Study Title: Kappa-PET imaging and naltrexone in alcohol drinking behaviors

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COMPOUND AUTHORIZATION AND CONSENT FOR PARTICIPATION IN A RESEARCH PROJECT
YALE UNIVERSITY SCHOOL OF MEDICINE – YALE-NEW HAVEN HOSPITAL

Study Title: Kappa-PET imaging and naltrexone in alcohol drinking behaviors
Principal Investigator: Suchitra Krishnan-Sarin, Ph.D., Associate Professor of Psychiatry
Funding Source: NIAAA

Invitation to Participate and Description of Project

You are invited to take part in a research study designed to help identify important new targets for the development of new pharmacotherapies to treat alcohol dependence. The primary purpose of the study is to increase our knowledge of receptor function in the brains of people who are heavy drinkers and taking naltrexone, a medication that has been approved for the treatment of alcohol dependence. Receptors are special molecules in the brain to which other molecules (neurotransmitters) attach during the normal every-day workings of the brain. Drugs can bind to those receptor molecules as well. Recent evidence suggests that kappa opioid receptors (KOR's) may play an important role in alcohol drinking behavior. This study will try to determine if naltrexone's ability to attach to these receptors is related to its effectiveness. We will use PET (positron emission tomography) for this study. PET is a type of imaging device found in nuclear medicine. It is used for tracking the presence of injected radioactive materials in the body.

You have been chosen to participate because you report being a heavy alcohol user, are currently using alcohol, not regularly using other street drugs, are not seeking treatment for your alcohol use, and you may or may not have a family history of alcohol-related problems. Since this is not a treatment study, you should not participate in this project if you are seeking treatment for your drinking.

In addition, in this project we would also like to study genes that might be related to your drinking behavior. All cells in the body contain genes. Blood contains genes. Genes provide instructions for processes (such as binding of molecules) in the body and for traits such as eye color. Everyone's genes are a little different. Information about these differences among people may help researchers understand how best to use drugs to treat disease.

In order to decide whether or not you wish to be a part of this research study you should know enough about its risks and benefits to make an informed decision. This consent form gives you detailed information about the research study. A member of the research team will discuss the study with you. This discussion will go over all aspects of our research: the goals, the procedures that will be performed, the risks, and the possible benefits. Once you understand the study, you will be asked if you wish to participate; if so, you will be asked to sign this form.

Description of Procedures

The study contains seven parts: *1) Evaluation*: We will obtain informed consent and evaluate your eligibility for the study using clinical assessments, a physical exam, and a Magnetic

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Resonance Imaging (MRI) scan. If you are eligible, you will be scheduled for the rest of the study; *2) Practice PET: You may or may not participate in a mock (practice) PET (Positron Emission Tomography) scan; 3) First PET Scan*; *4) First Alcohol Drinking Session:* Baseline ADP and overnight stay at the Hospital Research Unit (HRU) of Yale Center for Clinical Investigation (YCCI) at Yale New Haven Hospital; *5) Medication period:* After baseline PET scan and ADP are complete, the medication period begins (5-11 days depending on scheduling*); 6) Second Alcohol Drinking Session*: Second ADP and stay overnight at YNHH; 7*) Second PET Scan*.

1) Evaluation

At the Substance Abuse Center (SAC) in Connecticut Mental Health Center (CMHC) (34 Park Street, New Haven), we will check whether or not you are eligible to participate in the study. This will require two to four hours of your time. You will be asked to not use any drugs while you are participating in this study. If you test positive for any drugs or alcohol, you may not be paid for your appointment and may be asked to reschedule. Females will have a pregnancy test and will only be allowed to participate if the result is negative. You will be interviewed and asked to fill out questionnaires. Following this, at your convenience, we will schedule you for a complete physical examination that will include an electrocardiogram, and blood and urine tests, which will require about 1½ hours of your time. You will also get a psychiatric evaluation to confirm your eligibility and may be scheduled to meet with the study physician. During the physical exam, if you have agreed to participate in the genetic portion of this study, we will also draw blood for genetic testing. We plan to study the genes that might be related to the medication's effects on drinking behavior. In addition, we may study other genes. Since all of the genes cannot be anticipated at this time, we will store the samples to study in the future. These samples will only be used for the following purposes: to learn about relationships between genes and characteristics of yours that relate to alcohol drinking and to learn about natural variation of genes between different groups of individuals.

If you choose to participate in this study, you do not have to participate in the genetics portion of this study. Please indicate below whether you wish to participate in the genetic (DNA) portion of this study.

Yes, I will participate in the genetics portion:_____
No, I do not want to participate in the genetics portion:_____

On a different day, you will be asked to go to the MR center at The Anlyan Center for Medical Research & Education at Yale University (TAC, 300 Cedar Street, New Haven) to have an MRI scan of your brain. The MRI scan is a routine way to get pictures of the inside of the body. MRI scans are painless, do not involve the use of radiation, and are used routinely to diagnose neurological problems. You will be asked to lie still on your back, on a comfortable mattress, in the MRI scanner for about 20 minutes. Your head will be held still in a cushioned head rest, and you will wear earplugs to reduce the level of noise. You will not be able to see out of it, but you will be able to hear us and be heard if you wish to say anything. You will hear a drumming noise when the camera is taking pictures of your brain. Some people feel mildly anxious in the scanner. If it is too difficult for you to be in the scanner, we can end the scan. However, if you cannot complete the MRI scan, you will not be able to continue your participation in the study.

