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CONSENT TO ACT AS A SUBJECT IN A RESEARCH STUDY

TITLE: Is there selective regulation of individual CYP enzymes in studies with paroxetine, disulfiram and rifampin?

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TO PERSONS BEING ASKED TO PARTICIPATE IN THIS STUDY:

The following information is provided to inform you about a research project that you are being asked to participate in. Please read this form carefully. Any questions you may have about this study will be answered. Please feel free to ask any questions you may have about this study and/or about the information given below.

DESCRIPTION: You are being asked to participate in this research study because you are a normal healthy volunteer who does not smoke and is not taking any prescription or over the counter drugs. The purpose of this study is to determine how one drug can influence the metabolism (breakdown) of another drug and learn more information about the mechanisms involved in drug interactions. The drug interactions we are investigating will be assessed by blood and urinary measures of drugs and their metabolites (break down products), and we do not anticipate you being able to notice any drug related effects. If you agree to participate in this study, you will receive on two separate occasions, single doses of the following medications: caffeine 100 mg (same as about 3 cups of coffee), flurbiprofen 50 mg (a drug normally used to relieve pain and inflammation), mephenytoin 100 mg (a drug normally used to prevent seizures), debrisoquine 10 mg (a drug normally used to decrease blood pressure), dapsone 50 mg (a drug used to treat a variety of skin disorders), and chlorzoxazone 250 mg (a drug normally used as a muscle relaxant). These six medications are collectively known as the six drug cocktail. You will also receive a single dose of midazolam 4 mg (a drug normally used to make someone sleepy or relaxed before a medical test). Each of these drugs is taken by mouth as either a tablet or syrup. Each of these drugs has been approved for use by the US Food and Drug Administration for the treatment of certain disorders, except debrisoquine, which is still an investigational drug in the US. These medications are not FDA approved for the purposes of this study.

In addition, you will be asked to take a drug for 8 days. You will be assigned based on previously met criteria to take one of the following three drugs: disulfiram (a drug used to discourage people from drinking alcohol), paroxetine (a drug used to treat depression), and rifampin (a drug used to treat certain infections). Sixteen (16) men or women, 18-45 years of age, will participate in this study. This study will require two 36 hour visits and two outpatient (half an hour) visits to the General Clinical Research Center (GCRC) in UPMC-Montefiore hospital (see Table below).

Study day 1	Study day 2	Study day 3	Study day 5	Study day 8	Study day 9
First 36-hour visit to GCRC		Outpatient visit	Outpatient visit	Second 36-hour visit to GCRC	
Blood volume pre dose = 35 ml	Blood volume pre dose = 38 ml	Blood volume = 28 ml	Blood volume = 28 ml	Blood volume pre dose = 35 ml	Blood volume pre dose = 38 ml
Blood volume post dose = 63 ml over 10 hours	Blood volume post dose = 90 ml over 10 hours			Blood volume post dose = 63 ml over 10 hours	Blood volume post dose = 90 ml over 10 hours
Midazolam Blood sample for genetic analysis	Caffeine Flurbiprofen Mephenytoin Debrisoquine Dapsone Chlorzoxazone Blood sample for genetic analysis	Blood sample for genetic analysis	Blood sample for genetic analysis	Midazolam Blood sample for genetic analysis	Caffeine Flurbiprofen Mephenytoin Debrisoquine Dapsone Chlorzoxazone Blood sample for genetic analysis

If you agree to be one of the 16 subjects, the following will be required of you:

