Vanderbilt University Institutional Review Board
Informed Consent Document for Research

Principal Investigator: Stephen Bruehl, Ph.D. **Revision Date: 6/26/18**
Study Title: Reduced Opioid Analgesic Requirements Via Improved Endogenous Opioid Function
Institution/Hospital: Vanderbilt University School of Medicine

This informed consent applies to adult chronic low back pain patients aged18-55.

Name of participant: _____ Age: _____

The following is given to you to tell you about this research study. Please read this form with care and ask any questions you may have about this study. Your questions will be answered. Also, you will be given a copy of this consent form.

You do not have to be in this research study. You can stop being in this study at any time. If we learn something new that may affect the risks or benefits of this study, you will be told so that you can decide whether or not you still want to be in this study.

1. What is the purpose of this study?

You are being asked to take part in this research study because you are experiencing chronic low back pain. Use of opioid analgesics (commonly referred to as "pain medications") for treating chronic pain has increased dramatically, but so has the controversy regarding their side effects and potential for abuse when used for long periods. The effectiveness of opioid pain medications, such as morphine and hydrocodone, can vary widely between individuals. Our previous research indicates that one factor influencing responses to pain medications is the body's level of natural opioid painkillers (often referred to as "endorphins"). The overall purpose of this research study is to determine whether aerobic exercise training decreases chronic back pain intensity by increasing levels of natural opioid painkillers, and whether these changes in turn reduce the amount of opioid analgesics required to achieve the desired level of pain relief. A total of 100 chronic low back pain patients will participate in this study at Vanderbilt University Medical Center.

2. What will happen and how long will you be in the study?

All procedures described below will be for research purposes only.

You will only be allowed into the study if you are <u>not</u> taking opioid pain medications on a daily basis (for example, Morphine, Oxycontin, Tylenol #3, Vicodin, Ultram, etc.). This is because individuals who take opioid pain medications daily or who are dependent on prescribed or non-prescribed opiate medications (including heroin) may experience side effects (such as sweating and nausea) when the study medication, naloxone, is administered. Naloxone is an FDA-approved opioid antagonist that has been used clinically for decades for treatment of opiate overdose and for reversal of surgical anesthesia. In this study Naloxone is being given for research purposes only; this use of naloxone is considered investigational and not FDA-approved. You will receive naloxone during two laboratory sessions while participating in this study. Naloxone should have no noticeable side effects if you do not have a recent history of opioid dependence, and are not taking opioid medications on a daily basis. The other study drug, morphine, is an FDA-approved opioid pain medication. It can produce side effects including sedation, somnolence (sleepiness), nausea, brief vomiting, euphoria (feeling good), and slowing of your breathing rate. The dose used in this study will be based on your weight and represents a relatively low dose which should help limit any negative side effects. If you take opioid pain medications on an as-needed basis, you will be asked not to take any of these medications for 3 days before each laboratory session, in order to avoid altering your sensitivity to the experimental procedures used in the study (described below). You will also be asked not to take opioid pain medications for 24 hours after each session to avoid possible interactions with the medication used in this study. To insure your safety, prior to each study session you will be asked to provide a urine sample to confirm that you have not taken narcotic pain medications recently, and if you are female, to conduct a pregnancy test. You must test negative on both tests to participate.

You will first be asked to attend a baseline screening session during which you will undergo a screening to confirm that you are eligible to participate in the study, and complete several questionnaires. This will involve providing information on your

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You will first be asked to attend a baseline screening session during which you will undergo a screening to confirm that you are eligible to participate in the study, and complete several questionnaires. This will involve providing information on your

pain condition, your medical history, medications you are taking, and a brief examination to document the nature of any chronic pain. You will also be asked to complete several questionnaires asking about general information (for example, age, gender, etc.), your activity and exercise levels, your chronic pain and how it affects your life, and psychological factors that can affect pain and responses to pain medications. These psychological factors include anger-related factors, depression, anxiety, and how you cope mentally with pain. Information obtained from these questionnaires will be used to help interpret the laboratory results of this study, and for guiding future related studies. You will only be asked to complete these questionnaires during the initial baseline screening session. At the end of your baseline screening session, you will be given a personal digital assistant (PDA) containing an electronic pain diary. You will be asked to complete this brief electronic pain diary twice per day (at 9am and 6pm) for 5 days. For your safety, you must tell the study doctor or nurse about all the medications you are taking before you start the study and before taking any non-study medications while you are in the study.

Next, you will be asked to attend a series of 3 study sessions scheduled over an approximately 10 day period at the same time of day, during which you will receive naloxone, morphine, or placebo [an inactive substance]). All laboratory sessions will each last about 3.5 hours (or less). All laboratory procedures will be conducted while you are seated upright in a comfortable chair. Nursing staff (supervised by the study physicians) will be present during all procedures, and emergency medical supplies will be available on site. You will be asked about recent medication use, and if necessary, will be rescheduled. All study drugs will be administered by a trained clinical research center staff nurse under physician supervision. You will receive placebo during one of the sessions, naloxone (a temporary blocker of your body's natural opioids) during one of the sessions, and morphine (an opioid pain medication often used in hospitals) during one of the sessions. You will have an equal likelihood of receiving the placebo, the naloxone, or the morphine first, with the order of medications determined using a procedure similar to flipping a coin. Both you and the research nurse will be unaware of the specific medication you have been assigned on each visit, although this information will be available if necessary. Because of the side effects of morphine and because we do not know which study session you will be assigned to receive morphine, **you will need to arrange for someone to drive you home from all three study sessions and refrain from driving for at least 6 hours after the study drug was given**. Prior to beginning the first part of the laboratory study in session 1, you will undergo a standardized thermal pain task training test.