On the day of your MRI or at one of your previous appointments, we will walk you over to YNHH to show you the HRU, the layout of the rooms, and walk you through the ADP procedures. You will also be given a list of what to bring and not to bring when you come for your overnight stays.

If for some reason more than six months elapses between the MRI scan and PET scan, we will ask you to come back and complete a second MRI for a current scan of your brain..

2) Practice PET
You may undergo a mock (dry-run) in the PET scanner. This means that you will just be walked through the steps to get familiar with the process. During the mock PET scan, you will lie in a real PET scanner or a replica of the PET scanner, be told when the scanner is being "turned on" and when blood samples are "being drawn".

3) First PET Scan
You will participate in your first (baseline) PET scan. You will be asked to arrive at the Yale University PET Center (801 Howard Ave, New Haven) for your PET scan by no later than 7:00 am. We will check your vital signs and have you complete some questionnaires. We will measure your breath alcohol level by asking you to blow into a meter. If you arrive with a positive breath alcohol level, indicating recent alcohol consumption, then the session will have to be rescheduled. A urine drug screen will also be done and if you are female, we will conduct a urine pregnancy test. If you test positive for either, you will be discharged from the study

Before your PET scan, the research nurse or technologist will help get you settled and check your vital signs. A trained nurse or CNMT (Certified Nuclear Medicine Technologist) will place an IV line in your arm to inject the radiotracer. The radiotracer is injected as a bolus only (over a minute) and the scan is 90 minutes long. You will feel little, if any, pain during this process.

An experienced physician will insert an arterial catheter in your wrist area. The arterial catheter is about 2 inches long and looks like a regular IV tube, but it is inserted into an artery, not a vein. The blood flow in the arteries can tell us about your blood pressure. If an arterial catheter is in place, we can measure your blood pressure continuously. The other main reason to put in an arterial catheter is to be able to draw blood samples rapidly, repeatedly, and without causing you pain. Here is what happens when an arterial line in placed. First, the skin is cleaned with betadine solution (contains iodine) so that it is sterile and protected against infection. Second, the insertion area is numbed with a local anesthetic, so that you feel less pain when the catheter is inserted. You will probably just feel pressure but may also feel pain. This pain is usually like the pain you feel when an IV is placed and only rarely is it worse. Third, the catheter will be flushed regularly during your scan with a salt solution, which prevents clogging of the catheter with a blood clot. The arterial line will remain in place for the whole scanning period. After the catheter is removed, local pressure is applied for a minimum of 15 minutes to prevent bleeding under the skin. A pressure dressing (coban) and a clear dressing (tegaderm) will then be applied and you will be asked to keep it clean and dry, refrain from lifting objects weighing more than 5 pounds, and to avoid repetitive movements for 48 hours. You may remove the pressure dressing at

bedtime and the clear dressing after 48 hours, but do not submerge your hand in water for a full 72 hours. Strenuous activity is prohibited for at least 48 hours after removal of the arterial catheter. After this time, mild physical activity can be resumed. Since the catheter is in for a minimal period, there is a low risk of infection.

If for some reason, an arterial catheter cannot be inserted, after no more than three attempts per arm are made, the scan will be rescheduled for another day. You will still be paid $50 for your time. At the rescheduled scan, the physician will try to insert an arterial catheter again and the scan will be conducted regardless of whether or not the catheter was inserted.

As part of the PET scanning, you will be asked to lie very still on a table. At the beginning of the scan, you are positioned in the scanner and will undergo a "transmission scan" to calibrate the PET scanner. The radiotracer will then be injected into the catheter in your wrist. Following the injection, the PET scanner camera will detect the radiotracer present in brain areas. This information will be used to create pictures of the receptors in your brain. Each PET scan will take about two hours. If you ask, we can stop the scan at any time. However, if you can't complete the PET scan, you may not be able to complete this study. You will be asked to drink several glasses of water at the close of the PET scanning session to wash out the radiotracer. We will monitor your vital signs throughout the study to see how you are feeling, before, during and after scanning. You will also have several electrocardiograms (ECG's). We will also draw blood for routine blood tests to measure levels of substances found naturally in your blood, the levels of the radiotracer and its metabolites, and to measure the same chemical in your blood that we will measure in your brain.

After the PET scan, you will be provided with a light meal, discharged and allowed to go back home. Depending on the start time of the PET scan, you may be at the PET Center until at least the early afternoon. You will be provided with a telephone number you can call any time after the study if you need assistance for problems related to the study procedures.

4) First Alcohol Drinking Session

On the day before or after your PET scan, you will participate in your first ADP. We will ask you to arrive at the Hospital Research Unit (HRU) (20 York Street, New Haven) by 9:00am. We ask that you not consume any alcohol after 5 pm on the evening prior to each ADP. When you arrive at the HRU, we will monitor your breath alcohol level by asking you to blow into a meter. If you arrive with a positive breath alcohol level and your breath alcohol level is above 0.05 and/or is increasing, indicating recent alcohol consumption, then the session will have to be rescheduled. If your breath alcohol level is less than 0.05 and is decreasing, we will have to wait until it comes down to 0 before conducting any assessments. If your breath alcohol level is above 0.05 and the session has to be rescheduled, we will have to keep you at the HRU and advise you to not drive until it comes down to 0.02; alternatively, we could provide you with transportation. We will also collect a urine sample to screen for the use of drugs (e.g., cocaine, opiates, marijuana, benzodiazepines); this test will have to be negative for you to continue in the ADP. If you test positive for marijuana, we will ask you to discontinue use until you complete the study and we will get quantitative levels at your next 2 appointments to ensure that the levels are going down. If the levels increase, you will not be able to continue in this study.

