Project Title:	**Low dose naltrexone for chronic pain in osteoarthritis and inflammatory arthritis**	
Principal Investigator:	**Paul Monach, MD, PhD**	**Version #:4**

1. Overview of the Research Study:

We are asking you to be in a research study that is being supported by a VA grant to Dr. Monach. Before you decide to take part, you should know why the study is being done and what it will involve. This form tells you what to expect if you agree to be in the study. Taking part in this study is completely voluntary; it is your decision whether or not to participate in the study.

We are doing the research to see if a drug called naltrexone reduces pain caused by arthritis. If you agree, you will provide blood samples, complete questionnaires, and take study medication. You will be in the study for 16 weeks if you decide to stay for the whole study. We will describe your involvement in more detail later in this form.

You might choose to volunteer in the study because pain interferes with your daily activities and you would like to contribute to research that may help researchers identify new ways to treat chronic pain. You will find more information about benefits later in this form.

You may choose not to volunteer to be in the study if you feel that you need opioids to control your pain as naltrexone can interfere with how the body responds to opioid medications. You will find more information about potential risks later in this form.

You will find more information about alternate treatment/procedures later in this form.

Your doctor may also be an investigator in this research study. Being an investigator means your doctor is interested in both you and the study. You may want to get a second opinion about being in the study. You can do so now or at any time during the study. Another doctor who is not an investigator can give you a second opinion about being in the study. You do not have to agree to be in this study even though it is offered by your doctor.

If you decide to take part in the study, it should be because you really want to volunteer. You will not lose any services, benefits or rights you would normally have if you choose not to volunteer.

2. WHAT IS THE PURPOSE OF THIS STUDY?

This is a research study. The purpose of the study is to see whether a drug called naltrexone reduces pain caused by arthritis. Naltrexone is a prescription drug approved for a different reason at a much higher dose than will be used in this study. However, "low dose naltrexone" is widely used, outside the VA and without insurance coverage, for a wide range of painful conditions. Its possible benefit in arthritis has not been studied scientifically. Sixty (60) patients will be enrolled

at the VA Boston Healthcare System. The study is funded by a VA grant to Dr. Monach.

To be eligible for the study, you must have chronic pain caused by either osteoarthritis or inflammatory arthritis (rheumatoid arthritis, psoriatic arthritis, or related diseases). Your main source of pain needs to be from arthritis, not from a different cause. Your overall severity of pain needs to be stable, meaning it has been at about the same level on average every week for the past 8 weeks. It is important that no other approaches to improving your pain have been started in the past 8 weeks, and that no other approaches to reducing pain are planned for the next 16 weeks (the length of the study). Patients with severe kidney disease, severe liver disease, or severe mental illness cannot participate in the study. Patients who are currently using opioid medications (such as tramadol, oxycodone, and fentanyl) or have used opioid medications in the last seven days for pain relief cannot participate. This is because naltrexone can affect how the body responds to opioid medications.

You will participate in the study for 16 weeks. For 8 of those weeks, you will receive low dose naltrexone, and for the other 8 weeks, you will receive a placebo. A placebo is a pill that looks and tastes the same as the drug being tested but contains no medication. You will not be told when you will be switching back and forth between naltrexone and placebo. The reason that this type of research study needs to include a placebo is that persons who think they are taking a medication are likely to feel better. In order to know how much naltrexone is helping, it is necessary to compare it to the "placebo effect" for each person.

3. HOW LONG WILL I BE IN THE STUDY? WHAT WILL HAPPEN AND WHAT CAN I EXPECT IF I TAKE PART IN THIS STUDY?

You may participate in the study at either the Jamaica Plain, West Roxbury, or Brockton campus of the VA Boston Healthcare System.

You will be asked to make three visits to the outpatient clinic during the course of this study: at screening / enrollment, and approximately 8 weeks after enrollment, and approximately 16 weeks after enrollment. In addition to these visits, you will be asked to complete questionnaires related to pain once per week, at home.

There are two types of in-person visits:

Screening / Enrollment Visit

The screening visit will determine if you can be in this study. If you can be in the study, you will enroll in the study at that time. If you cannot be in the study, you will not receive medication and the screening visit will end your involvement in the study. The screening visit is expected to take up to 2 hours.