During each laboratory session, you will first complete a 5-minute seated rest. Then a venous cannula (similar to an i.v. like you might get in the hospital) will be placed in your nondominant arm by the research nurse. In the first and fourth sessions only, a 4ml blood sample (about 1 teaspoon) will then be obtained from this cannula to assess levels of natural cannabinoids (chemicals produced naturally by your body that are similar to the active ingredient in marijuana) that may impact on pain and medication responses. Following blood sampling, you will complete a questionnaire to describe your current low back pain intensity. You will then receive 4 infusions of the medication that has been assigned for that laboratory session, each approximately 20 minutes apart. During the session in which you receive morphine, you will receive small doses of morphine in all 4 infusions. During the naloxone session, you will receive naloxone during 2 of the 4 infusions. In the placebo session, you will receive placebo in all 4 infusions.

Ten minutes after each dose of medication is received (to allow peak drug activity to be achieved), you will be asked to complete a brief questionnaire to describe your chronic back pain intensity. Then, you will undergo a thermal pain task to assess heat pain threshold and tolerance. This task will involve repeated brief applications of a computer-controlled heat stimulus to several areas of your non-dominant forearm. The equipment used in this task is safe and only produces heat at 127 degrees Fahrenheit or less, which is below the level that causes burns. You will be asked to participate in three brief heat stimulation trials during which you will be asked to indicate when the heat stimulus first becomes painful (your heat pain threshold), and three brief trials during which you will be asked to indicate when your heat pain tolerance has been reached. For each trial, as soon as your tolerance is reached, the equipment will rapidly cool your skin to normal body temperature, ending the pain stimulus. Immediately upon completion of the final heat pain tolerance trial, you will be asked to rate the quality and intensity of the pain you experienced, as well as any drug-related side effects. These same thermal pain task procedures will be repeated after all 4 of the drug infusions.

After completing the first three laboratory sessions, you will next be randomly assigned (like flipping a coin) to either the 6-week aerobic exercise training group or the no-intervention control group. You will have an equal chance of being assigned to either group. If you are assigned to the no-intervention control group, you will be asked to maintain the same activity level throughout your study participation that you maintained prior to beginning the study. After completing your study participation, you may engage in any additional exercise activities if you choose to. You will also complete a brief (less than 15 minutes) assessment regarding your pain, function, and emotional state over the phone on a weekly basis. If you are assigned to the aerobic exercise training intervention, you will be asked to participate in 3 aerobic exercise sessions supervised by a certified personal trainer per week for 6 weeks (18 sessions total). Exercise in these sessions will be of progressively increasing intensity over the 6 week period, with the goal of optimizing your level of aerobic conditioning. Each exercise session will consist of a 5 minute warm-up, 30 minutes of aerobic exercise, followed by a 5 minute cool-down period. You will be able to select your preferred form of aerobic exercise from the following options: treadmill walking/running, stair stepping, the elliptical machine, or stationary cycling. Your back pain, heart rate, and perceived level of exertion will be monitored by the personal trainer regularly during each exercise session, with activities adjusted during each session to help you increase your level of aerobic conditioning while minimizing any exacerbations of back pain. Each week during this exercise intervention period, you will also be asked to complete a brief (less than 15 minutes) assessment regarding your pain, function, and emotional state over the phone.

After the intervention period, regardless of which group you are assigned to, you will be asked to return for 3 final laboratory sessions identical to those described above during which you will again receive the 3 study drugs in random order. Between the first and second laboratory session during this post-treatment follow-up assessment, you will again be asked to complete a 5-day electronic diary monitoring period using procedures identical to those described above.

Giving samples for genetic research is your free choice and you may be in the study even if you do not want your samples used or stored for genetic research. There will be a separate section at the end of this form where you can indicate whether or not you would like to participate in this genetic part of the study.

Your participation in the study will end after the sixth laboratory visit.

3. Costs to you if you take part in this study:

There is no cost to you for taking part in this study. All procedures described above are solely for the research purposes of this study. However, you are still responsible for paying for the usual care you would normally receive for the treatment of your illness. This includes treatments and tests you would need even if you were not in this study. These costs will be billed to you and/or your insurance.

4. Side effects and risks that you can expect if you take part in this study:

You may find completing questionnaires regarding your pain and psychological state to be mildly distressing. This level of distress is likely to be similar to what would occur if you were discussing these issues with your physician or a family member.

You may find certain aspects of the evaluation of your pain-related symptoms to be mildly uncomfortable.

You will experience brief, moderate intensity acute pain upon application of the thermal pain stimuli that will be used for assessment of your natural pain control systems and your responses to morphine. However, you have total control over the duration of your exposure to these pain stimuli because you stop each task by indicating when you have reached your

tolerance limit. Previous research indicates that these tasks are safe, but to further maximize safety, individuals experiencing cardiovascular problems will be excluded from this study. Because you have total control over the duration of the task, its psychological impact is expected to be minimal.

You will experience very brief, mild pain upon insertion of a cannula (for study drug administration) during each study session. This event is similar to what you have likely experienced at some point during medical treatment when blood samples were drawn, or if you have ever received an IV while hospitalized. Insertion will be performed by a trained nurse or physician to minimize discomfort associated with insertion of the cannula. There is a risk of infection and local inflammation at the site of cannula insertion. Precautions will be taken to insure that such risks are minimized.