Once you are settled in your room, you will be presented with a sample of two of your preferred drink choices to taste. You will be asked to take a sip of each drink; swish it around in your mouth and then spit it out. You will then choose your favorite drink to be used during the alcohol drinking session later that day. We will get your height and weight, take measurements of heart rate and blood pressure, and have you complete some assessments and computer tasks between 10:00 and 12:30. You will also complete a task to measure how your body responds to cold water, during which you will be asked to place your hand in a bucket of ice-cold water for as long as you can. You will be provided with lunch at 12:30 pm. If you are a smoker, you will be provided with a "smoke-break" which you will be escorted out and allowed to smoke up to 2 cigarettes. Non-smokers will also be given the option of taking 'breaks' at predetermined intervals. When you are not completing assessments, you will be able to relax and watch TV.

Later that same day, you will participate in the ADP. A video camera will be recording this session to monitor your drinking behavior. Prior to the start of this session, you will be asked to complete some questionnaires and rating scales. We will put an IV catheter in your arm to avoid having to stick you more than once for the blood collections. These blood samples will be analyzed for naturally occurring chemicals that your body produces regularly. A cuff will be placed on your arm to monitor heartbeat and blood pressure.

You will be provided with your first drink at 3:00 pm. The alcohol content of this drink will vary according to your weight and will be equivalent to one typical mixed drink. You will be asked to drink it in 5 minutes. You will be monitored for the next 55 minutes and complete assessments. Following this, at 4:00 p.m., you will be presented with four drinks, each of which we consider to be worth $3, for a total of $12. During the next 50 minutes, you can either choose to drink or keep the monetary value of the drinks ($3 per drink that you do not drink). If you choose the money, it will be given to you after the session is completed. At 4:50 p.m. the old drinks will be removed and at 5 pm you will be presented with four fresh, new drinks, each worth $3. These will be available to you for the next 50 minutes. Again, you can choose to drink them or keep the money. The drinks will be removed at 5:50 pm and at 6 pm you will be presented with four fresh new drinks, which will be available to you for the next 50 minutes. The drinks will be removed at 6:50 pm at which time the session is over. You will be given dinner and allowed to retire for the night. Breath alcohol levels will be monitored periodically after completion of the laboratory session until they decrease to a level of 0.02. We will take measurements of heart rate and blood pressure throughout your stay. You will then spend the night in the HRU.

The next morning, we will check your vital signs and you will be asked to complete some assessments. You will then be given breakfast. You will either receive your first dose of study medication, naltrexone, before you are discharged from the HRU or you will be asked to walk over to the PET Center for your first scan and receive your medication there or you will start medication on a future day, depending on scheduling and availability.

In the event that your PET scan needs to be rescheduled due to technical issues, we will reschedule your PET scan to a later date and ask you to stay overnight at the HRU the evening prior to ensure that you arrive at the PET Center on time with a negative BAC. We will admit you between 3 and 4 pm and you will spend the night with no other study obligations.

5) Medication Period
You will come to our clinic at CMHC every day to receive your naltrexone and be monitored for any side effects. In the event that this may be challenging due to your work schedule or other obligations, we will discuss alternative options, such as meeting you in a local hospital or providing you with additional doses to take home accompanied by a phone call reminder to take your medication and to ask you about side effects. You will take medication over the next 5-11 days, depending on scanner availability and scheduling conflicts. The dose of medication will slowly be tapered up to 100 mg, beginning at 25mg. If you are experiencing excessive side effects, you may be scheduled to meet with the study physician and may be asked to discontinue your participation. You do not need to change your drinking behavior while participating in this study. We will give you a medical card indicating that you are taking naltrexone. Any doctor may find out what dose of naltrexone you are getting by calling the Yale-New Haven Investigational pharmacy (203-688-2978). You should carry this phone number with you in case of an emergency.

6) Second Alcohol Drinking Session
You will come in for your second ADP session and 24-hour overnight stay at the HRU after at least 5 days of medication, depending on scheduling. You will follow the same procedure as in the first ADP.

7) Second PET Scan
You will participate in a second PET scan, very similar to the first. This scan will ideally be scheduled the day after the second ADP session, but depending on scanner availability, it may be scheduled the day prior to the ADP session. Either way, you will arrive at the PET Center at 7:00am, be injected with a radiotracer and be scanned. If the first arterial line cannot be placed for any reason, the scan will still be completed. You will remain at the PET Center for one-hour after completion of the scan for observation and then discharged to home. Again, plan to be at the PET Center until early afternoon or later.

When you have completed all parts of the study, you will be scheduled for a 1-week follow up appointment. We will record any remaining adverse events that you may have as well as your current drinking behavior. A clinical psychologist will talk to you about your drinking behavior and if you are interested, will provide you with treatment referrals. You will also be interviewed and asked to complete some questionnaires. This appointment should last approximately one hour.

