg – 700mg. Rare side effects from chronic *Passiflora* use included vasculitis, asthma, rhinitis, and urticaria (15). One case study from 2000 revealed a toxic reaction to *Passiflora incarnata*, in which the patient experienced various cardiovascular effects, including ventricular tachycardia (16). Passionflower extract also contains harmine and hardline which may stimulate uterine contractions, and is therefore contraindicated in pregnancy. It has theoretical action as a platelet inhibitor, so it is contraindicated before surgery. A 2017 trial comparing *Passiflora incarnata* to midazolam before dental extraction found that both *Passiflora* and midazolam improved patients pre-procedure anxiety levels, and they concluded that the *Passiflora* was safe and effective in this one-time dosage (17). 50% of the participants in this trial experienced drowsiness as a side effect of the 260mg preoperative dosage. 20% experienced muscle relaxation, 5% experienced dizziness, 2.5% experienced an allergy, and 2.5% experienced epistaxis. A 2013 study evaluated the effects of 500mg *Passiflora incarnata* on anxiety levels before periodontal treatment. This study found significant reductions in anxiety in those taking the botanical extract with no reports of any adverse effects (18). Lastly, a 2001 study on 36 patients found comparative anxiolytic effects between *Passiflora* and oxazepam with mild-moderate dizziness, drowsiness, impairment of job performance, and confusion listed as the most frequent side effects for both interventions. In the *Passiflora* group, two participants experienced a mild-moderate allergic reaction and two participants experienced mild-moderate ataxia (19). There is no evidence in the current literature that *Passiflora* is an abortifacient or teratogen. To our knowledge, no recent human trials have been done to investigate the effects of *Passiflora incarnata* on blood pressure. A related plant, *Passiflora edulis* has demonstrated antihypertensive properties in rats (20, 21).

- 1) Lucini D, Di Fede G, Parati G, Pagani M. Impact of chronic psychosocial stress on autonomic cardiovascular regulation in otherwise healthy subjects. *Hypertension*. 2005; 46: 1201-1206.
- 2) Ulrich-Lai YM, Herman James P. Neural regulation of endocrine and autonomic stress responses. *Nat Rev Neurosci*. 2009; 10: 397-409.
- 3) Häfner S, Baumert J, Emeny RT, Lacruz ME, Bidlingmaier M, Reincke M, et al. To live alone and to be depressed, an alarming combination for the renin-angiotensin-aldosterone-system (RAAS). *Psychoneuroendocrinology*. 2012; 37: 230-237. 34.

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- 4) Yang G, Wan Y, Zhu Y. Angiotensin II--an important stress hormone. *Biol Signals*. 1996; 5: 1-8. 35.
- 5) Yang G, Xi ZX, Wan Y, Wang H, Bi G. Changes in circulating and tissue angiotensin II during acute and chronic stress. *Biol Signals*. 1993; 2: 166-172
- 6) Ayada C, Toru Ü, Korkut Y. The relationship of stress and blood pressure effectors. *Hippokratia*. 2015;19(2):99-108.
- 7) Rosenzweig S, Reibel DK, Greeson JM, et al. Mindfulnessbased stress reduction lowers psychological distress in medical students. *Teach Learn Med Spring* 2003;15: 88–92.
- 8) Warnecke E, Quinn S, Ogden K, et al. A randomised controlled trial of the effects of mindfulness practice on medical student stress levels. *Med Educ* 2011;45:381– 388
- 9) Yang E, Chamber E, Meyer RML, Gold JI. Happier Healers: Randomized Controlled Trial of Mobile Mindfulness for Stress Management. *J Altern Complement Med*. 2018;24(5):505-513.
- 10) Adams ZW, Sieverdes JC, Brunner-jackson B, et al. Meditation smartphone application effects on prehypertensive adults' blood pressure: Dose-response feasibility trial. *Health Psychol*. 2018;37(9):850-860.
- 11) Dhawan K, Kumar R, Kumar S, Sharma A. Correct Identification of *Passiflora incarnata* Linn., a Promising Herbal Anxiolytic and Sedative. *J Med Food*. 2001;4(3):137-144.
- 12) Meier S, Haschke M, Zahner C, et al. Effects of a fixed herbal drug combination (Ze 185) to an experimental acute stress setting in healthy men - An explorative randomized placebo-controlled double-blind study. *Phytomedicine*. 2018;39:85-92.
- 13) Movafegh A, Alizadeh R, Hajimohamadi F, Esfehiani F, Nejatfar M. Preoperative oral *Passiflora incarnata* reduces anxiety in ambulatory surgery patients: a double-blind, placebo-controlled study. *Anesth Analg*. 2008;106:1728-32. 12.
- 14) Aslanargun P, Cuvas O, Dikmen B, Aslan E, Yuksel MU. *Passiflora incarnata* Linneaus as an anxiolytic before spinal anesthesia. *J Anesth*. 2012;26:39-44
- 15) Smith GW, Chalmers TM, Nuki G. Vasculitis associated with herbal preparation containing *Passiflora* extract. *Br J Rheumatol*. 1993;32(1):87-8