1. You will have a physical exam and laboratory tests (requiring 15 mL or three teaspoonfuls of blood), and a urine sample to check kidney function to determine if you are eligible to participate in the study. The exam and laboratory tests will be done within four (4) weeks prior to the start of the study. If you are a woman of childbearing age, you will have a pregnancy test. If this is positive, you will not be eligible to participate in this study. You will be asked if you are allergic to sulfa and if so, you will not be given Dapsone during the study. You will also be asked if you are allergic to nonsteroidal anti-inflammatory drugs, and if so, you will not be given flurbiprofen in the study.
2. You will not have any alcoholic beverages for 48 hours prior to the screening or the study days or during the duration of the study. You will not have any grapefruit or grapefruit juice 24 hours prior to or during the study. You will not have any caffeine containing beverages or food for 24 hours prior to or during the study visit. You will not eat any food after 11:30 PM on the night before the GCRC study visits. If you are taking medications, you may be asked to withhold them or modify the way you are taking them for 48 hours prior to and during the study if your primary care provider considers it to be safe for you. In the event that you accidentally consume caffeine containing products

within the 24 time period, you may still be permitted to participate in the research study at the discretion of the Primary Investigator.

3. For the first study visit, you will report to the GCRC by 8:00 AM. If you are female and capable of bearing children, a urine pregnancy test will be performed again. If the pregnancy test is positive, you will not be allowed to participate in this study. A urine drug screen will be done. Prior to the study, you will avoid taking narcotics and any other medication that may cause a false positive to the urine drug screen. If the drug screen is positive, you will not be allowed to participate in this study. Baseline vital signs consisting of blood pressure, pulse, respirations and temperature will be taken prior to the first blood draw. A catheter will be placed in a forearm vein of one of your arms. You will give a pre-dose blood sample (7 ml or one and one half teaspoonful) from your blood draw site. At approximately 9:00 AM, you will be given Midazolam syrup 4 mg by mouth with 8 ounces of water. A 7 ml blood sample (one and one half teaspoonful) will be obtained from the blood collection site at 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 10 hours after midazolam administration. Vital signs will be taken at 0.5, 1, 2, and 4 hours after oral midazolam administration. For the first hour after oral midazolam administration, you must remain in bed with the head of the bed elevated at least 45 degrees. You will remain in bed until 6 hours after the Midazolam dose (until about 3:30 p.m.). If you need to use the bathroom, you must notify a nurse for assistance. After 6 hours, you will be able to walk around with supervision for 15-minute intervals as desired. You will be allowed to eat regularly, with the exception of caffeine, two hours after you take Midazolam.

You will remain in the GCRC overnight and will not have anything to eat after midnight (you may have water as needed). The following morning, you will give a pre-dose blood sample (10 ml or two teaspoonfuls) from your blood draw site. At approximately 8:00 AM, you will be given Caffeine 100mg, Chlorzoxazone 250mg, Debrisoquine 10mg, Flurbiprofen 50mg, Dapsone 50 mg and Mephenytoin 100mg by mouth with 8 ounces of water. A 10 ml blood sample (two teaspoonfuls) will be obtained from the blood collection site at 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 10 hours after administration of the study drugs. Vital signs will be taken at 1, 2, 4, and 8 hours after cocktail administration. You will collect all of your urine from 0-8 and 8-10 hours after you take the study drugs. The catheter will be removed after the last blood sample is collected (10 hour). You will be discharged from the GCRC after your 10 hour blood sample is drawn (approximately at 6:00 PM).

Approximately six teaspoonfuls of blood will be taken on the first and second day of the visit to analyze the drug metabolizing enzymes in your mRNA along with blood to analyze your pattern of proteins (proteomics) present in your body and how these patterns do or do not change with time, and blood samples to measure cytokine levels, which are markers of immune response (your ability to fight off diseases) which can be altered in some disease states. Individuals vary in the level of these enzyme activities due to both genetic and environmental factors. No other testing will be done or information obtained using your mRNA. No genetic testing will be done on the obtained samples. The mRNA expression analyses will be used to screen for differences between people in the amount

of metabolizing enzymes which break down drugs. The mRNA, cytokine and proteomic blood samples will be stored indefinitely in Dr. Marjorie Romkes' and Dr. William Bigbee's laboratory.

. 4. At the end of the first study visit you will be given one of the following drugs: Paroxetine 20 mg, Disulfiram 125 mg, or Rifampin 600 mg. You will be told which drug you are taking. You will take the first dose in the end of the overnight visit to GCRC, i.e. in the evening of study day 2. You will also be given the doses of the drug to take at home for the next 7 days. You are to take the drug at approximately 8 A.M. each morning with a full glass of water. A study coordinator will phone you to ask about taking the study drugs and to ask you if you are experiencing any side effects from the drug.