A follow-up appointment will be conducted with all participants, even those who do not complete the entire study. You will be told of any significant new findings that are developed during the course of your participation in this study that may affect your willingness to continue to participate.

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.

Risks and Inconveniences

1) *Magnetic resonance (MR):* Magnetic resonance is a technique that uses magnetism and radio waves, not x-rays, to take pictures and measure chemicals of various parts of the body. The United States Food and Drug Administration (FDA) has set guidelines for magnet strength and exposure to radio waves, and we carefully observe those guidelines.

   You will be watched closely throughout the MR study. Some people may feel uncomfortable or anxious. If this happens to you, you may ask to stop the study at any time and we will take you out of the MR scanner. On rare occasions, some people might feel dizzy, get an upset stomach, have a metallic taste or feel tingling sensations or muscle twitches. These sensations usually go away quickly but please tell the research staff if you have them.

   There are some risks with an MR study for certain people. If you have a pacemaker or some metal objects inside your body, you may not be in this study because the strong magnets in the MR scanner might harm you. Another risk is the possibility of metal objects being pulled into the magnet and hitting you. To reduce this risk, we require that all people involved with the study remove all metal from their clothing and all metal objects from their pockets. We also ask all people involved with the study to walk through a detector designed to detect metal objects. It is important to know that no metal can be brought into the magnet room at any time. Also, once you are in the magnet, the door to the room will be closed so that no one from outside accidentally goes near the magnet.

   We want you to read and answer very carefully the questions on the MR Safety Questionnaire related to your personal safety. Take a moment now to be sure that you have read the MR Safety Questionnaire and be sure to tell us any information you think might be important. This MR study is for research purposes only and is not in any way a clinical examination.

   The scans performed in this study are not designed to find abnormalities. The primary investigator, the lab, the MR technologist, and the Magnetic Resonance Research Center are not qualified to interpret the MR scans and are not responsible for providing a diagnostic evaluation of the images. If a worrisome finding is seen on your scan, a radiologist or another physician will be asked to review the relevant images. Based on his or her recommendation (if any), the primary investigator or consulting physician will contact you, inform you of the finding, and recommend that you seek medical advice as a precautionary measure. The decision for additional examination or treatment would lie solely with you and your physician. The investigators, the consulting physician, the Magnetic Resonance Research Center, and Yale University are not responsible for any examination or treatment that you receive based on these findings. The images collected in this study are not a clinical MR exam and for that reason, they will not be made available for diagnostic purposes.

   If you become uncomfortable for any reason or at any time, you should inform the MRI technician or research assistant immediately.

2) *PET Scans*

a) Risks Associated with Use of an Arterial Catheter

Putting in the plastic tube into the artery in the wrist area may cause bruising, and potentially infection. The arterial puncture may also cause spasm or clotting of the artery with a temporary decrease in blood flow, this may cause tingling or numbness at the injection site and/or in the hand/fingers. In rare instances blocking of the artery, poor healing, infection, hematoma (a solid swelling of blood within the tissues), or inflammation at the catheter insertion site may occur. Insertion of arterial catheters for giving drugs or sampling blood may be associated with mild-to-moderate pain or bruising at the puncture site. To minimize these risks, an experienced physician will insert the arterial line and a trained nurse will oversee subject care.

For two days following the placement of the arterial line, you should check your wrist/arm daily. The study team will also be in touch with you daily either via phone, or in person, during this two-day period. If you experience any excessive pain, tenderness, swelling, redness, drainage, skin color changes, numbness, pins and needles, or decreased strength in the arm that had the catheter, you should immediately call the study team (203-464-6015). You can also contact the study PI Dr. Krishnan-Sarin (860-575-9895), or the PET center physician, Dr, David Matuskey (203-370-1403), or the study physician, Dr. Julia Shi (203-781-4640).

You may experience a rare allergic reaction to the medicine used to numb your skin prior to placement of the arterial catheter. If you have had a bad reaction to lidocaine or other anesthetic agents used to numb the skin in the past, please tell us about this experience before you go through the arterial line placement. Severe allergic reactions can be life threatening. Important: If you have a history of a bleeding disorder or are taking medication to thin your blood, you will not be allowed to participate in this study. You will also be asked to abstain from using aspirin and other anti-inflammatory drugs (such as Motrin or Aleve) for 7-10 days before arterial line placement and 7-10 days after arterial line removal.

b) Risks Associated with Radiation

This research study involves exposure to radiation from positron emission tomography (PET). Please note that this radiation exposure is **not** necessary for your medical care and is for research purposes only. The radiation you will receive in this study is from **[11C]LY2975050** scan(s) and from transmission scans of your head used to help obtain the PET images.

The total amount of radiation you will receive during the **2** PET scan sessions in this study is from **2** injection(s) of the tracer, **[^{11}C]LY2795050,** and from transmission scans of your head.

Although each organ will receive a different dose, the amount of radiation exposure you will receive from this study is equal to a uniform whole-body exposure of **1.44** rem, which is the equivalent of approximately **4** years of natural environmental exposure. This value is known as the "effective dose" and is used to relate the dose received by each organ to a single value. This amount of radiation exposure is below the annual limit of 5 rem set by the federal

government for research subjects.