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- 16) Fisher AA, Purcell P, Le couteur DG. Toxicity of *Passiflora incarnata* L. *J Toxicol Clin Toxicol*. 2000;38(1):63-6.
- 17) Dantas LP, De oliveira-ribeiro A, De almeida-souza LM, Groppo FC. Effects of *passiflora incarnata* and midazolam for control of anxiety in patients undergoing dental extraction. *Med Oral Patol Oral Cir Bucal*. 2017;22(1):e95-e101.
- 18) Kaviani N, Tavakoli M, Tabanmehr M, Havaei R. The efficacy of *passiflora incarnata* linnaeus in reducing dental anxiety in patients undergoing periodontal treatment. *J Dent (Shiraz)*. 2013;14(2):68-72.
- 19) Akhondzadeh S, Naghavi HR, Vazirian M, Shayeganpour A, Rashidi H, Khani M. Passionflower in the treatment of generalized anxiety: a pilot double-blind randomized controlled trial with oxazepam. *J Clin Pharm Ther*. 2001;26(5):363-7.
- 20) Ichimura T, Yamanaka A, Ichiba T, et al. Antihypertensive effect of an extract of *Passiflora edulis* rind in spontaneously hypertensive rats. *Biosci Biotechnol Biochem*. 2006;70(3):718-21.
- 21) Konta EM, Almeida MR, do Amaral CL, et al. Evaluation of the antihypertensive properties of yellow passion fruit pulp (*Passiflora edulis* Sims f. *flavicarpa* Deg.) in spontaneously hypertensive rats. *Phytother Res*. 2014;28(1):28-32.

4) Setting of the Human Research

The research will take place within the Health Sciences Center on the University of Bridgeport Campus.

We aim to recruit 70 naturopathic medical students for participation in the study in 4 independent groups. Each naturopathic cohort contains between 15-25 students, so we will have 4 different days of research sessions processing 15-25 students each time.

5) Resources available to conduct the Human Research

- The naturopathic medical program currently has 77 students, so we are aiming for a high participation rate from the students.
- Recruitment will take place from May 2019 until August 2019. We expect the research activity to take place during the Fall 2019 semester.
- The UB Naturopathic Clinic has 19 treatment rooms and 1 large classroom which provides ample space for the research to occur.
- We have one pulse-oximetry device for calculating heart rate
- We have five sphygmomanometers for performing manual blood pressure readings
- We need one 4oz. bottle of *Passiflora incarnata* solid extract by Wise Woman Herbals, which has been donated by the company.
- The co-investigators are:

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- Kimberly Sanders, ND has been associated with the UB Naturopathic Clinic for 3 years as a supervising physician. She has full knowledge of UB Naturopathic Clinic culture and policies.
 - Mark Mattie, PhD, MD who has vast research experience both at UBSNM and at Yale.
 - Devon Fox – Student Research Assistant, current first year ND student, has research and biology experience from Stonybrook University
 - Weronika Lewkowicz – Student Research Assistant, current second year ND student– has research experience from Eastern Connecticut State University
 - Anthony Pascucci – Student Research Assistant, current second year ND student– has research experience at the University of Bridgeport School of Naturopathic Medicine in the Anatomy Lab with Dr. David Terfera
- In the event of an adverse reaction to the *Passiflora incarnata* extract or the meditation, Student Health Services is available on the first floor of the Health Sciences Building
 - The research team will meet and have a training session before the research session occurs
 - All research team members are CITI-certified

