Informed Consent

Study Title: Improving Treatment Outcomes for Prescription Opioid Dependence

NCT Number: NCT02543944

Version 20

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University of Arkansas for Medical Sciences Informed Consent Form

- **We are asking you to be in a research study.**
- **You do not have to be in the study.**
- **If you say yes, you can quit the study at any time.**
- **Please take as much time as you need to make your choice.**
- **You can still get your medical care from UAMS even if you are not in the study.**
- **During the study, we will tell you if we learn any new information that might affect whether you wish to stay in the study.**

Why am I being asked to be in this research study?

- We are asking people like you who have a problem stopping pain med use to help us. Up to 200 people aged 18-64 years old will be part of this study.
- We want to learn more about how to help people who have uncomfortable, flu-like symptoms (called "opioid withdrawal") when they try to stop using pain meds, and how to help them not go back to using.
- This study will help us learn more about whether certain drugs will decrease these uncomfortable symptoms that occur once a pain med is stopped.
- During the study, you will be given by mouth buprenorphine, approved by the FDA for opioid dependence, and naltrexone, approved by the FDA for opioid dependence in people who no longer physically need opioids.
- You may also get gabapentin, a drug that is approved by the FDA for nerve pain and may help decrease opioid withdrawal symptoms, or a placebo (inactive drug). You will not know whether you are getting gabapentin or the placebo. All drugs on the list are approved by the FDA, but gabapentin is not a treatment for opioid withdrawal.

What if I don't understand something?

- This form may have words you don't understand. The research staff will read it with you, if you like.
- You may ask as many questions as you like before you decide whether you want to be in this study.
- You are free to ask questions at any time before, during, or after you are in the study.

How long will this study take and where will it take place?

- The study will last about 12 weeks in total and will include:
  - ✓ Taking buprenorphine to help ease withdrawal symptoms
  - ✓ Getting either gabapentin or placebo (inactive pill)
  - ✓ While getting either gabapentin or placebo, you will be gradually taken off buprenorphine and start taking naltrexone
  - ✓ You will be gradually taken off gabapentin (or placebo) while taking naltrexone

  The study will take place at the Psychiatric Research Institute (PRI) at UAMS. The screening part, outpatient clinic visits, and follow up interview will take place on the 4th floor of PRI.

What if I say yes, I want to be in this study?

If you have already been screened, you don't need to read this part. If not, we will make sure you don't have any major medical problems so you can safely be in the study.

- The screening will include
  - ✓ a medical history
  - ✓ physical exam
  - ✓ mental health exam
  - ✓ routine blood tests
  - ✓ heart test (electrocardiogram)
  - ✓ urine (pee) tests (1 test will tell us what drugs you may have used)
- Women will also have a pregnancy test.
- We will not charge you for the screening.
- You and your doctor can ask for screening results.
- The screening usually is done in a week, but could take longer if you
  - ✓ miss visits
  - ✓ have to get a doctor's record
  - ✓ have to get treated first for a minor health issue
  - ✓ have certain drugs in your system that need to be cleared
- If you are healthy and do have a problem using prescription pain meds, you can be in the study.

What will I have to do if I am in the study?

- You will be asked to stop your use of pain pills the day before you start in the study.

- You may receive the following medications while in the study:

Name of medication	What the FDA has approved the medication to do
Buprenorphine	Decrease opioid withdrawal symptoms
Naltrexone	Prevent relapse to opioid use
Vivitrol (Naltrexone injection)	Prevent relapse to opioid use
Gabapentin	Decrease nerve pain
Placebo	N/A – no active medication
Clonidine	Lower high blood pressure

- During clinic visits the following will usually occur:

  - ✓ Complete assessments of mood, behavior, symptoms, decision making, drug craving and drug use
  - ✓ Measure how long you can hold your breath and how much you can handle stress at intake and a few other times during the study
  - ✓ Give a supervised urine (pee) sample to test for drug use and breath sample to test for alcohol three times per week
  - ✓ Have sensors attached to your body and finger in order to measure heart rate variability, a way to see how balanced your autonomic nervous system is in terms of stress/relaxation.
  - ✓ Give a blood sample to test for medication blood levels, how well your liver is working, and possibly levels of substances indicate inflammation in the body (week 4)
  - ✓ Have vital signs (blood pressure and pulse) done weekly and orthostatic vital signs (get blood pressure and pulse while lying down, sitting and standing) done before and after clonidine/naltrexone administration on days 1-4 of week 4
  - ✓ At least once per week you will meet privately, either in person or via telephone or video conference, with a counselor who will give aspects of behavioral naltrexone therapy, cognitive behavioral therapy and case management, discuss long-term treatment goals and give treatment referrals, if desired.

