[INSERT SITE NAME]
Consent to Act as a Research Subject

A Phase 2 Randomized, Open-Label Study of RRx-001 vs Regorafenib in Subjects with Metastatic Colorectal Cancer
Protocol No. RRx001-21-02

INTRODUCTION:

[INSERT PI Name] and his colleagues are conducting a research study sponsored by EpicentRx Inc. to find out more about the experimental drug called RRx-001. You are being asked to take part because you have colorectal cancer.

Your participation in this research study is voluntary. The purpose of this Informed Consent Form is to inform you about the nature of this research study so that you may make an informed decision as to whether you would like to participate. If you have any questions, please ask your study doctor or coordinator to explain any words or information that you do not understand.

PURPOSE

The purpose of this study is to test the survival of subjects with advanced metastatic colorectal cancer that is not responsive (meaning standard treatments are not working), when given the investigational drug, RRx-001, compared to the standard drug, regorafenib.

This study is also being done to see how safe an investigational drug (RRx-001) is compared to the standard drug, regorafenib, and if it can resensitize your tumors, in other words make them susceptible again to treatments which you previously received, but failed.

The study has two stages of treatment: during the first stage you will be treated with either RRx-001 or regorafenib until your tumor(s) stop responding (disease progression). At this time you will enter the second stage and receive irinotecan, provided that you are well enough to receive it. When and if you progress on irinotecan, your participation in the study will end.

RRx-001 is a drug that selectively and temporarily changes the blood flow to tumors and increases the production and delivery of free radicals (unstable particles in your body). Both the changes in blood flow and increase in free radicals may help prevent the tumor from growing. It is believed RRx-001 selectively targets tissues with low levels of oxygen. Compared to healthy tissues that have higher levels of oxygen, tumor tissues have a low-oxygen environment. RRx-001 is then thought to deliver the free radicals to the cancerous tissue with the low oxygen, causing their targeted destruction without harming the healthy cells. Colorectal cancer is thought to be especially vulnerable to free radicals.

In addition to free radical delivery, RRx-001 has been found to activate the immune system to attack tumors, which sometimes makes it difficult to interpret the CT scans, since as you may

have seen if you've ever tried to "pop" a pimple, immune cells, which rush in to the area to repair the damage, cause inflammation and swelling that only gets better over time. What is true for pimples is also true for tumors: when inflammation occurs due to entry of immune cells the tumors may look angry and aggravated, as if they're worse, when, in fact, they're better. The longer the physician waits to scan the tumors, the greater the chance that he or she will see them when they're getting smaller, in the same way that it may take several weeks for a popped pimple to look less inflamed.

RRx-001, which is considered experimental because the FDA has not approved it, will be compared to an FDA approved drug called regorafenib. Regorafenib is a drug that has been approved by the FDA to treat colon cancer after previous chemotherapies have failed to be effective. Regorafenib blocks the cancer cells from growing.

Participation in this study is entirely voluntary. Approximately 190 subjects will take part in this study at [INSERT SITE] and up to ten (10) other sites in the US.

DURATION OF THE STUDY / HOW LONG IS EACH VISIT?

While you participate in this study, you may receive RRx-001, regorafenib (in Stage 1) or irinotecan (in Stage 2) for as long as your disease is not progressing and you can tolerate the treatment; study dosing will stop when your cancer progresses (gets worse), the side effects become unacceptable, the study ends, or you withdraw your consent; whichever comes first.

Each of your study visits should not last more than 8 hours.

PROCEDURES

The study will consist of 3 periods:

1) A Screening Period (up to 28 days before receiving your first dose of RRx-001 or regorafenib)

2) A Treatment Period, which will continue indefinitely until your cancer has progressed or you develop intolerable side effects. The Treatment Period will consist of two stages followed by the option to receive additional therapies:

   - 'Stage 1' – You will be randomly assigned to a study 'arm' and receive either RRx-001 or regorafenib
     - When your tumors progress during 'Stage 1,' the doctor will determine, based on your tumors and overall health, if you are eligible to enter 'Stage 2.'
   - 'Stage 2' – You will receive irinotecan.