6) Study Design

a) Recruitment Methods

- i) We will recruit from the naturopathic medical program, which currently has 77 enrolled students.
- ii) A flyer will be posted and emailed out to the naturopathic student body (*see Attachment A*)
- iii) Naturopathic student participants will NOT be recruited during class time with Dr. Sanders or Dr. Mattie to reduce any conflict of interest or feeling of persuasion that the student may have.
- iv) All naturopathic students will be invited to participate. Once a student expresses interest, he/she will be given the inclusion/exclusion criteria checklist (*see Attachment B*) to ensure eligibility.
 - (1) Exclusion criteria: Those taking hypertensive, blood-thinning, or anti-anxiety medications (including MAOI medications), those with surgery in the past 2 weeks or coming in the next 2 weeks, those females who are currently pregnant or could be pregnant
 - (a) “Day Of” exclusion criteria: consuming food, caffeine, use of stimulant medication, use of MAOI medication, alcoholic beverages, consumption of tyramine containing foods (i.e. blue cheese, gorgonzola cheese, red wine, cured meat, cured fish, sauerkraut, sourdough bread, soy sauce, teriyaki sauce, miso tempeh, or overripe fruits), consumption of cold medicine, antihistamine medication,

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decongestant medication, cough suppressant medication, or use of stimulant energy drinks within 2 hours before the study period.

(2) Participants will not be given any incentive to participate (i.e. no payment or “extra credit” will be given).

v) Interested participants will be screened for eligibility (see Attachment B) and allowed to participate if they do not meet any of the exclusion criteria

b) Inclusion and Exclusion Criteria*

i) **Inclusion criteria** – all naturopathic medical students are invited to participate

(1) Participants must have a smartphone with access to the Headspace application and headphones to listen to the session

ii) **Exclusion criteria**

(1) Those taking hypertensive medication

(2) Those taking anti-anxiety medication, including MAOI medication

(3) Those taking blood-thinning medication

(4) Those who are pregnant

(5) Those who could be pregnant

(6) Those who will have surgery 2 weeks before the research date

(7) Those who are scheduled to have surgery 2 weeks after the research date

(8) Those who do not have a smartphone or access to Headspace application

(9) Those who have consumed caffeine, food/tyramine containing foods, stimulant medication, cold medicine, decongestant medicine, antihistamine medicine, cough suppressants, alcoholic beverages, or stimulant energy drinks within 2 hours before the study period.

iii) Interested participants will be contacted by phone or in-person by one of the investigators (Dr. Sanders or Dr. Mattie) and screened for exclusion criteria

iv) We aim for 70 subjects to participate but can complete the research with 45-60 subjects to achieve 80-90% power, respectively.

c) Study Endpoints*

i) **Primary endpoints:** Blood pressure readings in mm/Hg and heart rate in beats per minute (bpm)

(1) According to the American Heart Association, blood pressure readings are as follows:

(a) Normal: Less than 120/80mmHg

(b) Elevated: 120-129/<80 mmHg

(c) Stage I Hypertension: 130-139/80-89 mmHg

(d) Stage II Hypertension: >140/>90 mmHg

(e) Hypertensive Crisis: >180/>120 mmHg

ii) **Primary safety endpoints:** Adverse events will be recorded for both *Passiflora incarnata* extract and the audio-guided meditation

d) Procedures involved in the Human Research*

i) This will be a randomized, double-blind, placebo controlled trial.