5. You will return to the GCRC for blood samples (28 mls or approximately 6 teaspoonfuls) to obtain mRNA (genetic material), cytokines and proteomics on study days 3 and 5 (at approximately 8 A.M.). You will be given a calendar to remind you which days you are to come to the GCRC.

On study day 8, you will return to the GCRC to repeat Day 1 and 2 procedures..

Drug Information: drugs used in this study include paroxetine, rifampin, disulfiram, caffeine, chlorzoxazone, flurbiprofen, midazolam, dapsone, mephenytoin and debrisoquine. All drugs except debrisoquine are FDA (Food and Drug Administration) approved for the treatment of certain diseases. Debrisoquine is an investigational anti-hypertensive (decreases blood pressure) agent that has not been approved for general use in the U.S. (IND #32,497; R.A. Branch, M.D., University of Pittsburgh, Center for Clinical Pharmacology).

6. The total blood withdrawn from you during the study will be approximately 35 tablespoonfuls or 523 ml. The amount of blood withdrawn when someone donates a unit of blood is approximately 30 tablespoonfuls or 450 ml.

RISK AND BENEFITS:

Associated with taking part in this study are the discomfort, inconveniences and/or risk related to having blood samples drawn and having timed urine collections. There is a small risk of bruising; bleeding or infection at the site the blood is drawn. In addition, drugs can have side effects. The drugs used in this program may cause all, some or none of the side effects listed. In addition, as with any investigational drug study, there may be adverse events or side effects that are currently unknown and it is possible that certain of these unknown risks could be permanent, serious or life-threatening.

All drugs have the potential to induce side effects. The drugs used in this program have been selected on the basis that when used in the doses indicated they cause minimal side effects which has been shown in more than 300 subjects. With the use of the six drug cocktail, dizziness has been observed in about one in every six subjects lasting between

15 minutes and, in a few individuals, about 2 hours. This usually resolves with a meal that is allowed two hours after taking the drugs listed below. The side effects described are those seen in subjects receiving each drug on a repeated basis.

Side effects are listed below for each of the drugs used in this study. Side effects are listed below for each of the drugs used in this study. Side effects that are considered **likely**, occur in more than 25% of people (more than 25 out of 100 people) who take the drug, **common** side effects occur in approximately 10% to 25% of people (10 to 25 out of 100 people), **infrequent** occurs in 1% to 10% of people (1 to 10 out of 100 people) and **rare** side effects occur in less than 1% of people (less than 1 out of 100 people).

You will receive only one of the following drugs:

Disulfiram (125 mg) is a FDA (Food and Drug Administration) approved drug used to discourage or prevent a person from drinking alcohol.

Likely - None.

Common - None

Infrequent - In the absence of alcohol, disulfiram during routine clinical use (125 to 500 mg per day) may cause transient and mild drowsiness, fatigue, impotence, headache, and metallic- or garlic-like aftertaste.

Rare - allergic dermatitis (inflammation or swelling of the skin with itching and redness), acneiform eruptions (disorder caused by inflammations of skin glands and hair follicles, resembles pimples).

When taken with alcohol, disulfiram causes several uncomfortable symptoms including flushing, difficult breathing, nausea, thirst, chest pain, palpitation (fluttering sensation in chest), vertigo (dizziness), hyperventilation (excessive rate and depth of breathing), tachycardia (rapid heart rate), vomiting, hypotension (low blood pressure), fainting and confusion. While taking disulfiram in this study and for two weeks after stopping disulfiram, no alcoholic beverages should be consumed. Subjects should also avoid other products containing alcohol such as over-the-counter cold relief products, mouthwashes, and baking extracts (e.g. vanilla extract).

Paroxetine (20 mg) is a FDA approved drug used to treat depression.

Likely - None

Common - Dizziness, headache, somnolence, insomnia.