The following risks relate to the medications to be used in the study. The medication used for opioid blockade, naloxone, has been used clinically for decades for treatment of opiate overdose and for reversal of surgical anesthesia. It is not an experimental or new drug, and is FDA-approved for those purposes. Previous studies indicate that it is safe for individuals who are not opiate dependent, do not have liver disease, and do not have cardiovascular problems. Potential subjects experiencing these types of problems will be excluded from this study to insure a maximal level of safety with drug administration. Individuals taking daily opiates, even if not dependent, will also be excluded from the study to avoid precipitating minor withdrawal symptoms. In some individuals, naloxone may increase pain sensitivity to the acute pain tasks somewhat, but again, you may terminate these tasks if you reach your tolerance limit. Based on previous studies, naloxone is expected to have limited if any direct effects on your back pain intensity, and therefore, there appears to be little risk of exacerbating your chronic pain condition. Even if such changes do occur, the brief half-life of naloxone (on average, approximately 45-60 minutes) insures that any pain exacerbation will be of short duration. With the exception of possible effects on pain sensitivity, naloxone is not known to be associated with other clinically significant effects in healthy individuals who are not opiate dependent or using daily opiates.

The other study drug, morphine, is an FDA-approved opioid analgesic with a very long history of use in standard clinical practice. It can produce dose-dependent side effects including sedation, somnolence (sleepiness), allergic reactions (which may be life threatening), itching, nausea, vomiting, euphoria (feeling good), hallucinations, vision changes, urinary retention, constipation, and slowing of breathing rate. The dose used in this study will be adjusted to your weight, and the total dose you will receive represents a relatively low dose within the normal range of dosages used in standard clinical practice. This should help limit any negative side effects. The effects of morphine can last for four hours or more. You will be kept under observation in each study session until all side effects remit to the point where it is safe for you to leave. You will need to arrange for someone to drive you home from the appointment and refrain from driving for at least 6 hours after the study drug was given. If morphine side effects are severe, these effects will be immediately reversed by administration of naloxone as determined appropriate by the study physician.

As part of this study, you may be assigned by chance to undergo a 6-week aerobic exercise intervention as described above. To maximize safety with this type of exercise, individuals with a history of cardiovascular disease are excluded from participating in this study. The intensity of this aerobic exercise training will start low but progressively increase over the 6-week intervention period. It is possible that you may experience short-term increases or decreases in your chronic pain following your exercise sessions. Safety and possible discomfort associated with these increases in exercise intensity will be minimized via close monitoring by a certified personal trainer of your heart rate, perceived exertion levels, and your back pain during exercise. Exercise intensity will be adjusted as appropriate to maximize your level of conditioning while minimizing exacerbation of your back pain. In addition, you will be able to choose your preferred form of exercise from several available options.

5. Risks that are not known:

In the event new information becomes available that may affect the risks or benefits associated with this study or your willingness to participate in it, you will be notified so that you can make an informed decision whether or not to continue your participation in this study.

6. Payment in case you are injured because of this research study:

If it is determined by Vanderbilt and the Investigator that an injury occurred as a direct result of the tests or treatments that are done for research, then you and/or your insurance will not have to pay for the cost of immediate medical care provided **at Vanderbilt** to treat the injury. There are no plans for Vanderbilt to pay for the costs of any additional care. There are no plans for Vanderbilt to give you money for the injury.

7. Good effects that might result from this study:

a) The benefits to science and humankind that might result from this study are an improved understanding of endogenous opioid mechanisms by which aerobic exercise may improve chronic pain, and how these changes impact on responsiveness to opioid analgesic medications. This study has the potential to significantly advance knowledge regarding mechanisms underlying individual differences in responsiveness to opioid analgesics, and how these mechanisms can be manipulated through non-drug interventions in a way that may reduce reliance upon high-dose opioid analgesics for chronic pain management.

b) If you are assigned by chance to the aerobic exercise intervention and you complete this intervention, you may experience a decrease in the intensity of your low back pain as a result. Any improvement might be temporary, but would be more likely to continue if you continue to engage in similar exercise activities.

8. Other treatments you could get if you decide not to be in this study:

This is not a study designed to determine the effectiveness of a new treatment for back pain. Exercise interventions like those used in this study are available through most physical therapy providers and personal trainers.

9. Payments for your time spent taking part in this study or expenses

If you are assigned to the exercise condition, you will be compensated for your time with $75 for the baseline screening session and electronic diary monitoring period, $100 for each completed laboratory session (6 sessions if you complete the full protocol), $30 for each completed exercise session (up to 18 sessions), $30 each week for completing phone follow-up questionnaires, and $75 for the follow-up electronic diary monitoring period, all paid by check upon completion of all study procedures or your withdrawal from the study. If you are assigned to the control condition, you will be compensated for your time with $75 for the baseline screening session and electronic diary monitoring period, $100 for each completed laboratory session (6 sessions if you complete the full protocol), $30 each week for completing phone follow-up questionnaires, and $75 for the follow-up electronic diary monitoring period, all paid by check upon completion of all study procedures or your withdrawal from the study. We may ask you for your Social Security Number and address before you are compensated for taking part in this study. You may receive up to $1,470 for taking part in this study. This amount may be taxable and will be reported to the Internal Revenue Service. Your payment cannot be processed until the PDA electronic diary provided to you has been returned. If you lose this device, its' replacement cost ($150) may be deducted from your final compensation.