ii) Students will be randomized to Group I, II, or III before the study begins

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- iii) Naturopathic medical students will come to the study area in groups of 15-25 (each naturopathic cohort will be studied on a different day)
- iv) Naturopathic medical students will be studied on the day of a classroom examination with three left arm seated blood pressure readings and one heart rate reading taken 15 minutes after the end of the exam and then 15 minutes after that.
- v) All participants will be instructed to download Headspace app onto their smartphone prior to the research date
- vi) The participants will be randomized into three groups
 - (1) Group I
 - (a) Baseline (15 minutes post-exam) blood pressure readings (three left arm seated readings, average will be calculated) and one heart rate reading taken after at least 5 minutes of rest time without talking, eating, or caffeine consumption.
 - (b) This group will not be given any intervention. Subjects will sit quietly for 15 minutes and can read a book, surf the internet, etc. Subjects may not consume caffeine, eat food, or listen to any meditation during this time.
 - (c) Three left arm seated blood pressure readings and one heart rate will be taken 15 minutes after the baseline reading.
 - (2) Group II
 - (a) Baseline (15 minutes post-exam) blood pressure readings (three left arm seated readings, average will be calculated) and one heart rate reading taken after at least 5 minutes of rest time without talking, eating food, or caffeine consumption.
 - (b) 15 minutes after classroom examination – will be given 1/4 tsp of blackstrap molasses placebo and a 10 minute audio-guided mobile meditation session via the Headspace App. Subjects may not consume caffeine or eat food during this time.
 - (c) Three left arm seated blood pressure readings and one heart rate will be taken 15 minutes after the baseline reading.
 - (3) Group III
 - (a) Baseline (15 minutes post-exam) blood pressure readings (three left arm seated readings, average will be calculated) and one heart rate reading taken after at least 5 minutes of rest time without talking, eating, or caffeine consumption.
 - (b) 15 minutes after examination – will be given 1/8 tsp (900mg) of *Passiflora incarnata* solid extract by Wise Woman Herbals mixed with 1/8 tsp of blackstrap molasses to mask the taste and a 10 minute audio-guided mobile meditation session via the Headspace App. Subjects may not consume caffeine or eat food during this time.
 - (c) Three left arm seated blood pressure readings and one heart rate will be taken 15 minutes after the baseline reading.

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vii) Safety considerations

- (1) All participants will be given a paper survey about adverse events (*see Attachment C*) which will be returned to the research team by the end of the same study day. Any participant who marks a moderate-severe adverse event will be followed up by Dr. Sanders for appropriate management.
- (2) Dr. Sanders' phone number and contact information will be given to the study subjects so they can contact her in the event another adverse event arises after the survey has been returned.
- (3) The research will last for about 45 minutes. Three Blood pressure readings (all left arm seated) and one heart rate reading will be taken at baseline and again 15 minutes later.
- (4) Procedures taken to lessen the probability or magnitude of risks
 - (a) Adverse events related to *Passiflora incarnata* use have been found with chronic dosage. We attempt to minimize these risks by providing one-time acute dosage.
 - (b) We are attempting to minimize adverse events by excluding participants who are taking hypertensive medication, anti-anxiety medication, MAOI medication, or blood-thinning medication.
 - (c) We are attempting to minimize adverse events by excluding participants who are pregnant or may be pregnant.
 - (d) We are attempting to minimize adverse events by excluding participants who recently consumed cold medicine, cough suppressants, decongestant medication, antihistamine medication, stimulant medication, or tyramine containing foods to avoid interaction with *Passiflora incarnata*.
- (5) Initial data collected from the subjects
 - (a) The inclusion/exclusion criteria data will be collected from the participants before the start of the research (*see Attachment B*). This data will be collected in private with Dr. Sanders or Dr. Mattie.
 - (b) Age, sex, significant past medical history (previous diagnoses), and medication usage. This information will be gathered via questionnaire (*see Attachment D*) before the start of the research. This data will be collected in private with Dr. Sanders or Dr. Mattie.
 - (c) Adverse event survey will be collected from the participants by the end of the research day (*see Attachment C*)

e) **Data management***

- i) Participants will be assigned a de-identifying code upon participation in the research
- ii) This code will be used to randomize the participants into Group I, II, and III
- iii) This code will be placed on both their initial questionnaire, inclusion/exclusion checklist, BP and HR readings, and their adverse events survey