Buprenorphine and Detox Phase (weeks 0-3)

- The intake procedures may last up to 4 hours. During the first 3 weeks of the study, you will typically attend clinic three to six days per week (thrice weekly or Monday through Saturday) to receive a dose of buprenorphine.
- You will be asked to take part in some computer tasks. If you qualify for these, we will do these things:

- ✓ Give you some computer games. In one game, you decide between making easy or difficult button presses for points.
- ✓ In the other game, you will be asked to move a mouse cursor around the shape of a star shown onscreen.
- ✓ If you make a mistake, the computer game will make a loud noise. Both of these tasks take about 20 minutes to play.
- ✓ Taking part in these activities gives you the chance to earn some extra money. You may earn $20 plus an extra $5 per task based on how well you do.

- On Wednesday during week 1, you will also start getting gabapentin or placebo (inactive substance) when you receive your buprenorphine as well as a take-home dose of gabapentin or placebo to take that evening.

- If attending clinic on Saturdays, you may be given a double-dose of buprenorphine and your doses of gabapentin or placebo to take Saturday evening and on Sunday. Alternatively, you may be given additional take-home doses of gabapentin as well as take-home doses of buprenorphine to take on holidays or if participating under truncated study visits due to the COVID-19 virus. Which drug you get (gabapentin or placebo) will be by random assignment (the luck of the draw) and you have a 50% chance of getting gabapentin. Neither you nor the staff will know which one you are receiving. However, we can find out in the event of an emergency.

- The buprenorphine will be given by mouth in a tablet form to hold under the tongue until dissolved along with capsules to swallow that contains your dose of gabapentin or placebo.

- Each visit will take typically about 30-120 minutes.

- During weeks 2-3, you will undergo detoxification from buprenorphine. At this time, your dose of buprenorphine will be gradually lessened over this period of time, while your dose of gabapentin or placebo remains the same. This will tell us if gabapentin helps reduce withdrawal symptoms.

- If you miss a scheduled assessment, you may need to complete it at the next possible appointment. At any point during week 1 of the study, if you miss medications on any two days you will be immediately discharged. In weeks 2-4, you will be immediately discharged if you miss medications three times in a row or miss attending clinic visits. If attending clinic Monday through Saturday and you miss a Saturday dosing, this counts as two missed days.

- During week 4, if you do not take home your weekly medication blister packs, you will be discharged.

- You may be discharged from the study if you submit breath samples positive for alcohol.

- In addition, the investigators can stop your participation at any time. If you are discharged from the study, you will be offered detoxification from buprenorphine and given a referral to

an appropriate treatment provider, such as an outpatient methadone or buprenorphine program, a residential therapeutic community, or an inpatient treatment program.

Transition to Injection (shot) Naltrexone (week 4)

- On days 1 (Monday or Tuesday) through 4 (Thursday) of week 4, you will need to give a supervised urine sample to help the research staff members decide whether you have relapsed to opioid use. If the urine sample is negative for opioids or relapse has not happened, research staff will take your blood pressure and pulse while you are lying down, sitting and standing before and after a low dose of clonidine as well as after a low dose of naltrexone given by mouth. Your blood pressure and pulse may be repeated if the readings indicate possible low blood pressure.

- Your clinic visit will last for about 2-3 hours each day.

- After taking clonidine, if your blood pressure is outside of study safety limits and/or you are experiencing side effects, your blood pressure will be taken again in 30 minutes. If it is still outside study safety limits, naltrexone will not be given and you may be asked to return the next day to try again.

- On days 3 and 4 you will receive increasing doses of naltrexone given by mouth. On day 5 you will receive the injection (shot) of naltrexone.

- You normally will have up to Wednesday during week 4 to start the transition to naltrexone. If you do not submit a urine negative for opioids and/or relapse has happened, you will be offered buprenorphine.

- If you miss clinic or leave clinic prior to completing the drug administration and monitoring procedures, you will not be able to transition to injection naltrexone.

- If you have not relapsed to opioid use and did not transition to injection naltrexone you will be offered treatment referrals or continued weekly study participation without naltrexone therapy.

Naltrexone Maintenance (weeks 5-12)

- During weeks 5-12 you will attend clinic once a week.

- A second naltrexone shot will be given during your week 8, if you are eligible and choose to receive it. Your last visit will be during week 12, at which final assessments will be done.

- At study discharge, we will help you with a referral to an appropriate treatment program, if you wish it.