10. Reasons why the study doctor may take you out of this study:
You may be withdrawn from the study if the study doctor determines that your medical condition makes your

participation in the study unsafe. If you are taken out of the study, you will be told the reason why.

11. What will happen if you decide to stop being in this study?

Your participation in this study is voluntary. You are also free to withdraw from this study at any time. Withdrawal or refusal to participate will not change your regular medical care in any way.

12. Who to call for any questions or in case you are injured:

If you should have any questions about this research study or if you feel you have been hurt by being a part of this study, please feel free to contact Stephen Bruehl, Ph.D. at (615) 936-1821, or his assistant, Melissa Chont, at (615) 936-5664**.** If you experience a medical emergency you believe is related to your study participation, you should immediately go to the Vanderbilt Emergency Room.

For additional information about giving consent or your rights as a person in this study, to discuss problems, concerns, and questions, or to offer input, please feel free to call the Vanderbilt University Institutional Review Board Office at (615) 322-2918 or toll free at (866) 224-8273.

13. Confidentiality:

All published data will be reported in a manner in which individual data for specific patients are not identifiable. Data will be coded on paper and in the computer by subject number rather than name to help further insure confidentiality. All hardcopy study records will be maintained in a filing cabinet in a locked office at the investigator's office suite (324 Medical Arts Building), and will be accessible only to the principal investigator and his designees. All subject records in the study computer database will be maintained on password protected computers stored in the locked offices of the principal investigator. If you have received medical care at Vanderbilt previously, your medical information at Vanderbilt may be visible to study staff during the course of this study.

Vanderbilt may share your information, without identifiers, to others or use it for other research projects not listed in this form. Vanderbilt, Dr Bruehl, and his staff will comply with any and all laws regarding the privacy of such information. There are no plans to pay you for the use or transfer of this de-identified information.

This study is supported by the National Institutes of Health (NIH). Therefore, your study information is protected by a Certificate of Confidentiality. This Certificate allows us, in some cases, to refuse to give out your information even if requested using legal means.

It does not protect information that we have to report by law, such as child abuse or some infectious diseases. The Certificate does not prevent us from disclosing your information if we learn of possible harm to yourself or others, or if you need medical help.

Disclosures that you consent to in this document are not protected. This includes putting research data in the medical record or sharing research data for this study or future research. Disclosures that you make yourself are also not protected.

14. Authorization to Use/Disclose Protected Health Information

All efforts, within reason, will be made to keep your protected health information (PHI) private. PHI is your health information that is, or has been gathered or kept by Vanderbilt as a result of your healthcare. This includes data gathered

for research studies that can be traced back to you. Using or sharing ("disclosure") such data must follow federal privacy rules. By signing the consent for this study, you are agreeing ("authorization") to the uses and likely sharing of your PHI. If you decide to be in this research study, you are also agreeing to let the study team use and share your PHI as described below.

As part of the study, Dr. Bruehl and his study team may share the results of your study participation to the groups named below. These groups may include people from the Federal Government Office for Human Research Protections, the Vanderbilt University Institutional Review Board, and the National Institutes of Health. Federal privacy rules may not apply to these groups; they have their own rules and codes to assure that all efforts, within reason, will be made to keep your PHI private.

The study results will be kept in your research record for at least six years after the study is finished. At that time, the research data that has not been put in your medical record will be kept for an unknown length of time. Any research data that has been put into your medical record will be kept for an unknown length of time.

Unless told otherwise, your consent to use or share your PHI does not expire. If you change your mind, we ask that you contact Dr. Bruehl in writing and let him know that you withdraw your consent. His mailing address is: 701 Medical Arts Building, VUMC, 1211 21st Ave. South, Nashville, TN 37212. At that time, we will stop getting any more data about you. But, the health data we stored before you withdrew your consent may still be used for reporting and research quality.

If you decide not to take part in this research study, it will not affect your treatment, payment or enrollment in any health plans or affect your ability to get benefits. You will get a copy of this form after it is signed.

STATEMENT BY PERSON AGREEING TO BE IN THIS STUDY

I have read this consent form and the research study has been explained to me verbally. All my questions have been answered, and I freely and voluntarily choose to take part in this study.

_____ _____
Date Signature of patient/volunteer

_____ _____-_____-_____
Name as Shown on Tax Forms Social Security Number

_____
Preferred Mailing Address (for Payment Purposes)

Consent obtained by:

_____ _____
Date Signature

_____
Printed Name and Title

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Consent for Genetic Research

The purpose of this study is to look at genes (DNA) and how they affect health and disease. Genes are the instruction manual for your body. The genes you get from your parents decide what you look like and how your body behaves. They can also tell us a person's risk for certain diseases and how they will respond to treatment.

You are being asked to give a blood sample for genetic research. What we learn about you from this sample will not be put in your health record. Your test results will not be shared with you or your doctor. No one else (like a relative, boss, or insurance company) will be given your test results. Your sample will only be used for research at Vanderbilt University and will not be sold. Health insurance companies and group health plans may not request your genetic information that comes from this research.

A single blood sample of about ½ teaspoon will be obtained through the cannula already inserted in your arm as part of the study for extraction of genetic samples.