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- iv) This code will be linked with the participants' baseline and 15-minute blood pressure readings
 - v) A master sheet linking the code back to the subject's name will be stored on the password-protected University laptop belonging to only the co-investigators in a password-protected Excel sheet.
 - (1) This master sheet will not be printed or emailed between investigators.
 - vi) Hard copies of the inclusion/exclusion criteria checklist, the initial data questionnaire, BP and HR readings, and the adverse event survey will be stored in a locked file cabinet in the primary investigator's office. These forms will be shredded after three years.
 - vii) Power analysis – 45-60 subjects are needed to obtain 80%-90% power, respectively
 - viii) Data analysis will be done by our student research assistants and Dr. Mark Mattie
- f) Provisions to monitor the data for the safety of subjects***
- i) Dr. Sanders will evaluate the adverse events survey and follow up with any participant who experience a moderate-severe adverse event
 - ii) Participants will be encouraged to report additional adverse events to Dr. Sanders directly in the days following the research even once the survey has been handed in.
- g) Withdrawal of subjects***
- i) Participants can voluntarily withdraw at any time
 - ii) Once a participant has withdrawn from the research, his/her data will not be included in our analysis
 - iii) Withdrawal may occur without the participants' consent if:
 - (1) His/Her smartphone or Headspace application is not functioning within 30 minutes after the end of his/her classroom examination
 - (2) He/She did not take the classroom examination that day
 - (3) He/She eats food/tyramine containing food, stimulant medication, alcoholic beverages, cold medicine, decongestant medication, antihistamine medication, cough suppressant medication, stimulant energy drinks, or consume caffeine within 2 hours before the study period or during the study period.
- 7) Risks to subjects***
- a) Privacy Risks**
- i) Since naturopathic medical students will be studied in groups in one large room, the subjects will be informed that his/her classmates in the same room will know that he/she is participating in the study.
 - b) To minimize any privacy risks, all medical information will be collected in private before the day of the study. On the day of the study, we will not read the participants' blood pressure and heart rate readings out loud. We also will ask the participant to write down what medications or drinks taken on the day of the study

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- so that the participant does not have to say this information out loud in order to protect privacy.
- c) **Inconveniences: Time Invested/Timing with Classroom Examination**
 - i) The participants may be inconvenienced by sparing 45 minutes after his/her classroom examination
 - ii) The participant may feel distracted during his/her examination in anticipation of the research taking place after the examination
 - (1) This is unlikely, as the research is intended to have a relaxing benefit on the participant
 - iii) The participant may be late to his/her next class by participating in the research
 - (1) This may be unforeseeable and may be likely. However, the research period will last only 45 minutes.
 - iv) The subject may not eat any food/tyramine containing foods or consume caffeine, cold medicine, cough suppressant medication, antihistamine medication, decongestant medication, alcoholic beverages, stimulant medications, or stimulant energy drinks for 2 hours before the study period or during the study period, which might inconvenience the student
 - d) **Blood Pressure Reading**
 - i) Participants may feel a slight discomfort when the blood pressure cuff is tightened around his/her arm. This is a temporary sensation that will last no more than 1 minute on each occasion.
 - e) **Audio-Guided Mobile Meditation Application**
 - i) The participant may be inconvenienced by having to download the Headspace application onto his/her smartphone
 - (1) This should be a minor inconvenience, as detailed instructions will be provided ahead of time (*see Attachment E*)
 - ii) The participant may use data or wifi on his/her smartphone by downloading and utilizing the Headspace application
 - (1) This is an unforeseeable risk, as everyone's cellular data plan is different. Participants will be encouraged to connect to wifi to download and use the application to avoid accruing data usage charges (*see Attachment E*)
 - iii) The participant may have to purchase headphones to listen to the Headspace meditation on his/her smartphone if he/she does not already own them
 - (1) This is unlikely, as most students already own headphones
 - iv) There are no known serious adverse effects related to meditation
 - (1) An unforeseeable adverse effect is possible, but unlikely, according to existing literature.
 - f) ***Passiflora incarnata* extract**
 - i) Some participants may dislike the flavor of the *Passiflora incarnata* extract (mixed with molasses to hide the taste) or the blackstrap molasses placebo
 - ii) Studies on *Passiflora incarnata* have generally found mild-moderate adverse effects when taken for weeks-months including:

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- (1) Drowsiness (very common, up to 50% reported this adverse effect in studies). Due to this very common side effect, we advise the subject to exercise caution and avoid operating a vehicle or heavy machinery for one hour after taking the dose.
- (2) Muscle relaxation (common, up to 20% reported this in studies). Due to this very common side effect, we advise the subject to exercise caution and avoid operating a vehicle or heavy machinery for one hour after taking the dose.
- (3) Dizziness (common, up to 5% reported this in studies). Due to this very common side effect, we advise the subject to exercise caution and avoid operating a vehicle or heavy machinery for one hour after taking the dose
- (4) Headache
- (5) Abdominal Pain
- (6) Flatulence
- (7) Vasculitis (rare)
- (8) Asthma
- (9) Rhinitis
- (10) Urticaria/Allergic Reaction
- (11) Cardiovascular effects, including Ventricular Tachycardia (one case study, rare)
- (12) Uterine contractions
- (13) Nosebleed, blood-thinning
- (14) Impairment of Job Performance
- (15) Confusion
- (16) Ataxia
- (17) Other unforeseeable adverse reactions

iii) Our exclusion criteria is intended to reduce the risk of adverse events. Our study will involve a one-time acute dosing of *Passiflora incarnata* to reduce the risk of adverse events from chronic, long-term usage.

8) Potential benefits to subjects*

a) Relaxation

- i) *Passiflora incarnata* has been found to have anxiolytic properties and might reduce sympathetic tone. The participants may note a sense of well-being and relaxation after participating in the research
- ii) Meditation has been found to improve well-being in medical students. The participants may note an improved sense of well-being and sense of relaxation after participating in the research
- iii) These relaxation effects are likely and should last for the rest of the research day

9) Provisions to protect the privacy interests of subjects

- a) Initial data to be gathered only by Dr. Sanders or Dr. Mattie include information regarding age, sex, past medical history (i.e. previous medical diagnoses), and medication usage (*See Attachment D*). This information will be linked to the

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- participants' de-identified code. The code will only be linked back to the patient's name on a password-protected Excel sheet on the password-protected University computer belonging to the investigators.
- b) Blood pressure and heart rate readings will be linked to the participants' de-identified code. The code will only be linked back to the patient's name on a password-protected Excel sheet on the password-protected University computer belonging to the investigators.
 - c) The adverse event survey (*see Attachment C*) will be linked to the participants' de-identified code. The code will only be linked back to the patient's name on a password-protected Excel sheet on the password-protected University computer belonging to the investigators.
 - d) Only Dr. Kimberly Sanders and Dr. Mark Mattie will have access to the participants' data. The student RAs will not have access to the subject's data with the exception of their blood pressure and heart rate readings, as the student RAs will be collecting these measurements.
 - e) Being that the participants are students, they will be assured that their data will be kept completely confidential and stored only on password-protected excel sheets and password-protected computers. They will be assured that their questionnaire answers will not be used for any other academic means other than the intended research. They will be assured that the inclusion/exclusion criteria checklist, initial data questionnaire, and adverse events questionnaire will not be accessible by the student RAs. They will be assured that their willingness to participate in the research will in no way affect the way that they are treated in the classroom by their professors. They will be assured that choosing to participate or not to participate in the research will not affect their grade in their naturopathic classes. There will be no extra credit given for participating in the research.
 - f) Since naturopathic medical students will be studied in groups in one large room, the subjects will be informed that his/her classmates in the same room will know that he/she is participating in the study. To minimize any privacy risks, all medical information will be collected in private before the day of the study. On the day of the study, we will not read the participants' blood pressure and heart rate readings out loud. We also will ask the participant to write down what medications or drinks taken on the day of the study so that the participant does not have to say this information out loud in order to protect privacy.

10) Provisions to maintain the confidentiality of data

- a) Initial data to be gathered by Dr. Sanders or Dr. Mattie include information regarding age, sex, past medical history (i.e. previous medical diagnoses), and medication usage (*See Attachment D*). This information will be linked to the participants' de-identified code. The code will only be linked back to the patient's name on a password-protected Excel sheet on the password-protected University computer belonging to the investigators.
- b) Blood pressure and heart rate readings will be linked to the participants' de-identified code. The code will only be linked back to the patient's name on a

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- password-protected Excel sheet on the password-protected University computer belonging to the investigators.
- c) The adverse event survey (*See Attachment C*) will be linked to the participants' de-identified code. The code will only be linked back to the patient's name on a password-protected Excel sheet on the password-protected University computer belonging to the investigators.
 - d) Only Dr. Kimberly Sanders and Dr. Mark Mattie will have access to the participants' data. Student RAs will be recording blood pressure readings and heart rate data, but will not have access to the inclusion/exclusion checklist, initial data questionnaire, and adverse events questionnaire.
 - e) The initial questionnaire and the adverse event survey will be performed on paper and turned into the research team. Once the answers are transcribed to password protected Excel sheets, they will be stored in a locked file cabinet in Dr. Sanders' locked office for a period of 3 years. After this time, they will be shredded. These paper forms will contain only the subjects' de-identified code.
 - f) Signed consent forms will be stored in Dr. Sanders' locked office in a locked file cabinet.