The effects of radiation exposure on humans have been studied for over 60 years. In fact, these studies are the most extensive ever done of any potentially harmful agent that could affect humans. In all these studies, no harmful effect to humans has been observed from the levels of radiation you will receive by taking part in this research study. However, scientists disagree on whether radiation doses at these levels are harmful. Even though no effects have been observed, some scientists believe that radiation can be harmful and may cause cancer at any dose- even low doses such as those received during this research.

Please tell your study doctor if you have taken part in other research studies at Yale or other places/hospitals that used radiation. This way we can make sure that you will not receive too much radiation. You should consider x-rays taken in radiology departments, cardiac catheterization, and fluoroscopy as well as nuclear medicine scans in which radioactive materials were injected into your body. Before you take part in any future studies that use radiation, you should also tell those study doctors about your participation in this study.

If you are pregnant or breast feeding, you may not participate in this research study. We will perform urine pregnancy tests prior to your participation on your PET and MRI scan days.

3) *Risks Associated with Alcohol*

A number of medical conditions could potentially be worsened by acute alcohol administration (e.g., liver disease, cardiac abnormality, pancreatitis, diabetes, neurological problems, and gastrointestinal disorders). As a result, if you have any of these medical problems, you should not participate in this study. Alcohol may also cause nausea in high doses; however, nausea is not expected at the dose being used in this study. In order to ensure that you do not fall and hurt yourself after consuming alcohol, we will ask you to stay in the HRU overnight after the drinking session. Alcohol is a reinforcing agent, which may cause changes in behavior including repetitive or excessive alcohol consumption. We do not endorse drinking alcohol in the quantities used in this research study.

4) *Risks Associated with Naltrexone*

Naltrexone, an opioid antagonist, is widely used in the treatment of opioid addiction and more recently has been found to be beneficial in the treatment of alcoholism. Numerous studies have found naltrexone use to be safe and rarely associated with toxicity or severe side effects. The most frequently reported side effects are gastrointestinal in nature. Those include stomach pain, nausea and vomiting. Other, less frequent side effects include dizziness, nervousness, headaches, blurred vision, low energy, fatigue, sleepiness, joint and muscle pain and insomnia. Liver toxicity, the most serious potential side effect, has been shown in studies using very high doses of naltrexone (1400 to 2100 mg per week). At the doses used in this study naltrexone has not been reported to produce damaging effects on the liver. If you use opiates (like heroin, morphine, codeine or Tylenol # 3) on a regular basis you should not participate in this study since naltrexone can also cause or worsen withdrawal from opiates. During your participation in this study we will monitor you daily for side effects from naltrexone. If while participating in this study you require emergency surgery or

are involved in a situation where you might need an opioid anesthetic, your doctor should be aware that you are on naltrexone.

5) *Risks Associated with Interactions of Naltrexone and Alcohol*
There are no known risks to contraindicate the administration of alcohol to subjects on naltrexone.

6) *Risks Associated with Blood Drawing and Urine Collection*
Urine samples will be used for drug and pregnancy tests and there is no risk. Drug tests will be done at the initial appointment, the PE, the 2 ADP sessions, the 2 PET sessions, and Day 4 of medication.

Drawing blood and inserting an intravenous line (IV) into an arm vein are safe and standard medical procedures. Sometimes a bruise will occur at the puncture site and rarely a blood clot or infection will occur in the vein. You should not donate blood for at least 6 weeks after the study. Some people feel lightheaded but this effect is temporary. The total volume of blood collected during this study will be about **19** tablespoons. This amount of blood loss is safe for healthy persons.

Here are the amounts of blood to be drawn during different parts of the study:

Screening procedures at start of week…	1 tablespoon
First ADP session …	2 tablespoons
Two PET scans…	13 tablespoons
Second ADP session…	2 tablespoons
Genetics portion…	1 tablespoon

7) *Risks Associated with Pregnancy and Breastfeeding*
You may not participate in this study if you are currently pregnant, might become pregnant during the study, or you are breastfeeding an infant. Alcohol drinking is harmful to an unborn child and acceptable levels of radioactivity are lower for pregnant individuals. It is best to avoid radiation exposure to unborn or nursing children since they are more sensitive to radiation than adults. You will be tested for pregnancy as part of the routine lab tests. If the test is positive, you will not be included in the study. Before starting the study, we will ask you to avoid becoming pregnant and ask you what precautions you plan to take. If you change your mind about becoming pregnant or how you will avoid becoming pregnant, we ask that you to tell us immediately. You will be given one pregnancy blood test during the initial physical evaluation, and you will also be given a urine pregnancy test on the day of the MRI and on the day of each PET scan.

8) *Risks Associated with Alcohol Withdrawal*
We are not going to ask you to alter your drinking behavior while you are participating in this study. However, you should know that some individuals who reduce or stop their drinking can experience alcohol withdrawal symptoms such as mild agitation, anxiety, restlessness, tremor, loss of appetite and difficulty sleeping or even more severe (but rare) symptoms like extreme restlessness, nervousness, disorientation, confusion, hallucinations

(hearing and seeing things that are not there) and seizures, but these are extremely rare. We will monitor you very closely for withdrawal symptoms during your daily visits to our clinic. If you experience worsening of withdrawal symptoms, you may have to be hospitalized and will be given medications that are typically used to treat and manage withdrawal. These medications include benzodiazepines, such as chlordiazepoxide (librium), and other medications such as carbamazepine (tegretol).