One risk of giving samples for this research may be the release of your name that could link you to the stored samples and/or the results of the tests run on your samples. This may cause problems with insurance or getting a job.

Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums. Employers with 15 or more employees may not use your genetic information that comes from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

To prevent this, these samples will be given a code. Only the study staff will know the code. The name that belongs to the code will be kept in a locked file or in a computer with a password. Only Dr. Stephen Bruehl and his study designee will have access to your name.

Your sample will be used to extract DNA that will be kept for an unknown length of time (maybe years) for future research. The sample will be destroyed when it is no longer needed.

Your samples will be used for research only and will not be sold or used to make products that could be sold for money.

You will not receive any benefit as a result of the tests done on your samples. These tests may help us learn more about the causes, risks, and treatments of chronic pain, or how to prevent this and other health problems.

Giving samples for research is your free choice and you may be in the study even if you do not want your samples used or stored for gene research.

At any time, you may ask to have your sample destroyed. You should contact Dr. Stephen Bruehl at 701 Medical Arts Building, VUMC, 1211 21st Ave. South, Nashville, TN 37212, (615) 936-1821 to have your sample destroyed and no longer used for research. We will not be able to destroy research data that has already been gathered using your sample. Also, if your identity was removed from the samples, we will not be able to locate and destroy them.

There will be no costs to you for any of the tests done on your samples. You will not be paid for the use of your samples.

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Please check Yes or No to the questions below:

My blood sample may be used for gene research on pain.

☐ Yes ☐ No

My blood sample may be stored/shared for future gene research on pain.

☐ Yes ☐ No

My blood sample may be stored/shared for future gene research for other health problems (such as cancer, heart disease, etc).

☐ Yes ☐ No

Signature: _____ Date: _____

pain condition, your medical history, medications you are taking, and a brief examination to document the nature of any chronic pain. You will also be asked to complete several questionnaires asking about general information (for example, age, gender, etc.), your activity and exercise levels, your chronic pain and how it affects your life, and psychological factors that can affect pain and responses to pain medications. These psychological factors include anger-related factors, depression, anxiety, and how you cope mentally with pain. Information obtained from these questionnaires will be used to help interpret the laboratory results of this study, and for guiding future related studies. You will only be asked to complete these questionnaires during the initial baseline screening session. At the end of your baseline screening session, you will be given a personal digital assistant (PDA) containing an electronic pain diary. You will be asked to complete this brief electronic pain diary twice per day (at 9am and 6pm) for 5 days. For your safety, you must tell the study doctor or nurse about all the medications you are taking before you start the study and before taking any non-study medications while you are in the study.

Next, you will be asked to attend a series of 3 study sessions scheduled over an approximately 10 day period at the same time of day, during which you will receive naloxone, morphine, or placebo [an inactive substance]). All laboratory sessions will each last about 3.5 hours (or less). All laboratory procedures will be conducted while you are seated upright in a comfortable chair. Nursing staff (supervised by the study physicians) will be present during all procedures, and emergency medical supplies will be available on site. You will be asked about recent medication use, and if necessary, will be rescheduled. All study drugs will be administered by a trained clinical research center staff nurse under physician supervision. You will receive placebo during one of the sessions, naloxone (a temporary blocker of your body's natural opioids) during one of the sessions, and morphine (an opioid pain medication often used in hospitals) during one of the sessions. You will have an equal likelihood of receiving the placebo, the naloxone, or the morphine first, with the order of medications determined using a procedure similar to flipping a coin. Both you and the research nurse will be unaware of the specific medication you have been assigned on each visit, although this information will be available if necessary. Because of the side effects of morphine and because we do not know which study session you will be assigned to receive morphine, **you will need to arrange for someone to drive you home from all three study sessions and refrain from driving for at least 6 hours after the study drug was given**. Prior to beginning the first part of the laboratory study in session 1, you will undergo a standardized thermal pain task training test.

During each laboratory session, you will first complete a 5-minute seated rest. Then a venous cannula (similar to an i.v. like you might get in the hospital) will be placed in your nondominant arm by the research nurse. In the first and fourth sessions only, a 4ml blood sample (about 1 teaspoon) will then be obtained from this cannula to assess levels of natural cannabinoids (chemicals produced naturally by your body that are similar to the active ingredient in marijuana) that may impact on pain and medication responses. Following blood sampling, you will complete a questionnaire to describe your current low back pain intensity. You will then receive 4 infusions of the medication that has been assigned for that laboratory session, each approximately 20 minutes apart. During the session in which you receive morphine, you will receive small doses of morphine in all 4 infusions. During the naloxone session, you will receive naloxone during 2 of the 4 infusions. In the placebo session, you will receive placebo in all 4 infusions.

Ten minutes after each dose of medication is received (to allow peak drug activity to be achieved), you will be asked to complete a brief questionnaire to describe your chronic back pain intensity. Then, you will undergo a thermal pain task to assess heat pain threshold and tolerance. This task will involve repeated brief applications of a computer-controlled heat stimulus to several areas of your non-dominant forearm. The equipment used in this task is safe and only produces heat at 127 degrees Fahrenheit or less, which is below the level that causes burns. You will be asked to participate in three brief heat stimulation trials during which you will be asked to indicate when the heat stimulus first becomes painful (your heat pain threshold), and three brief trials during which you will be asked to indicate when your heat pain tolerance has been reached. For each trial, as soon as your tolerance is reached, the equipment will rapidly cool your skin to normal body temperature, ending the pain stimulus. Immediately upon completion of the final heat pain tolerance trial, you will be asked to rate the quality and intensity of the pain you experienced, as well as any drug-related side effects. These same thermal pain task procedures will be repeated after all 4 of the drug infusions.