At the screening visit, you will be asked to read and sign this consent document and you will be asked to provide basic clinical data to confirm eligibility:

- A medical history, including
  - Confirmation that you have osteoarthritis or inflammatory arthritis
  - Detailed review of medications used for the previous 8 weeks, including making sure that you are not taking any opioid drugs (such as morphine, oxycodone, hydrocodone, hydromorphone, codeine, methadone, suboxone, or tramadol)
  - Average levels of pain, and the extent to which pain interferes with your ability to function, during the past 4 weeks, using a questionnaire
  - Severity of depression, using a questionnaire
  - List of other medical problems
- Basic demographic information (age, sex, race or ethnic background)

If the screening visit confirms that you can be in the study, then you will undergo some further study procedures and begin study treatment on that day or at another time within the next 14 days.

Several study procedures will be performed at the Screening/ Enrollment visit if you are eligible and agree to participate:

- You will complete your first set of questionnaires (listed in detail below).
- For patients with inflammatory arthritis, you will be asked detailed questions about joint pain, and an examination of your joints will be performed to calculate a score of disease activity. This procedure is used in many research studies and is also used by many doctors in routine clinical practice.
- Blood will be collected for laboratory testing, as is routine practice for a patient starting a new medication.
- You will be given questionnaires to complete weekly at home.

Delivery of Study Drug

We hope that most patients will be able to receive the study drug on the day of enrollment. However, if that is not possible, then the pharmacy will mail the drug to you, with instructions on when and how to take it. The instruction is simply to take one capsule every day, and it doesn't matter whether you have recently eaten. The order in which you will receive naltrexone or placebo throughout the study will be determined randomly (like flipping a coin).

- You will receive two bottles containing either naltrexone (4.5 mg per dose) capsules or placebo capsules. They will be numbered 1 and 2, and it is important that you use all of the doses in bottle 1 before using bottle 2.

8 Week and 16 Week Visits

At each of these visits, you will be asked to return all questionnaires that you completed at home, and to bring in medication bottles that you received at the previous visit. The 8 Week and 16 Week visits are each expected to take approximately 1 hour.

At the 8 Week visit:

- You will receive two bottles containing either naltrexone or placebo. They will be numbered 3 and 4, and it is important that you use all of the doses in bottle 3 before using bottle 4. If you are not able to receive the medication in-person on the day of your visit, the pharmacy will mail the study drug to you.
- You will be given questionnaires to complete weekly at home.

During both the 8 Week and 16 Week visits, the following procedures will be performed:

- A medical history, including
  - Medication review
  - New medical problems
  - Possible side effects of the study drug

- For patients with inflammatory arthritis, you will be asked detailed questions about joint pain, and an examination of your joints will be performed, in order to calculate a score of disease activity (DAS28 or BASDAI).

- Blood tests will be collected, as at the Screening/Enrollment Visit. If your lab results are abnormal and suggest that you may need treatment for a medical condition, you will be informed of these results by a study physician.
- You will complete a set of questionnaires (listed in detail below).

Questionnaires

You will be asked to complete questionnaires at home, and in-person at the three study visits described above.

The study coordinator may call you once per week to remind you to complete the questionnaires and to see whether you have been hospitalized, or had infections requiring treatment with antibiotics, or had medication side effects.

You should complete a set of questionnaires on the day you plan to start the study drug. If you receive study drug in-person on the day you enroll, then the questionnaires you completed at that visit will be used as the "Baseline." If you receive the study drug later, then you will be asked to complete the first set of weekly questionnaires as the Baseline at home, on the day you plan to start taking the study drug.

You will be asked to complete the following forms once per week:

- Brief Pain Inventory (2 pages)
- Clinical Global Impression of Severity and Improvement (2 questions on scales of 1-7)
- One question whether you think you are taking naltrexone, or placebo, or cannot tell (does not apply to the Baseline questionnaires)

These questionnaires should take a total of 5 minutes to complete.