Follow-up Visit (week 16)

- We will ask for information on two stable contacts in order to keep in contact with you, schedule your follow up visit and provide appointment reminders.

- At the follow up visit, you will be asked to submit a supervised urine sample to test for drugs of abuse as well as complete several study assessments as before.

Who will see the information about me that is collected?

- The study team will know your name and have access to your information.
- We will do our best to make sure no one outside the study knows you are part of the study.
    - ✓ All research data will be labeled with a code that is linked to your name on a master list that is kept in a locked file cabinet in a secured room.
    - ✓ When we share the results of the study in presentation, posters and articles, we will not include your name or any other details that might identify you.
- We have a Certificate of Confidentiality from the Department of Health and Human Services. This means researchers cannot be made to release information, even by a court order or subpoena. This is not a guarantee. Your information might be released if:
    - ✓ You have a disease others could catch from you (such as TB or HIV)
    - ✓ Researchers report current abuse (such as child or adult abuse) you may be involved in
    - ✓ Researchers think you are in danger of hurting yourself or others
    - ✓ A federal agency or UAMS office asks for information
    - ✓ The Certificate of Confidentiality does not mean the Department of Health and Human Services recommends this study.
- Researchers may also give medical information without your permission in the event of an emergency.
- Your personal information that can identify you may be removed from identifiable data or specimens for future research without additional consent.
- There are also people who make sure the study is run the right way. These people may see information from the study about you. They are:
    - ✓ OHRP (Office for Human Research Protections), a federal agency
    - ✓ UAMS Institutional Review Board and/or other UAMS institutional oversight offices
    - ✓ FDA (Food and Drug Administration)

Where and how long will my information and samples be kept?

- We will code your information and study samples and keep the code in a locked file.
- Research records will be kept for up to 5 years after the study results are published.

- Only research staff members will have access to the code for your information.
- We will not put information about you from the study in your UAMS medical record.

What if I say no, I do not want to be in this study?

- Nothing bad will happen.
- You can still get medical care at UAMS.

What happens if I say yes, but change my mind later?

- Being in the study is completely up to you. You may leave the study at any time.
- If you decide to not be in the study (now or later), nothing bad will happen.
- You can still get health care at UAMS.
- We will refer you to a drug treatment program, if you want.
- If you change your mind after starting the study, your lab samples and study records will stay in the study files

If you decide to stop being in the study, call the research staff at 501-526-7969.

Can I be taken out of the study even if I want to continue?

Yes, the study doctor (or head researcher) can take you out of the study if:

- You do not follow study instructions.
- It is not in your best interest to continue.
- The study is stopped for any reason.
- If you have to quarantine due to COVID-19.
- You do not behave properly on the unit.
- For any reason that may not be known at this time.

If I stop being in the study, what will happen to any information or samples collected from me in the study?

We will not be able to take your information or samples out of the study after it has started.

Will my personal information or samples from the study be used for anything else, including future research?

No. Your personal information and samples will be used only in this study.

Will it cost me anything to be in the study?

The study will not cost you anything.

Will I be paid?

- Yes. We will give you money to thank you for your time.

- Every day that you come in, you will get draws from the fishbowl. The number of draws per day depends on which week of participation you are in. You can also earn bonus draws if you have perfect attendance for a given week. The tables below show the possible amounts of money earned during the study.

Number of Each Ticket and Value in the Fishbowl:

Prize	Number of Tickets
"Good Job!"	250
$1	229
$5	10
$25	10
$100	1

Number of Possible Draws and Money Paid:

	Draws	Bonus Draws per Week for Attendance	Maximum Total Possible Draws per week	Money paid for attendance and returning blister packs
Week 0 (Screening & Intake)	0	0	0	$10 for physical, $25 for intake
Week 1 (M-F or THRICE WEEKLY)	1	1	6	0
Week 2 (M-F or THRICE WEEKLY)	2	2	12	$5 weekly for returning blister packs
Week 3 (M-F or THRICE WEEKLY)	4	4	24	$5 weekly for returning blister packs
Week 4 (M or T-F Naltrexone Transition)	5	5	30	$20 daily for attendance, $5 weekly for returning blister packs
Weeks 5-12 (1 Visit per Week, Naltrexone	5	0	0	$50 once weekly for attendance, $5 weekly in weeks 5-6 for returning blister packs

Maintenance)				
Week 16 (1 time follow-up visit)	0	0	0	$50 for attendance
Total $				$610 (not including fishbowl draws)*

* On average, your earnings (fishbowl plus fixed monetary payment) will be up to $35 upon completion of intake, $90 during weeks 1-3, $150 during week 4 and $480 during weeks 5-12, for a possible total of $755. This amount is randomly determined (luck of the draw), and cannot be guaranteed due to the random nature of the fishbowl pulls.