Infrequent - Palpitations, flushing, restlessness, yawning, confusion, skin sensations (such as burning, itching, etc) with no apparent physical cause, nervousness, anxiety.

Rare: anemia, disturbances of blood clotting (nosebleed, rectal bleeding, subcutaneous bleeding), changes in blood cell count, arrhythmia, low blood pressure, psychomotor impairments, sleep disorders, involuntary trembling or quivering, seizures.

Patients with a major depressive disorder may experience worsening of their depression and/or the emergence of ideas of suicide and suicidal behavior. For this reason, if you have a diagnosis of a past or present history of depression, you will be excluded from the study. *Patients with migraine headaches treated with triptans together with paroxetine may cause a life-threatening condition called serotonin syndrome. The symptoms of serotonin syndrome may include restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overactive reflexes, nausea, vomiting, and diarrhea. For this reason, if you have a diagnosis of migraine headaches, and are taking a triptan medication, you will be excluded from the study.*

Rifampin (600 mg) is a FDA approved antibacterial drug used to treat certain infections such as tuberculosis or meningitis.

Likely - None

Common - None.

Infrequent - Reddish-orange to reddish-brown coloration of urine, stools, saliva, and tears, diarrhea, stomach cramps or upset.

Rare - Discoloration of soft contact lens, nausea, vomiting, reddish-orange to reddish-brown coloration of sweat, skin rash, and itching.

All subjects will receive the following drugs on day 2 and day 9

Flurbiprofen (50 mg) is a FDA (Food and Drug Administration) approved drug used to treat inflammation and pain. In the low single dose being used in this study, it is not expected to cause any significant effect.

Likely - None.

Common - None.

Infrequent - In some people who are taking it continuously for a long time, it has been shown to cause liver damage, indigestion, diarrhea, abdominal pain, nausea, constipation, gastrointestinal bleeding, flatulence (bloating from stomach gas) and vomiting.

Rare - In larger doses rare side effects such as amnesia (loss of memory), headache, nervousness with the potential for anxiety, insomnia (difficulty sleeping), tremor (shaking), somnolence (sleepiness) and malaise (a feeling of illness).

Mephenytoin (100 mg) is a FDA approved drug which has been used in the control of epileptic seizures. A relatively low dose will be given to minimize the side effect of drowsiness.

Likely - Mild drowsiness lasting 30 to 90 minutes.

Common - None.

Infrequent - Double vision, unsteadiness, fatigue, nausea, dizziness.

Rare - A small number of patients taking this drug for the treatment of seizures have had an irreversible reduced ability to make blood cells (called "aplastic anemia"), which could

be fatal. However, this has occurred after prolonged, sustained use at high doses. Fever and rash have also occurred with prolonged use. Because of the relatively small dose and low frequency of the use of mephenytoin in this study, serious side effects are not expected.

Mephenytoin causes abnormalities in the offspring of pregnant rodents and in epileptic women taking this therapy during early pregnancy; for this reason mephenytoin should not be given to pregnant women. A urine pregnancy test will be performed within 24 hours of receiving mephenytoin in all women of childbearing potential. However, although these and other rare side effects are always possible, they are considered unlikely.

Caffeine (100 mg) is a FDA approved drug which is present in coffee, tea, chocolate and many soft drink beverages. The amount of caffeine used in this study is equivalent to approximately 1-2 cups of coffee. If you are a regular caffeine user, the day after stopping intake of caffeine containing foods and beverages, you can expect to have a low grade headache and feel a bit low. We expect these symptoms to resolve as soon as you take caffeine as a tablet and then later resume your caffeine intake.

Likely - None.

Common - None.

Infrequent - Restlessness, excitement, nervousness, fast heart rate, and may also cause a small increase in your blood pressure.

Rare - Caffeine may also cause spontaneous abortion in women which is another reason why we will be performing pregnancy tests in women who participate in this study. Side effects other than those listed here may also occur.

Chlorzoxazone (250 mg) is a FDA approved drug that has been in use since 1958 to treat muscle spasms and pain. It is generally well tolerated and rarely produces undesirable side effects.