9) *Risks Associated with Taking Blood Samples for Genetic Testing*

The blood samples obtained from you for the purpose of genetic testing will be stored in the laboratory of a co-investigator on this project, Dr. Joel Gelernter. Genetic testing will only be conducted for research purposes and the results will only be available to investigators on this study. Variation in some genes is known to be directly related to risk for certain illnesses and drug dependence. Other genes we will be studying may be shown at some point in the future to be related to illness. Since the results of these genetic tests may allow prediction of risk of illness in some cases, only scientists working on this research project will know the results. We will not make any of our laboratory results available to you, nor will we add them to your medical record. (If you want to know your risk for genetic diseases, we will refer you to a genetics counselor.)

The genetics blood samples obtained from you will also be stored indefinitely and will be used only for research purposes. If after you provide the sample, you decide that you want to withdraw from this portion of the study you are certainly free to do as specified in the "Voluntary Participation" section below.

There is a federal law called the Genetic Information Nondiscrimination Act (GINA). In general, this law makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. However, it does not protect you against discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

10) Risks Associated with Completing Laboratory Tasks

The computer and cold water tasks can produce some uneasiness at the time of the task. However, once the task is over, there is very little anxiety that carries over, thus posing minimal risk. Moreover, you will have total control over these tasks and can stop performing any of them if you get too uncomfortable.

Benefits

There are no direct benefits to you for your participation. We expect that the results of the study, however, will benefit science and others through increasing our knowledge about the use of naltrexone as a treatment for alcohol drinking and its efficacy through the use of PET.

Compensation

You will be paid
$50 for the initial interview
$50 for the physical examination

$250 for the first PET scan
$50 for each arterial catheter insertion
$50 for the MRI scan
$150 for participating in the first drinking paradigm
$170 for taking medication (up to 11 days)
$10 per day for transportation to our clinic to take medication - (up to $110)
$250 for participating in the second lab drinking paradigm
$450 for the second PET scan
$30 for completing a one week follow-up

Appointment	Cash	Check
Intake	$50	
Physical Exam	$50	
MRI Scan	$50	
PET scan #1		$250
Arterial Catheter insertion- Scan 1		$50
Overnight (ADP) #1		$150
Medication (5-11 days)		$170
Transportation (medication appts)	Up to $110	
Overnight (ADP) #2		$250
Computer assessments- ADP 1 and ADP 2	Up to $30	
PET Scan #2		$450
Arterial Catheter insertion- Scan 2		$50
1 Week Follow Up	$30	

You will receive up to a total of $1370.00 in the form of a check if you complete the study. This check can take 4-6 weeks to process. You will receive up to a total of $180 in cash for completing the intake, physical exam, MRI, and follow-up.

Subjects **may** also earn these payments in cash:
$50 if the first arterial line cannot be placed at the first PET scan and you need to be rescheduled
$36 (depending on your drink consumption) during the first alcohol-drinking period
$36 (depending on your drink consumption) during the second alcohol-drinking period
Up to $30 for computer assessments at ADP sessions
$50 to show up for additional ADP/PET scan as a standby participant in case the primary scheduled participant has a conflict for the ADP and/or PET scan. (if the scheduled participant arrives, you will be paid asked to come back at a later date to complete your scheduled appointments).
$50 for an additional MRI scan
$100 to spend an additional overnight at HRU if PET is rescheduled
$25 if you are asked to come back for a repeat lab appointment (bloodwork or EKG)

You may be responsible for paying taxes on payments you receive to the IRS for your participation in this study, since payments over $600 are usually reported on Form 990 to the IRS. However, your confidentiality will be protected by the Certificate of Confidentiality (described below). The business office will not identify or link a payment to any research study and will neither confirm nor deny any details whatsoever about your participation.

Treatment Alternatives

This is not a treatment study. You should not participate in this study if you want to stop drinking. If you are currently interested in changing your drinking behavior, we will provide you with a treatment referral and you will not be eligible to participate in this study.

Subject Obligation

We ask that you do not use any medicines except the study medications or participate in any other research study without discussing this with us first while you are in our study. Please let us know if you use any other medications or drugs during this time, since we may need to reschedule your study sessions. The ways in which you might be dismissed from the study are if you repeatedly do not show up, lie about your alcohol and drug use, or don't take your study medication. The Principal Investigator may decide to discontinue your participation in the study based on data collected at the first overnight appointment. In that case, the initial PET scan and all other appointments will be cancelled. Although your participation will be discontinued at this point, you will receive payment for all completed appointments.

We will be monitoring your urine periodically for use of alcohol and other drugs and will also check your breath alcohol level. If your breath alcohol level is positive, you will have to wait until it drops to 0.02 before we can allow you to leave or we can arrange for an alternate form of transportation for you. Similarly, if your drug tests are positive, the sessions will have to be rescheduled if possible.

Confidentiality and Privacy

There are two separate statutes which provide the means to protect your confidential information related to your health information. One statute of protection is called HIPAA and the second is called a Certificate of Confidentiality (CoC).