You will be asked to complete additional questionnaires 5 times during the study: Screening/Enrollment (in-person), week 4 (at home), week 8 (in-person), week 12 (at home), and week 16 (in-person). It is important that you complete these additional questionnaires at these times, because those are times when study treatment may change.

- painDETECT

- Brief Fatigue Inventory
- PROMIS-29 (a survey of quality of life related to your overall health)
- Beck Depression Inventory-II
- Use of medications "as needed" for pain

These questionnaires should take about 15-20 minutes to complete.

After the last participant in the study completes their last study visit, the study staff will be unblinded, meaning they will be told when you received naltrexone and when you received placebo. At that time, you and your rheumatologist or primary care doctor (if you do not have a rheumatologist at the VA) will be informed about the treatments you received.

4. WHAT POSSIBLE RISKS OR DISCOMFORTS MIGHT I HAVE IF I TAKE PART IN THIS STUDY?

Needlesticks to draw blood may cause temporary pain or bruising.

Completion of weekly questionnaires and 3 in-person visits may be inconvenient. Answering questions related to pain, depression, and quality of life may make you uncomfortable.

Risks of low-dose naltrexone (LDN)

In studies of low-dose naltrexone (LDN) that included about 170 patients, no liver injury or severe depression has been reported. No other dangerous side effects have been reported, either, but the number of patients in these studies is too small to be confident that there are no dangers that might occur rarely. The only common side effect repeatedly reported for LDN has been vivid dreams (sometimes but not usually described as nightmares). Headaches, dizziness, insomnia, fatigue and nausea have been reported in some studies but not others.

At doses 11 times higher than those used in this study (50 mg rather than 4.5 mg), naltrexone use has been associated with the following:

- Liver injury: usually this was mild, only apparent on blood testing, and without symptoms, but some cases of hepatitis (abdominal pain, loss of appetite, and jaundice) have been reported. Serious liver injury has only been reported with much higher doses (300 mg daily) that are no longer used.
- Depression and suicidal thoughts

- Symptoms of opioid withdrawal in patients also taking opioid pain relievers

Persons at high risk for these problems cannot participate in the study: poor liver function, active severe depression, or current use of opioid medications.

The treatment may involve risks that are currently unforeseeable. In addition to the risks listed above, you may experience a previously unknown risk or side effect.

If you are or became pregnant, the study drug might involve risks to the embryo or fetus, which are currently unforeseeable. Women that can have children should use a reliable and effective method of contraception (such as a condom with spermicide, an oral contraceptive, an intrauterine device) to prevent pregnancy for the duration of the study. If you are not sure if the method of contraception you are using is effective or reliable, please ask the study doctor. If you become pregnant or think you might be, you should inform study personnel as soon as possible.

5. WHAT ARE THE POSSIBLE BENEFITS OF THIS STUDY?

There are no known direct benefits to you for being in this study.

6. DO I HAVE TO TAKE PART IN THE STUDY?

Participation in this research study is voluntary. If you do not wish to take part, you will not suffer any penalties or loss of benefits to which you are otherwise entitled to receive.

If you are a VA employee or student, refusal to take part in the study will in no way influence your employment, ratings, subsequent recommendations, or academic progress as applicable.

You may discontinue your participation in the study at any time for any reason without any penalty or loss of benefits. If you withdraw, you will continue to receive the same standard of care that you would otherwise have received.

If you end your participation in the study prior to completing the study, the data that was already collected for the study will continue to be used, but no additional information will be collected for research purposes after the date you withdraw from the research study. If you wish to withdraw from

the study, please contact Dr. Monach at 857-364-5552 or the study coordinator, Britte Beaudette-Zlatanova at 857-364-5695.

7. WHAT OTHER CHOICES DO I HAVE IF I DO NOT WANT TO JOIN THIS STUDY?

Other treatments to that described above may include medications and behavioral therapies commonly used to try to reduce pain and will be under the supervision of your doctor or caregiver.