- If you do not come to all visits or drop out before the end of the study, you will get a check for the amount you had earned. If you do not come to the follow up visit, the check will be mailed to you at the address you give us.
- If you receive more than $600 in one year (January-December) from UAMS, UAMS may report the amount earned to the Internal Revenue Service (IRS) and send you a tax form, if required by law
- If you are attending clinic during weeks 1 – 3 on the truncated schedule (thrice weekly) due to the COVID-19 virus, you will receive the same total number of fishbowl pulls as above, redistributed according to your days of clinic attendance.

Will being in this study help me in any way?

- This study may or may not help you.
- It might help you quit pain meds and/or stay sober.
- Even if the study does not help you, what is learned from the study might help others who want treatment for a pain med problem.

What are the risks of being in this study?

It is important that you stop using pain pills or heroin at least 24-48 hours before starting buprenorphine.

The main risks include the following:

- ***Taking buprenorphine can cause:***

✓ Feeling drowsy	✓ Feeling weak, tired	✓ Nausea, vomiting
✓ Dry mouth	✓ Dreaming	✓ Dizziness
✓ Anxiety	✓ Flushing (hot, red skin)	✓ Sweating
✓ Depression	✓ Chills	✓ Low blood pressure
✓ Slurred speech	✓ Very small pupils	✓ Tingling skin
✓ Ears ringing	✓ Problems breathing	✓ Fast heartbeat

- ✓ Bloodshot eyes
- ✓ Vision problems
- ✓ Problems urinating
- ✓ Confusion
- ✓ Bad itching
- ✓ Difficulty know what is and isn't real
- ✓ Constipation
- ✓ Feeling "high"

- ***Detox from buprenorphine can cause:***

- ✓ Anxiety
- ✓ Nausea
- ✓ Diarrhea
- ✓ Hot and cold sweats
- ✓ Hot flashes
- ✓ Muscle cramps
- ✓ Flushing
- ✓ Joint pain
- ✓ Yawning
- ✓ Restlessness
- ✓ Watery eyes
- ✓ Runny nose
- ✓ Chills / chill bumps
- ✓ Sneezing
- ✓ Stomach cramps
- ✓ Backache
- ✓ Feeling tense
- ✓ Feeling jittery
- ✓ Depression
- ✓ Feeling sleepy
- ✓ Noise sensitivity
- ✓ Clammy / damp skin

These symptoms can be unpleasant, are not dangerous and only last for a while.

- ***Taking gabapentin can cause:***

- ✓ Sleepiness
- ✓ dizziness
- ✓ Problems moving
- ✓ Serious breathing difficulties*
- ✓ Nausea/vomiting

* While taking gabapentin, serious breathing difficulties can occur if you use certain medicines that decrease central nervous system activity (for example: opioid pain medicines, antihistamines, or medicines that help with anxiety or depression), have a medical condition that lowers the lungs' ability to work, and/or are 65 or older.

- ***Taking buprenorphine combined with gabapentin can cause:***

- ✓ Sleepiness
- ✓ Loss of motor skills
- ✓ Nausea/vomiting
- ✓ Lightheadedness
- ✓ Sleep disturbances
- ✓ Serious breathing difficulties*

- ***Taking clonidine can cause:***

- ✓ Dry mouth
- ✓ Drowsiness
- ✓ Tiredness
- ✓ Dizziness
- ✓ Headache
- ✓ Sleepiness
- ✓ Changes in heart rate and blood pressure

- ***Taking naltrexone and/or clonidine and/or gabapentin can cause:***

- ✓ tearfulness
- ✓ Mild nausea
- ✓ Stomach cramps
- ✓ Abdominal pain
- ✓ Constipation
- ✓ Restlessness
- ✓ Bone, joint or muscle pain
- ✓ Runny nose
- ✓ Low energy
- ✓ Increased thirst
- ✓ Difficulty sleeping
- ✓ Anxiety
- ✓ Nervousness
- ✓ Diarrhea
- ✓ Increased energy

- ✓ Feeling down
- ✓ Skin rash
- ✓ Chills
- ✓ Irritability
- ✓ Delayed ejaculation
- ✓ Dizziness
- ✓ Decreased sexual potency

You may not benefit from opioid containing medicines, such as certain cough and cold meds, antidiarrheal meds, and opioid pain relievers.