A Personal Health Information (PHI) record is routinely created whenever you see a physician or go to the hospital or you are seen in an outpatient clinic. Personal health information is also called a medical record. Your medical record is considered confidential under the privacy statutes referred to as HIPAA. However, there are certain circumstances when medical records can be demanded without your written permission. In some cases, medical records can be requested, for example, by an insurance company, the government, or an attorney representing another person. HIPAA allows the court to order such information to be provided to them for good reasons.

When you participate in a research study, your identity as a research participant—and all the identifiers that could lead to your identity will be held confidentially. The investigator cannot be forced to release your identifiers to anyone outside of the research team if a Certificate of

Confidentiality is issued. Thus, to protect your sensitive information, we have obtained a Certificate of Confidentiality (CoC) from the National Institute on Alcohol Abuse and Alcoholism (NIAAA) which is part of the National Institutes of Health (NIH).
The CoC protects the identity of individuals in a study and protects the investigators from being forced to tell people that are not connected with this study about your participation in this study, even under a subpoena. This protection, however, is not absolute. The protection offered by the CoC does not stop us from voluntarily reporting information about suspected or known sexual, physical, or other abuse of a child or older person, or a subject's threats of violence to self or others. If any member of the research team is given such information, he or she will make a report to the appropriate authorities. Individuals who participate as research subjects (i.e., about whom the investigator maintains identifying information) in the specified research project during any time the Certificate is in effect are protected permanently.. Also, because this research is sponsored by NIAAA, staff from NIAAA and other DHHS agencies may review records that identify you but only for the purposes of audit for quality and accuracy or program evaluation.

Even when a CoC is in place, you must still continue to actively protect your own privacy. If you voluntarily give your written consent to anyone to receive information about your participation in the research or freely volunteer information to anyone other than the study staff that you are a research participant in this study, then we may not use the CoC to withhold this information.

Further details about the limitations and protections of your medical records and the information you provide as a research participant are provided below.

<u>Use and Protection of Collected Medical Record information</u>
Health information about you will be collected if you choose to be part of this research study. Health information is protected by law as explained in the Yale University Privacy Notice. If you have not received this notice, please request a copy from the investigator. At Yale University, your medical record information will only be used or shared as explained and authorized in this consent form or when required by law.

We ask anyone who gets your health information from us to protect your privacy. However, there may be some cases beyond our control where we cannot protect your privacy but we expect that those instances will be rare and accidental disclosures.

To participate in this research you must allow the study team to use your health information. If you do not want us to use your medical record information, you may not participate in this study.

Documents that contain your name, such as this consent form signed by you, will be securely stored separately from your research data. All research data will be coded in a way that does not identify you by name or initials and will be kept in a secure place that allows only selected study personnel to have access to this information. The research data collected will be kept separate and distinct from the medical record.

The blood samples obtained from you for the genetics study will be stored indefinitely and will be used only for research purposes. Information from these samples will only be made available to the investigative team working on this project.

You should understand that there is a risk that you will be recognized by other patients or staff involved in the laboratory or hospital ward and it could be known that you are participating in this study. If you find this to be an unacceptable condition you should not sign this consent form.

You have the right to review and copy your health information in your medical record in accordance with institutional medical records policies.

Withdrawing Your Authorization to Use and Disclose Your Health Information

The use and disclosure of your information has no time limit. Any research information in your research record will be kept indefinitely. If you wish to revoke permission for the use and sharing of your health information, you may do so by notifying the study doctor, Dr. Krishnan-Sarin, but in doing so; you will no longer be able to participate in this research study.

If you withdraw your permission:

- No new health information identifying you will be gathered after that date.
- We will no longer use or share medical information about you for this research study, except when the law allows us to do so.
- We are unable to take back anything we have already done or any information we have already shared with your permission.
- We may continue using and sharing the information obtained prior to your withdrawal if it is necessary for the soundness of the overall research.
- We will keep our records of the care that we provided to you as long as the law requires.

MEDICAL RECORD INFORMATION COLLECTED DURING THIS STUDY

The investigator and staff involved with the study will keep your medical record information collected for the study strictly confidential. Medical record information covered by HIPAA, including your name, initials, and other identifying information will not be released or published without your permission unless required by law. The following medical record information will be collected and used for research:

- *Name*
- *Address*
- *Telephone number*
- *Information from a brief psychiatric examination*
- *Emergency contact information*
- *Initial telephone screening information*
- *Allergies*
- *Current and past medications and therapies*
- *Information from a physical examination that generally also includes blood pressure reading, heart rate, breathing rate and temperature*
- *Electrocardiogram*
- *Breath Alcohol Tests*

- *Urine Drug Screens*
- *Urine Pregnancy Tests if you are female*
- *Clinical laboratory Tests*
- *Healthcare, Social Functioning, and Addiction Questionnaires/Forms*

Information about you and your health which might identify you may be used by or given to:
• The U.S. Department of Health and Human Services (DHHS) agencies
• Representatives from Yale University and the Human Investigation Committee, who are responsible for insuring research compliance. These individuals are required to keep all information confidential.
- Those providers who are participants in the Electronic Medical Record (EMR) system. Members of the research team who are participants in the EMR system, including the study physicians and study psychologist, will have access to your medical information in the EMR to ensure eligibility and safety for research participation.