Likely - None

Common - None.

Infrequent - Drowsiness, dizziness and lightheadedness.

Rare - Chlorzoxazone has been shown to cause liver damage in a small number of patients on chronic therapy. Following repeated dosing (250 - 750 mg every 6 hours), other rare side effects including nausea, vomiting, rash, itching, heartburn, and diarrhea may occur. Chlorzoxazone may also cause your urine to turn orange or reddish-purple.

Debrisoquine (10 mg) is an investigational drug, not FDA approved, used to lower blood pressure.

Likely - None.

Common - None.

Infrequent - It is possible that your blood pressure might go too low after your dose is given, however this is rare with the small dose you will be taking. You may experience dizziness when standing up, this may last for up to 90 minutes. If these effects occurs,

lying down should correct the problem within four to six hours when the effects of the drug wear off.

Rare - In addition to the adverse events listed, there may be unforeseen reactions or even death associated with the use of any new drug or procedure. Because debrisoquine is an investigational drug, there may be other side effects that are still unknown at this time.

Dapsone (50 mg) is a FDA approved drug used to treat a variety of skin disorders

Likely: None

Common. Methemoglobinemia, a condition in which the iron in the hemoglobin molecule (the red blood pigment) is defective, making it unable to carry oxygen effectively to tissues. A sign of methemoglobinemia is cyanosis (bluish skin color). Methemoglobinemia is reversible and the effects on the hemoglobin molecule disappear after several hours. In severe cases, methemoglobinemia can be treated by giving a drug called methylene blue. Usually, methemoglobinemia with dapsone use does not cause any symptoms or require any treatment. However, dizziness, fatigue, headache, tachycardia (a heart rate that is faster than normal), and weakness may occur. In some cases, dyspnea (feeling short of breath), lethargy (feeling tired), and fainting may also occur.

Infrequent at high prolonged doses: nausea, vomiting, diarrhea, headache, dizziness and skin allergy.

Rare, during prolonged treatment: allergic reactions including liver damage and anemia (low blood count).

Midazolam (4 mg) is a drug usually used before surgery or certain medical tests to make the patient sleepy, drowsy, or relaxed. The dose used in this study is lower than the dose used before medical procedures. You will probably feel drowsy or sleepy for a few hours after midazolam is administered.

Likely - Drowsiness lasting 1 to 2 hours.

Common - None.

Infrequent - Hiccups, dizziness, confusion, headache, inability to remember events that occur within 8 hours after midazolam administration, slowing of response time and interference when operating automobiles or other machinery, dry mouth, light-headedness,- nausea, double vision, loss of coordination, and slurred speech. These usually occur after prolonged, sustained use of midazolam at high doses.

Rare - There is also a risk of apnea (stopping breathing temporarily) and death with midazolam. This is extremely rare and usually occurs with high doses given rapidly. This study will use low doses given slowly.

Midazolam may make you drowsy or dizzy for up to 2 days after you receive it. You should wait 24 hours or until the effects of the medicine have worn off (whichever is longer) before driving or using machinery. You should also not drink any alcohol or take any other sedative medications until two days after you received midazolam.

Six drug cocktail, when given together (Flurbiprofen, Mephenytoin, Caffeine,

Chlorzoxazone, Debrisoquine, Dapsone).

Likely- None

Common- Dizziness

Infrequent - Nausea, lightheadedness, and mild drowsiness.

The risks involved with this study also include those related to having an IV catheter placed and blood samples

Likely: Pain

Common: None

Infrequent: Bruising

Rare: Bleeding and infection.

There is a possibility that you may be allergic to one of the drugs used in this study. If you are allergic, a serious reaction including low blood pressure and difficulty breathing may occur. If this should happen, administration of medications called corticosteroids would reverse the reaction. As with any investigational study, there may be adverse events or side effects that are currently unknown and it is possible that certain of these unknown risks could be permanent, serious, or life-threatening.