After completing the first three laboratory sessions, you will next be randomly assigned (like flipping a coin) to either the 6-week aerobic exercise training group or the no-intervention control group. You will have an equal chance of being assigned to either group. If you are assigned to the no-intervention control group, you will be asked to maintain the same activity level throughout your study participation that you maintained prior to beginning the study. After completing your study participation, you may engage in any additional exercise activities if you choose to. You will also complete a brief (less than 15 minutes) assessment regarding your pain, function, and emotional state over the phone on a weekly basis. If you are assigned to the aerobic exercise training intervention, you will be asked to participate in 3 aerobic exercise sessions supervised by a certified personal trainer per week for 6 weeks (18 sessions total). Exercise in these sessions will be of progressively increasing intensity over the 6 week period, with the goal of optimizing your level of aerobic conditioning. Each exercise session will consist of a 5 minute warm-up, 30 minutes of aerobic exercise, followed by a 5 minute cool-down period. You will be able to select your preferred form of aerobic exercise from the following options: treadmill walking/running, stair stepping, the elliptical machine, or stationary cycling. Your back pain, heart rate, and perceived level of exertion will be monitored by the personal trainer regularly during each exercise session, with activities adjusted during each session to help you increase your level of aerobic conditioning while minimizing any exacerbations of back pain. Each week during this exercise intervention period, you will also be asked to complete a brief (less than 15 minutes) assessment regarding your pain, function, and emotional state over the phone.

After the intervention period, regardless of which group you are assigned to, you will be asked to return for 3 final laboratory sessions identical to those described above during which you will again receive the 3 study drugs in random order. Between the first and second laboratory session during this post-treatment follow-up assessment, you will again be asked to complete a 5-day electronic diary monitoring period using procedures identical to those described above.

Giving samples for genetic research is your free choice and you may be in the study even if you do not want your samples used or stored for genetic research. There will be a separate section at the end of this form where you can indicate whether or not you would like to participate in this genetic part of the study.

Your participation in the study will end after the sixth laboratory visit.

3. Costs to you if you take part in this study:

There is no cost to you for taking part in this study. All procedures described above are solely for the research purposes of this study. However, you are still responsible for paying for the usual care you would normally receive for the treatment of your illness. This includes treatments and tests you would need even if you were not in this study. These costs will be billed to you and/or your insurance.

4. Side effects and risks that you can expect if you take part in this study:

You may find completing questionnaires regarding your pain and psychological state to be mildly distressing. This level of distress is likely to be similar to what would occur if you were discussing these issues with your physician or a family member.

You may find certain aspects of the evaluation of your pain-related symptoms to be mildly uncomfortable.

You will experience brief, moderate intensity acute pain upon application of the thermal pain stimuli that will be used for assessment of your natural pain control systems and your responses to morphine. However, you have total control over the duration of your exposure to these pain stimuli because you stop each task by indicating when you have reached your

tolerance limit. Previous research indicates that these tasks are safe, but to further maximize safety, individuals experiencing cardiovascular problems will be excluded from this study. Because you have total control over the duration of the task, its psychological impact is expected to be minimal.

You will experience very brief, mild pain upon insertion of a cannula (for study drug administration) during each study session. This event is similar to what you have likely experienced at some point during medical treatment when blood samples were drawn, or if you have ever received an IV while hospitalized. Insertion will be performed by a trained nurse or physician to minimize discomfort associated with insertion of the cannula. There is a risk of infection and local inflammation at the site of cannula insertion. Precautions will be taken to insure that such risks are minimized.

The following risks relate to the medications to be used in the study. The medication used for opioid blockade, naloxone, has been used clinically for decades for treatment of opiate overdose and for reversal of surgical anesthesia. It is not an experimental or new drug, and is FDA-approved for those purposes. Previous studies indicate that it is safe for individuals who are not opiate dependent, do not have liver disease, and do not have cardiovascular problems. Potential subjects experiencing these types of problems will be excluded from this study to insure a maximal level of safety with drug administration. Individuals taking daily opiates, even if not dependent, will also be excluded from the study to avoid precipitating minor withdrawal symptoms. In some individuals, naloxone may increase pain sensitivity to the acute pain tasks somewhat, but again, you may terminate these tasks if you reach your tolerance limit. Based on previous studies, naloxone is expected to have limited if any direct effects on your back pain intensity, and therefore, there appears to be little risk of exacerbating your chronic pain condition. Even if such changes do occur, the brief half-life of naloxone (on average, approximately 45-60 minutes) insures that any pain exacerbation will be of short duration. With the exception of possible effects on pain sensitivity, naloxone is not known to be associated with other clinically significant effects in healthy individuals who are not opiate dependent or using daily opiates.

The other study drug, morphine, is an FDA-approved opioid analgesic with a very long history of use in standard clinical practice. It can produce dose-dependent side effects including sedation, somnolence (sleepiness), allergic reactions (which may be life threatening), itching, nausea, vomiting, euphoria (feeling good), hallucinations, vision changes, urinary retention, constipation, and slowing of breathing rate. The dose used in this study will be adjusted to your weight, and the total dose you will receive represents a relatively low dose within the normal range of dosages used in standard clinical practice. This should help limit any negative side effects. The effects of morphine can last for four hours or more. You will be kept under observation in each study session until all side effects remit to the point where it is safe for you to leave. You will need to arrange for someone to drive you home from the appointment and refrain from driving for at least 6 hours after the study drug was given. If morphine side effects are severe, these effects will be immediately reversed by administration of naloxone as determined appropriate by the study physician.