• Those individuals at Yale who are responsible for the financial oversight of research including billings and payments
• The Principal Investigator and selected members of the research team
• Collaborating research groups and research centers where research personnel from this study are also involved.
• Data and Safety Monitoring Boards and others authorized to monitor the conduct of the study

By signing this form, you authorize the use and/or disclosure of the information described above for this research study. The purpose for the uses and disclosures you are authorizing is to ensure that the information relating to this research is available to all parties who may need it for research purposes.

All health care providers subject to HIPAA (Health Insurance Portability and Accountability Act) are required to protect the privacy of your information. The research staff at the Yale School of Medicine and Yale New Haven Hospital is required to comply with HIPAA and to ensure the confidentiality of your information. Some of the individuals or agencies listed above may not be subject to HIPAA and therefore may not be required to provide the same type of confidentiality protection. They could use or disclose your information in ways not mentioned in this form. However, to better protect your health information agreements are in place with these individuals and/or companies that require that they keep your information confidential.

To protect your confidentiality, the videotapes of the drinking sessions will be identified by code number and erased within a period of 24 months after completion of the study.

In Case of Injury

If you develop any mental or physical problems as a direct result of being in this component of the study, we will refer you for treatment. You or your insurance carrier will be expected to pay the costs of this treatment. No additional financial compensation for injury or lost wages is available. Your legal rights are not waived by signing this consent form.

Voluntary Participation and Withdrawal

Participating in this study is voluntary. You are free to choose not to take part in this study. Refusing to participate will involve no penalty or loss of benefits to which you are otherwise entitled. It will not harm your relationship with your own doctors or with the researchers, YNHH, the PET Center, or the Connecticut Mental Health Center.
However, you will not be able to enroll in this research study and will not receive study procedures as a study participant if you do not allow use of your information as part of this study.

Withdrawing From the Study

If you do become a subject, you are free to stop and withdraw from this study at any time during its course. To withdraw from the study, you can call a member of the research team at any time and tell them that you no longer want to take part. You will also be paid for your participation up until the moment you withdraw from the study.

When you withdraw from the study, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others until the end of the research study, as necessary to insure the integrity of the study and/or study oversight.

Withdrawing from the study will involve no penalty or loss of benefits to which you are otherwise entitled. It will not harm your relationship with your own doctors or with the researchers, YNHH, the PET Center, or the Connecticut Mental Health Center.

Withdrawing Your Authorization to Use and Disclose Your Health Information

You may withdraw or take away your permission to use and disclose your health information at any time. You may withdraw your permission by telling the study staff or by writing to Dr. Suchitra Krishnan-Sarin at Yale University, CMHC, 34 Park Street, Room S-208, New Haven, CT 06519.

If you withdraw your permission, you will not be able to stay in this study.

When you withdraw your permission, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others until the end of the research study, as necessary to insure the integrity of the study and/or study oversight.

Participation in the genetics portion of this study is also completely voluntary. You are free to decline to participate in the genetics portion and still participate in the rest of the study. If you choose to withdraw from the genetic portion of this study, you can request that we either destroy all records in our research files connecting your name with your DNA sample, so that it would only be studied anonymously from that point forward. Alternatively, if you so request, we will also destroy your sample used for DNA testing.

You must follow up this request with a written request, mailed to: Suchitra Krishnan-Sarin, PhD, 34 Park Street, Room S-208, New Haven, CT 06519.

Questions

We have used some technical terms in this form. Please feel free to ask about anything you don't understand and to consider this research and the consent form carefully – as long as you feel is necessary – before you make a decision.

Authorization and Permission

I have read (or someone has read to me) this form and have decided to participate in the project described above. Its general purposes, the particulars of involvement and possible hazards and inconveniences have been explained to my satisfaction. My signature also indicates that I have received a copy of this consent form.

By signing this form, I give permission to the researchers to use [and give out] information about me for the purposes described in this form. By refusing to give permission, I understand that I will not be able to be in this research.

Name of Subject:_____

Signature:_____

Date:_____

_____ _____

Signature of Principal Investigator Date

or

_____ _____

Signature of Person Obtaining Consent Date

If you have further questions about this project or if you have a research-related problem/injury, you may contact the Principal Investigator, Suchitra Krishnan-Sarin, PhD at (203)974-7595 or the study physician, Julia Shi, M.D, at (203)781-4640. If you would like to talk with someone other than the researchers to discuss problems, concerns, and questions you may have concerning this research, or to discuss your rights as a research subject, you may contact the Yale Human Investigation Committee at (203) 785-4688. If after you have signed this form you have any questions about your privacy rights, please contact the Yale Privacy Officer at 203/436-3650.

CONSENT TO FILMING OR VIDEO-TAPING
FOR RESEARCH PURPOSES

I agree that videotape or motion pictures may be taken of me under the direction of Suchitra Krishnan-Sarin, Ph.D. as part of the study entitled "Kappa-PET imaging and naltrexone in alcohol drinking behaviors" under the following conditions:

These films will be erased within a period of 24 months after completion of the study.
It is specifically understood that, after filming, video cassettes will be identified by code number only to protect my confidentiality..

It is specifically understood that only those persons involved in this research project will view these videotapes or films and that my confidentiality will otherwise be maintained.

Signature _____

Date _____