- Other side effects can include a type of pneumonia with symptoms such as coughing, difficulty breathing and night sweats, accidental symptoms of opioid withdrawal, and possibly liver damage.

- In addition, symptoms such as vomiting and diarrhea can lead to dehydration and/or low blood pressure if you do not keep well hydrated. **It is very important that you drink lots of water before and after your clinic visits during week 4**; a beverage containing electrolytes will also be given to you during your week 4 clinic visits to help you stay hydrated.

- If you need opioid pain relievers, the amount of drugs required may be more than normal, and might cause breathing problems. **Trying to cancel out the effects of naltrexone by taking large amounts of opioids is very dangerous and may lead to a fatal overdose.**

- Also, the risk of overdose on opioids goes up as naltrexone's effects wear off. So, it is very important that you **avoid using opioids during the first two weeks after the effects of naltrexone have worn off, because using opioids during this time could result in overdose and even death.**

- The injection(s) may result in irritation, itching, soreness, swelling and/or bruising where the injection was given.

- ***Other risks or inconveniences***
  - ✓ You may feel pain and get a bruise from blood draws. You may feel faint.
  - ✓ Someone could find out that you were in the study and learn something about you that you did not want others to know. We will do our best to protect your privacy.
  - ✓ The questions could make you sad or upset.
  - ✓ This study may involve risks that are not currently known.

- **<u>WOMEN PLEASE NOTE:</u> This research may have bad effects on an unborn fetus.**
  - ✓ Do not be in the study if you are pregnant.
  - ✓ We must do a test to make sure you are not pregnant before letting you in the study.
  - ✓ If you agree to be in the study, you agree to not get pregnant and to use birth control during the study.

What if I get sick or hurt while I'm in this study?

- If you are hurt by being in the study, you may be treated. You or your insurance will pay for treatment in most cases. It may include
  - ✓ first aid
  - ✓ emergency treatment
  - ✓ follow-up care
- If you get hurt when you are here for the study we will help you get the care you need.
  - ✓ If you are thinking about hurting yourself or have another serious health problem, the study doctor will be told right away.
  - ✓ If you are at risk of hurting yourself or someone else, an ambulance and campus police will be called. You may be taken to the ER. You may be put in the hospital against your will.
- If you get hurt or sick when you are not here, call your doctor or 911 in an emergency.
- If you are quarantined due to COVID-19, you must tell staff immediately. You may be discharged from the study. If so, the researchers will refer you to treatment and make arrangements for you to finish the buprenorphine taper, if you have not completed the detox.
- If being sick has to do with being in the study
  - ✓ tell the emergency medical staff or your doctor about the study
  - ✓ give the name of the study and copy of this form if you have it
  - ✓ page one of the study doctors (501-688-6101) as soon as you can

What if new information comes up about the study?

- We will call you or send you a letter.
- We will tell you about anything that might change your mind about being in the study.

Where can I find more information about this clinical trial?

- A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Who do I call if I have questions about the study?

- Dr. Oliveto at 501-526-8441. After hours, page one of the study doctors at 501-688-6101.
- UAMS Institutional Review Board (IRB) representative at 501-686-5667, if you
  - ✓ have questions about your rights as a study subject
  - ✓ have questions concerning a research-related injury
  - ✓ can't reach the study team
  - ✓ need to speak to someone not directly involved with this study

- The IRB makes sure people in research studies are protected from harm by the study. For more information go to https://irb.uams.edu/about_us/

What should I do if I want to be in the study?
Sign this form. We will give you a copy of the form to keep.

By signing the document I am saying:

- I understand that joining this study is voluntary.
- I agree to be in the study.
- Someone talked with me about the information in this document and answered all my questions.
- I have been asked if I wish to talk directly to the head researcher or study doctor.

I know that:

- I can stop answering questions at any time and nothing will happen to me.
- I can call the office that supervises research (UAMS IRB) at 501-686-5667 if I have any questions about the study or about my rights.
- My decision will not change my medical care at UAMS.
- I do not give up any of my rights by signing this form.
- The purpose and voluntary nature of this study, as well as the potential benefits and risks that are involved have been explained to me. I have been able to ask questions and express concerns, which have been satisfactorily responded to by the study team. I understand that I have waived no rights by signing this consent form.
- I have been told that I will be given a signed copy of this consent form.

I agree to be part of this study:

_____ _____
Your name (please print) Your signature

_____
Date

_____ _____
Name of person obtaining consent (please print) Signature of person obtaining consent

_____
Date