As part of this study, you may be assigned by chance to undergo a 6-week aerobic exercise intervention as described above. To maximize safety with this type of exercise, individuals with a history of cardiovascular disease are excluded from participating in this study. The intensity of this aerobic exercise training will start low but progressively increase over the 6-week intervention period. It is possible that you may experience short-term increases or decreases in your chronic pain following your exercise sessions. Safety and possible discomfort associated with these increases in exercise intensity will be minimized via close monitoring by a certified personal trainer of your heart rate, perceived exertion levels, and your back pain during exercise. Exercise intensity will be adjusted as appropriate to maximize your level of conditioning while minimizing exacerbation of your back pain. In addition, you will be able to choose your preferred form of exercise from several available options.

5. Risks that are not known:

In the event new information becomes available that may affect the risks or benefits associated with this study or your willingness to participate in it, you will be notified so that you can make an informed decision whether or not to continue your participation in this study.

6. Payment in case you are injured because of this research study:

If it is determined by Vanderbilt and the Investigator that an injury occurred as a direct result of the tests or treatments that are done for research, then you and/or your insurance will not have to pay for the cost of immediate medical care provided **at Vanderbilt** to treat the injury. There are no plans for Vanderbilt to pay for the costs of any additional care. There are no plans for Vanderbilt to give you money for the injury.

7. Good effects that might result from this study:

a) The benefits to science and humankind that might result from this study are an improved understanding of endogenous opioid mechanisms by which aerobic exercise may improve chronic pain, and how these changes impact on responsiveness to opioid analgesic medications. This study has the potential to significantly advance knowledge regarding mechanisms underlying individual differences in responsiveness to opioid analgesics, and how these mechanisms can be manipulated through non-drug interventions in a way that may reduce reliance upon high-dose opioid analgesics for chronic pain management.

b) If you are assigned by chance to the aerobic exercise intervention and you complete this intervention, you may experience a decrease in the intensity of your low back pain as a result. Any improvement might be temporary, but would be more likely to continue if you continue to engage in similar exercise activities.

8. Other treatments you could get if you decide not to be in this study:

This is not a study designed to determine the effectiveness of a new treatment for back pain. Exercise interventions like those used in this study are available through most physical therapy providers and personal trainers.

9. Payments for your time spent taking part in this study or expenses

If you are assigned to the exercise condition, you will be compensated for your time with $75 for the baseline screening session and electronic diary monitoring period, $100 for each completed laboratory session (6 sessions if you complete the full protocol), $30 for each completed exercise session (up to 18 sessions), $30 each week for completing phone follow-up questionnaires, and $75 for the follow-up electronic diary monitoring period, all paid by check upon completion of all study procedures or your withdrawal from the study. If you are assigned to the control condition, you will be compensated for your time with $75 for the baseline screening session and electronic diary monitoring period, $100 for each completed laboratory session (6 sessions if you complete the full protocol), $30 each week for completing phone follow-up questionnaires, and $75 for the follow-up electronic diary monitoring period, all paid by check upon completion of all study procedures or your withdrawal from the study. We may ask you for your Social Security Number and address before you are compensated for taking part in this study. You may receive up to $1,470 for taking part in this study. This amount may be taxable and will be reported to the Internal Revenue Service. Your payment cannot be processed until the PDA electronic diary provided to you has been returned. If you lose this device, its' replacement cost ($150) may be deducted from your final compensation.

10. Reasons why the study doctor may take you out of this study:
You may be withdrawn from the study if the study doctor determines that your medical condition makes your

participation in the study unsafe. If you are taken out of the study, you will be told the reason why.

11. What will happen if you decide to stop being in this study?

Your participation in this study is voluntary. You are also free to withdraw from this study at any time. Withdrawal or refusal to participate will not change your regular medical care in any way.

12. Who to call for any questions or in case you are injured:

If you should have any questions about this research study or if you feel you have been hurt by being a part of this study, please feel free to contact Stephen Bruehl, Ph.D. at (615) 936-1821, or his assistant, Melissa Chont, at (615) 936-5664**.** If you experience a medical emergency you believe is related to your study participation, you should immediately go to the Vanderbilt Emergency Room.

For additional information about giving consent or your rights as a person in this study, to discuss problems, concerns, and questions, or to offer input, please feel free to call the Vanderbilt University Institutional Review Board Office at (615) 322-2918 or toll free at (866) 224-8273.

13. Confidentiality:

All published data will be reported in a manner in which individual data for specific patients are not identifiable. Data will be coded on paper and in the computer by subject number rather than name to help further insure confidentiality. All hardcopy study records will be maintained in a filing cabinet in a locked office at the investigator's office suite (324 Medical Arts Building), and will be accessible only to the principal investigator and his designees. All subject records in the study computer database will be maintained on password protected computers stored in the locked offices of the principal investigator. If you have received medical care at Vanderbilt previously, your medical information at Vanderbilt may be visible to study staff during the course of this study.

Vanderbilt may share your information, without identifiers, to others or use it for other research projects not listed in this form. Vanderbilt, Dr Bruehl, and his staff will comply with any and all laws regarding the privacy of such information. There are no plans to pay you for the use or transfer of this de-identified information.