It is important that you (for female participants) or your female sexual partner (for male participants) does not become pregnant during this research study. Avoiding sexual activity is the only certain method to prevent pregnancy. However, if you choose to be sexually active, you must agree to use an appropriate double barrier method of birth control (such as female use of a diaphragm, intrauterine device (IUD), or sponge and spermicide, in addition to the male use of a condom) or involve female use of prescribed "birth control pills" or a prescribed birth control implant. Both double barrier contraception and birth control pills or implants must be used for at least one week prior to the start of the research study and continuing for at least two weeks following the last study visit. If you are a female, there will be pregnancy tests (blood or urine) performed at each visit. If you choose to be sexually active during this study, you must accept the risk that pregnancy could still result, exposing you or your sexual partner to potential loss of pregnancy as well as other known effects on the developing fetus.

You will be under the observation and care of the investigators conducting the study following drug administration. You will remain on the Clinical Research Unit which is located at 8 North of Montefiore University Hospital for approximately 8 hours after dosing. The staff of the Clinical Research Unit has extensive experience conducting research studies and monitoring those subjects participating.

There is no direct personal benefit to you from this study. Information from the genetic material contained in the blood sample will not provide any immediate benefit to you since this genetic data cannot yet be interpreted or applied in a clinically relevant or meaningful manner. Study specimens (and associated subject information) that may be made available to secondary investigators will not include subject identifiers. Since there are no established links between the information obtained and possible genetic changes,

you will not be informed of the results of any gene testing. Should the genetic information become clinically relevant as a result of the availability of new strategies for the prevention or treatment of the respective disease, it will be provided to the subject. It is hoped that this study will help to explain the processes in the body that are responsible for the elimination of drugs and other chemicals. It may also help to develop a simple way to assess activity of these processes.

There is a potential for breach of confidentiality which could impact future insurability, employability, or reproduction plans, or have a negative impact on family relationships, and/or result in paternity suits or stigmatization.

As with any experimental procedure, there may be adverse events or side effects that are currently unknown, and certain of these unknown risks could be permanent, severe or life-threatening.

ALTERNATIVE APPROACHES: You can choose not to participate in this study.

NEW INFORMATION: You, or your representative, will be promptly notified if any new information develops during the course of this study which may cause you to change your mind about continuing to participate.

COSTS AND PAYMENTS: Participation in this study is voluntary. If you decide to participate in this study, you will not be billed or charged for any of the services, medications or procedures related to the study. The study will pay for all of the research services, medications, and procedures. Upon successful completion of the requirements of the study, you will be paid the sum of \$500 for your participation. If you decide to withdraw before finishing the study, or if you are withdrawn from the study by the investigators, you will be paid for the parts of the study completed. You will be paid \$200 for completion of the first overnight study visit (days 1 and 2), \$100 for completion of days 3 through 7, and \$200 for completion of the second overnight study visit (day 8 and 9).

Your blood sample mRNA used in this research study may contribute to a new invention or discovery. In some instances, these inventions or discoveries may be of commercial value and may be sold, patented, or licensed by the investigators and the University of Pittsburgh for use in other research or the development of new products.

If you agree to participate in this research study, you voluntarily and freely provide your blood sample and its mRNA to the investigators and the University of Pittsburgh. If you agree to participate in the research project, use of your biological sample and genetic material will be under the control of the principal investigator of this research project.

You will not retain any property rights to the blood sample and its MRNA, nor will you share in any money or other benefits that the investigators, the University of Pittsburgh,

or their agents may realize from the blood sample and its mRNA or their use in this research study. You retain the right to have your blood samples and its mRNA destroyed should you decide to withdraw from this research study.