8. RIGHT OF INVESTIGATOR TO TERMINATE MY PARTICIPATION

Taking part in this study is completely voluntary. If you decide to be in the study and then change your mind, you can withdraw from the study at any time. Your decision will not affect your being able to get health care at this institution. If you discontinue participation in the study before completing the study, the study staff may ask you to return any bottles of study drug that you have and to return any questionnaires that you have completed at home to the study site.

If there are any new findings during the study that may affect whether you want to continue to take part, you will be told about them as soon as possible.

The Principal Investigator may decide to discontinue your participation without your permission, because he may decide that staying in the study will be bad for you, or he/she may stop the study. Participants will be withdrawn from the study

- if they become pregnant and the pregnancy is reported to study staff
- if kidney function or liver function declines during the study and the study doctor feels it would be unsafe to continue study medication
- if they start a new medication to treat pain during the study
- if they take an opioid medication for greater than 2 days during the study

9. HOW WILL MY PRIVATE INFORMATION BE PROTECTED?

Information collected for the purpose of this research study will be kept confidential as required by law. The results of this study may be published for scientific purposes, but your records or identity will not be revealed unless required by law.

Information about you is protected in the following way: We will store your information in ways we think are secure.

The members of the research team who will have access to your study data include the Principal Investigator (Dr. Monach), the other doctors and nurses who also serve as Investigators, and the study coordinator, all of whom are employed by the VA Boston Healthcare System. Additional VA personnel who will analyze the data will not see information that could identify you.

Paper forms produced by this study (for example, completed questionnaires and this informed consent form) will be stored in a locked office or other secure facility for a minimum defined time period per VA and FDA regulations. All study information that is copied and maintained electronically will be stored on secure, password-protected VA servers. Some of these files will include information that could be used to identify you. However, most paper documents and electronic files will only include a study ID number that will be assigned when you enroll in the study, not your name. The file that links that ID number to information that could identify you will also be stored on a secure, password-protected VA server.

Your research records will be kept indefinitely or until the law allows their destruction in accordance with the VA Record Control Schedule (wwwl.va.gov/VHAPUBLICATIONS/RCSl0/rcsl0-1.pdf). Records will be destroyed, when allowed, in the following manner.

- Paper records will be shredded
- Electronic records will be destroyed in a manner in which they cannot be retrieved.

Data collected as part of the research, even if identifiers are removed, will not be used or distributed for future research studies.

While this study is being conducted, you will not have access to your research related health records. This will not affect your VA healthcare including your doctor's ability to see your records as part of your normal care.

We will record information from this study in your medical record, such as information related to the start and stop of your participation in the study, that you are taking naltrexone or placebo as part of the research study, and results of blood tests that are performed. Please ask us if you have any questions about what information will be included in your medical records. Information in your medical records is protected in the same way that information related to your non-research medical care is protected.

Please see the section below for a description of how your information is protected and how it may be used.

Your research records and the information within them will not be used for any purpose other than that described in this study as approved by the Institutional Review Board (IRB, an independent committee that protects the welfare of research participants).

Health Information Portability and Accountability Act (HIPAA)

There are rules to protect your private health information. Federal and state laws and the federal medical law, known as the HIPAA Privacy Rule, also protect your privacy. By signing this form, you provide your permission called your 'authorization,' for the use and disclosure of information protected by the HIPAA Privacy Rule.

The research team working on the study will collect information about you. This includes things learned from the procedures described in this consent form. They may also collect other information including your name, address, date of birth, and information from your medical records such as medical history, medications, allergies, lab results, progress notes, and radiological findings.

The research team may also need to disclose your health information and the information it collects to others as part of the study progress. Others may include VA employees that process requests for compensation for research participation; Institutional Review Board, Research & Development Committee, Research Compliance Officers, Food and Drug Administration, Office (FDA), Office of Human Research Protections (OHRP), the VA Office of Research Oversight (ORO), and the Government Accountability (GAO).

Your health information disclosed pursuant to this authorization may no longer be protected by Federal laws or regulations and may be subject to re-disclosure by the recipient.

You can revoke this authorization, in writing, at any time. To revoke your authorization, you must write to the Release of Information Office at this facility or you can ask a member of the research team to give you a form to revoke the authorization. Your request will be valid when the Release of Information Office receives it. If you revoke this authorization, you will not be able to continue to participate in the study. This will not affect your rights as a VHA patient to treatment or benefit outside of the study.