This study is supported by the National Institutes of Health (NIH). Therefore, your study information is protected by a Certificate of Confidentiality. This Certificate allows us, in some cases, to refuse to give out your information even if requested using legal means.

It does not protect information that we have to report by law, such as child abuse or some infectious diseases. The Certificate does not prevent us from disclosing your information if we learn of possible harm to yourself or others, or if you need medical help.

Disclosures that you consent to in this document are not protected. This includes putting research data in the medical record or sharing research data for this study or future research. Disclosures that you make yourself are also not protected.

14. Authorization to Use/Disclose Protected Health Information

All efforts, within reason, will be made to keep your protected health information (PHI) private. PHI is your health information that is, or has been gathered or kept by Vanderbilt as a result of your healthcare. This includes data gathered

for research studies that can be traced back to you. Using or sharing ("disclosure") such data must follow federal privacy rules. By signing the consent for this study, you are agreeing ("authorization") to the uses and likely sharing of your PHI. If you decide to be in this research study, you are also agreeing to let the study team use and share your PHI as described below.

As part of the study, Dr. Bruehl and his study team may share the results of your study participation to the groups named below. These groups may include people from the Federal Government Office for Human Research Protections, the Vanderbilt University Institutional Review Board, and the National Institutes of Health. Federal privacy rules may not apply to these groups; they have their own rules and codes to assure that all efforts, within reason, will be made to keep your PHI private.

The study results will be kept in your research record for at least six years after the study is finished. At that time, the research data that has not been put in your medical record will be kept for an unknown length of time. Any research data that has been put into your medical record will be kept for an unknown length of time.

Unless told otherwise, your consent to use or share your PHI does not expire. If you change your mind, we ask that you contact Dr. Bruehl in writing and let him know that you withdraw your consent. His mailing address is: 701 Medical Arts Building, VUMC, 1211 21st Ave. South, Nashville, TN 37212. At that time, we will stop getting any more data about you. But, the health data we stored before you withdrew your consent may still be used for reporting and research quality.

If you decide not to take part in this research study, it will not affect your treatment, payment or enrollment in any health plans or affect your ability to get benefits. You will get a copy of this form after it is signed.

STATEMENT BY PERSON AGREEING TO BE IN THIS STUDY

I have read this consent form and the research study has been explained to me verbally. All my questions have been answered, and I freely and voluntarily choose to take part in this study.

_____ _____
Date Signature of patient/volunteer

_____ _____-_____-_____
Name as Shown on Tax Forms Social Security Number

_____
Preferred Mailing Address (for Payment Purposes)

Consent obtained by:

_____ _____
Date Signature

_____
Printed Name and Title

Consent for Genetic Research

The purpose of this study is to look at genes (DNA) and how they affect health and disease. Genes are the instruction manual for your body. The genes you get from your parents decide what you look like and how your body behaves. They can also tell us a person's risk for certain diseases and how they will respond to treatment.

You are being asked to give a blood sample for genetic research. What we learn about you from this sample will not be put in your health record. Your test results will not be shared with you or your doctor. No one else (like a relative, boss, or insurance company) will be given your test results. Your sample will only be used for research at Vanderbilt University and will not be sold. Health insurance companies and group health plans may not request your genetic information that comes from this research.

A single blood sample of about ½ teaspoon will be obtained through the cannula already inserted in your arm as part of the study for extraction of genetic samples.

One risk of giving samples for this research may be the release of your name that could link you to the stored samples and/or the results of the tests run on your samples. This may cause problems with insurance or getting a job.

Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums. Employers with 15 or more employees may not use your genetic information that comes from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

To prevent this, these samples will be given a code. Only the study staff will know the code. The name that belongs to the code will be kept in a locked file or in a computer with a password. Only Dr. Stephen Bruehl and his study designee will have access to your name.

Your sample will be used to extract DNA that will be kept for an unknown length of time (maybe years) for future research. The sample will be destroyed when it is no longer needed.

Your samples will be used for research only and will not be sold or used to make products that could be sold for money.

You will not receive any benefit as a result of the tests done on your samples. These tests may help us learn more about the causes, risks, and treatments of chronic pain, or how to prevent this and other health problems.

Giving samples for research is your free choice and you may be in the study even if you do not want your samples used or stored for gene research.

At any time, you may ask to have your sample destroyed. You should contact Dr. Stephen Bruehl at 701 Medical Arts Building, VUMC, 1211 21st Ave. South, Nashville, TN 37212, (615) 936-1821 to have your sample destroyed and no longer used for research. We will not be able to destroy research data that has already been gathered using your sample. Also, if your identity was removed from the samples, we will not be able to locate and destroy them.

There will be no costs to you for any of the tests done on your samples. You will not be paid for the use of your samples.

Principal Investigator: Stephen Bruehl, Ph.D. **Revision Date: 6/26/18**
Study Title: Reduced Opioid Analgesic Requirements Via Improved Endogenous Opioid Function
Institution/Hospital: Vanderbilt University School of Medicine

Please check Yes or No to the questions below:

My blood sample may be used for gene research on pain.

☐ Yes ☐ No

My blood sample may be stored/shared for future gene research on pain.

☐ Yes ☐ No

My blood sample may be stored/shared for future gene research for other health problems (such as cancer, heart disease, etc).

☐ Yes ☐ No

Signature: _____ Date: _____