CONFIDENTIALITY: Any information about you or your study participation will be treated as confidential as other hospital records. When the study results are published, you will be anonymous and/or your identity will not be revealed. Therefore, you consent to such publication for scientific purposes. Your participation in the study will involve the development of a medical chart. This record will be subject to all the regulation that medical charts are routinely subject to with respect to confidentiality of information. Your identity on donated samples and mRNA will be indicated by initials and a code number. The link between code number and your identifiers will be stored in a separate, secured place. The information obtained by the investigators will be maintained in a confidential filing system and secure database system. Access to the research records that will be maintained in a manner that may allow to link directly the research data with subject's identity will be password controlled. All records will be kept in a locked cabinet for a period of five years after the study has ended. You will not retain any property rights to the samples and its mRNA. The blood, urine and mRNA- obtained will be stored indefinitely in the laboratories of Dr. Romkes, who along with Principal Investigator will assume the overall responsibility for the control of the storage areas. Should you decide to withdraw from the study or should you be withdrawn from the study by investigators, the samples and mRNA will be continued to be stored with a linkage code to your identity. You will retain the right to have samples and its mRNA destroyed if you decide to withdraw from this research study. There is a possibility that if the results of the research studies involving the subjects genetic material become generally known this information could impact future insurability, employability, or reproduction plans, or have a negative impact on family relationships, or stigmatization.

This research study will involve the recording of current and future identifiable medical information from your hospital and other health care provider (e.g., physician office) records. The information that will be recorded will be limited to information concerning your physical status, symptoms, lab values and medication regimens. This information will be used for the purpose of investigation of regulation of activity and mRNA for the drug-metabolizing enzymes. This research study will result in identifiable information that will be placed into your medical records held at UPMC Presbyterian Hospital. The nature of the identifiable information resulting from your participation in this research study that will be recorded in your medical record includes your medical history, information on your physical examination, symptoms, laboratory tests and medications.

In addition to the investigators listed on the first page of this authorization (consent) form and their research staff, the following individuals will or may have access to identifiable information (which may include your identifiable medical record information) related to your participation in this research study:

- authorized representatives of the University of Pittsburgh Research Conduct and Compliance Office may review your identifiable research information (which may include your identifiable medical record information) for the purpose of monitoring the appropriate conduct of this research study
- in unusual cases, the investigators may be required to release identifiable information (which may include your identifiable medical record information) related to your participation in this research study in response to an order from a court of law. If the investigators learn that you or someone with whom you are involved is in serious danger or potential harm, they will need to inform, as required by Pennsylvania law, the appropriate agencies
- your research records may be inspected by appropriate government agencies or be released in response to an order from a court of law

Authorized representatives of the sponsor of this research study may review and/or obtain identifiable information (which may include your identifiable medical record information) related to your participation in this research study for the purpose of monitoring the accuracy and completeness of the research data and for performing required scientific analyses of the research data. Authorized representatives of the study sponsor may also be present during your participation in certain research procedures. While the study sponsor understands the importance of maintaining the confidentiality of your identifiable research and medical record information, the University of Pittsburgh Medical Center and University of Pittsburgh cannot guarantee the confidentiality of this information after it has been obtained by the study sponsor. The investigators involved in the conduct of this research study may receive funding from another sponsor to perform the research procedures and to provide the sponsor with identifiable research and medical record information related to your participation in the study.

Authorized representatives of the U.S. Food and Drug Administration may review and/or obtain identifiable information (which may include your identifiable medical record information) related to your participation in this research study for the purpose of monitoring the accuracy of the research data. While the U.S. Food and Drug Administration understands the importance of maintaining the confidentiality of your identifiable research and medical record information, the University of Pittsburgh and the University of Pittsburgh Medical Center cannot guarantee the confidentiality of this information after it has been obtained by the U.S. Food and Drug Administration. Authorized representatives of the University of Pittsburgh Medical Center hospitals or other affiliated health care providers may have access to identifiable information (which may include your identifiable medical record information) related to your participation in this research study for the purpose of (1) fulfilling orders, made by the investigators, for hospital and health care services (e.g., laboratory tests, diagnostic procedures) associated with research study participation; (2) addressing correct payment for tests and procedures ordered by the investigators; and/or (3) for internal hospital operations (i.e. quality assurance).

The investigators may continue to use and disclose, for the purposes described above, identifiable information (which may include your identifiable medical record information) related to your participation in this research study indefinitely. It is a University policy that all research records must be maintained for at least 5 years following study completion. In accordance with the University of Pittsburgh Medical Center Notices of Privacy Practices document that you have been provided, you are permitted access to information (including information resulting from your participation in this research study) contained within your medical records filed with your health care provider.