11) Medical care and compensation for injury

- a) Participants can seek treatment at Student Health Services in relation to any adverse events experienced as a result of the treatment. Routine care should be covered by the participants' health insurance.

12) Cost to subjects

- a) Participants may incur a cost in the event that
 - i) They incur data usage charge for downloading and using the Headspace app
 - (1) Instructions will be given to the participants to use wifi to download and use the app to avoid this cost (*See Attachment E*)
 - ii) They purchase headphones to listen to the Headspace app

13) Consent process

- a) Once a participant expresses interest in participating and meets the eligibility criteria, he or she will meet with a member of the research team (i.e. Dr. Sanders or Dr. Mattie) to verbally review the consent document. Consent will take place in a clinic examination room or in the office of Dr. Sanders or Dr. Mattie. The consent process occurs before the research begins on a different day.
- b) Student RAs will not be involved in the consent process.
- c) The consent conversation will take about 20 minutes and should occur within a few days after informing the participant that he or she is eligible for participation in the study.
- d) The research team will make it **very** clear that the participant does not have to participate in this study and that participation is voluntary. It will be made very clear to the participant that he/she may withdraw at any time without any retaliation in the classroom, as Dr. Sanders and Dr. Mattie are instructors for these students in the naturopathic program. No extra credit will be given to students who choose to participate, and no "punishment" will be given to the students who

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- choose not to participate. They will be assured that their willingness to participate in the research will in no way affect the way that they are treated in the classroom by their professors. They will be assured that choosing to participate or not to participate in the research will not affect their grade in their naturopathic classes.
- e) All participants must give consent and sign the consent form in order to participate in the research study.
 - f) Signed consent forms will be stored in Dr. Sanders' locked office in a locked file cabinet.

14) Process to document consent in writing

- a) Once a participant expresses interest in participating and meets the eligibility criteria, he or she will meet with a member of the research team (i.e. Dr. Sanders, Dr. Mattie, or Student Research Assistant) to verbally review the consent document. Consent will take place in a clinic examination room or in the office of Dr. Sanders or Dr. Mattie.
- b) Participants may sign the consent document at that time, if they are comfortable, or they may think about it for a few days and sign the consent document at a later date. If more than a week has passed since the initial consent conversation, another consent conversation will occur to ensure that the participant remembers the details.

15) Vulnerable populations

- a) **The participants will be students in the naturopathic medical program, where Dr. Sanders and Dr. Mattie teach.**
- b) The research team will make it **very** clear that the participant does not have to participate in this study and that participation is voluntary. It will be made very clear to the participant that he/she may withdraw at any time without any retaliation in the classroom, as Dr. Sanders and Dr. Mattie are instructors for these students in the naturopathic program. No extra credit will be given to students who choose to participate, and no "punishment" will be given to the students who choose not to participate. They will be assured that their willingness to participate in the research will in no way affect the way that they are treated in the classroom by their professors. They will be assured that choosing to participate or not to participate in the research will not affect their grade in their naturopathic classes.
- c) Naturopathic students will not be recruited for the study during class time where the students are in class with Dr. Mattie or Dr. Sanders.
- d) Pregnant woman are excluded from the study

16) Drugs or Devices

17) Sharing of results with subjects

- a) Results will not be shared with the subject unless
 - i) If the patient's average baseline or 15 minute blood pressure falls into the Stage I (130-139/80-89 mmHg) or Stage II (>140/>90 mmHg) hypertensive range, he/she will be given this information at the conclusion of the study period in private, so as not to have his/her classmates hear the information.

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- ii)** If the patient's baseline or 15 minute heart rate falls into the bradycardic (<50 bpm) or tachycardic (>100 bpm), he/she will be given this information at the conclusion of the study period in private, so as not to have his/her classmates hear the information.