If you revoke this authorization, Dr. Paul Monach and his research team can continue to use information about you that was collected before receipt of the revocation. The research team will not collect information about you after you revoke the authorization.

Treatment, payment or enrollment/eligibility for benefits cannot be conditioned on you signing this authorization. This authorization will expire at the end of the research study unless revoked prior to that time.

An unsigned copy of this consent form will be posted on clinicaltrials.gov or Regulations.gov after all study participants have completed the study.

10. WILL I BE TOLD NEW INFORMATION ABOUT THIS STUDY?

You will be told of any significant new findings that come to light during the course of this study and that may relate to your wanting to stay in the study.

11. WHAT ARE THE COSTS TO ME IF I TAKE PART IN THIS STUDY?

A veteran participant will not be required to pay for medical care and services received as a participant in an approved VA research study. Some veterans are required to pay co-payments for medical care and services provided by the VA. These co-payment requirements will continue to apply to medical care and services (including, but not limited to, dental services, supplies, medicines, orthopedic and prosthetic appliances, and domiciliary or nursing home care) provided by the VA that are not part of this research study.

You will be compensated up to $80 for your time and effort taking part in this study. You will receive $20 for the in-person screening/enrollment visit, $20 for the week 8 in-person visit, $20 for the week 16 in-person visit, and an additional $20 for completing all 3 visits.

You can choose to receive a cash voucher or you can choose to receive a check within 2-6 weeks. If you choose to receive payment by check, you consent to the release of personally identifying information about you including your name, address, and social security number to the VA so that we may provide compensation to you. The government may garnish the compensation against outstanding debts a veteran has to the federal government. If you choose to receive payment by cash voucher from the agent cashier's office, you consent to the release of personally identifying

information about you including your name, address, and the last 4 of your social security number to the Fiscal Office of the VA Boston Healthcare System so that we may provide compensation to you.

If payment is made to you by the VA (whether by check or cash voucher), an IRS Form 1099 will be generated regardless of the amount you are paid.

12. WHAT WILL HAPPEN IF I AM INJURED BECAUSE OF MY BEING IN THE STUDY?

In the event that you are injured as a result of your being in this research study, you will receive medical care, including emergency treatment. This care or treatment is governed by federal law and VA policy. You would also have the right to file any legal action, as in any instance of alleged negligence.

13. WHO DO I CONTACT ABOUT THIS STUDY IF I HAVE QUESTIONS?

I understand that if I have any medical questions about this research study, I can call **Dr. Paul Monach at 857-364-5552** during normal working hours.

I understand that if I have any general questions about this research study, I can call **Dr. Britte Beaudette-Zlatanova at 857-364-5695** during normal working hours.

I understand that if I have any medical problems that might be related to this study that Monday through Friday excluding federal holidays **during normal working hours,** I can call **Dr. Paul Monach at 857-364-5552** and **on weekends, holidays, and after normal working hours Monday through Friday,** I can call the Medical Center operator at 617-323-7700 and ask for the rheumatology fellow on-call for the VA Boston Healthcare System. For medical emergencies, call 911.

I understand that, if at any point during or after this study I have any questions about my rights as a research participant or I want to discuss problems, complaints, concerns, and questions about the research, obtain information, or offer input, I may contact the Research Compliance Officer at (857) 364-4182.

14. AGREEMENT TO PARTICIPATE IN THE RESEARCH STUDY

I have read or have had read to me all of the above. Study staff have explained the study to me and answered all of my questions. I have been told of the discomforts and risks of the study. I have been told of other choices of treatment that I could have.

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I understand that my participation in this study is voluntary, that I do not have to take part in this study and that, if I do take part, I may withdraw from the study at any time. I also understand that, if I refuse to take part or if I decide to withdraw, I will not suffer any penalty, loss of rights, or loss of VA or other benefits that I have a right to receive.

I voluntarily consent to be in this study. I will receive a signed copy of this consent form.

Participant's Signature **Month Day Year** **Name (print)**