RIGHT TO WITHDRAW: Your participation in this research study, to include the use and disclosure of your identifiable information for the purposes described above, is completely voluntary. (Note, however, that if you do not provide your consent for the use and disclosure of your identifiable information for the purposes described above, you will not be allowed, in general, to participate in the research study.) Whether or not you provide your consent for participation in this research study will have no affect on your current or future relationship with the University of Pittsburgh. Whether or not you provide your consent for participation in this research study will have no affect on your current or future medical care at a University of Pittsburgh Medical Center hospital or affiliated health care provider or your current or future relationship with a health care insurance provider. Your doctor is involved as an investigator in this research study. As both your doctor and a research investigator, he is interested both in your medical care and the conduct of this research study. Before agreeing to participate in this research study, or at any time during your study participation, you may discuss your care with another doctor who is not associated with this research study. You are not under any obligation to participate in any research study offered by your doctor. You may withdraw, at any time, your consent for participation in this research study, to include the use and disclosure of your identifiable information for the purposes described above. (Note, however, that if you withdraw your consent for the use and disclosure of your identifiable information for the purposes described above, you will also be withdrawn, in general, from further participation in this research study.) Any identifiable research or medical record information recorded for, or resulting from, your participation in this research study prior to the date that you formally withdrew your consent may continue to be used and disclosed by the investigators for the purposes described above. To formally withdraw your consent for participation in this research study you should provide a written and dated notice of this decision-to the principal investigator of this research study at the address listed on the first page of this form. Your decision to withdraw your consent for participation in this research study will have no affect on your current or future relationship with the University of Pittsburgh. Your decision to withdraw your consent for participation in this research study will have no affect on your current or future medical care at a University of Pittsburgh Medical Center hospital or affiliated health care provider or your current or future relationship with a health care insurance provider. You may be removed from the research study by the investigators in the event

that you experience adverse events from this research study. Should you decide to withdraw from the study or should you be withdrawn from the study by investigators, the samples and mRNA will be continued to be stored with a linkage code to your identity. You will retain the right to have samples and its mRNA destroyed if you decide to withdraw from this research study.

COMPENSATION FOR INJURY: University of Pittsburgh investigators and their associates who provide services at the University of Pittsburgh Medical Center recognize the importance of your voluntary participation to their research studies. These individuals will make reasonable efforts to minimize, control, and treat any injuries that may arise as a result of this research.

If you believe that you are injured as the result of the research procedures being performed, immediately call the following number 412-565-8326. After hearing a beep, please dial the phone number including the area code in which you want to be reached. This phone number is the Emergency Beeper of the Center for Clinical Pharmacology and will be answered by one of the following investigators: Robert A. Branch, Howard Lee, Louise DeRiso, Yvonne Cannon or Amy Steele. Emergency medical treatment for injuries solely and directly related to your participation in this research will be provided to you by hospitals of the University of Pittsburgh Medical Center. It is possible that the University of Pittsburgh Medical Center may bill your insurance provider for the costs of this emergency treatment, but none of these costs will be charged directly to you. If your research-related injury requires medical care beyond this emergency treatment, you will be responsible for the costs of this follow-up care unless otherwise specifically stated. You will not receive monetary payment for, or associated with, any injury that you suffer in relation to this research.

IF YOU HAVE A QUESTION: If at any time in the study you wish to contact and discuss any aspect of the research study with investigators you may contact them at the phone numbers listed on the first page.

VOLUNTARY CONSENT:

The above information has been explained to me and all of my questions have been answered. I am encouraged to ask questions about any aspect of this research study during the course of this study. Any future questions I have about this research study will be answered by a qualified individual or by the investigator(s) listed on the first page of this consent document at the telephone number(s) given. I may always request that my questions be answered by a listed investigator. Any questions I have about my rights as a research subject will be answered by the Human Subject Protection Advocate of the IRB Office, University of Pittsburgh (866-212-2668). By signing this form I agree to participate in this research study.