   Each of these stages will continue indefinitely until your cancer has progressed or you develop intolerable side effects. If / when your tumor(s) progress during 'Stage 2', you will proceed to the "Post-treatment Survival Follow-Up Period".

3) A Post-treatment Survival Follow-Up Period. During the post-dosing follow-up phase, which will begin after discontinuation of RRx-001, regorafenib or irinotecan, you will be observed to see how you are feeling and any subsequent anti-cancer therapies that you receive. This post-treatment survival phase will continue until you withdraw consent, or the study ends, whichever occurs first.

STUDY PROCEDURES

Screening Period

The Screening Period will last approximately 28 days. If you agree to be in this research study, you will be asked to sign this consent form before the following screening procedures are performed to determine if you are eligible for the study. These screening tests may be performed over multiple days and can take between 4 and 8 hours to complete.

- A physical examination.
- An occupational, family, social and medical history which will include questions about your cancer diagnosis and treatment as well as your health and any past or present medical problems and a review of medications, vitamins, and dietary supplements you have taken in the past or are taking now.
- Your physician will administer a questionnaire called Edmonton Symptom Assessment System (revised) (ESASr). This questionnaire reviews nine symptoms common in patients with advanced cancer: pain, tiredness, nausea, depression, anxiety, drowsiness, appetite, wellbeing and shortness of breath, (there is also a line labeled "Other Problem"). The severity of each symptom is rated from 0 to 10 on a numerical scale, 0 meaning that the symptom is absent and 10 meaning that it is the worst. The ESASr will provide your physician with the framework or context to follow how severe your symptoms are over time. If your symptoms get worse, possibly indicating that the tumor is not responding to treatment, the doctor or study team may schedule an earlier imaging scan (i.e., CT or MRI) of your tumor before the scheduled twelve (12) week scan.
- Measurement of your height, weight and vital signs (including sitting blood pressure, heart rate, breathing rate and oral temperature).
- A urine sample for standard urine analysis
- Approximately 2 teaspoons of blood will be taken to check your overall health and the health of your organs (i.e. liver and kidneys). The blood will be collected from a vein in your arm.
- Approximately 2 teaspoons of blood will be taken to examine and analyze the genes and proteins of circulating tumor cells. The blood will be collected from a vein in your arm
- A pregnancy test if you are female and able to get pregnant. You must have a negative pregnancy test to enter this study and receive RRx-001 or regorafenib. Women, or men

whose partner is of child bearing potential will be asked to continue the use of non-hormonal methods of birth control while in the study and for up to 30 days after withdrawal from the study.

- CT or MRI imaging of your tumor(s).
    - The CT scanner is a free-standing machine with a large hole in the center. You will be asked to lie on your back with your arms raised above your head on a narrow table that slides into the hole. Subjects who have difficulty with enclosed spaces such as those found with some MRI scanners do not usually have a problem with this type of test. A dye may be injected into a peripheral vein (veins in the arms, feet, legs and hands that supply oxygenated blood to the body) to better evaluate certain diseases and organs. The radiologist will decide if this is necessary. Tell the technician or radiologist if you have any allergies to contrast dye or have had difficulty with prior CT scans. It is very important that you remain still throughout the exam and hold your breath when asked. This will allow for better images. The actual scan time is usually about two minutes, although the entire procedure may take up to 2 hours.
    - Magnetic Resonance Imaging (MRI) may be done to measure your tumor. This will involve lying still inside the center of a large, doughnut-shaped magnet for approximately 30-60 minutes.
    - During Stage 1 (treatment with RRx-001 or regorafenib), the imaging of your tumor(s) will be performed at twelve (12) weeks instead of the normal eight (8) weeks.
        - It is believed that RRx-001 works in part by recruiting immune cells to attack the inside or center of the tumors, which is sometimes really confusing to interpret on CT scans because all of the swelling and dead cell debris in the middle contributes to the impression that these tumors are much larger even though, technically speaking, they really aren't. The situation is similar to the phrase that you might have read before on the passenger car mirror of practically every modern car: "objects in the mirror are closer than they appear"; in the same way, physicians may misjudge the actual size of the RRx-001-treated tumors and make the decision to stop treatment even though the tumors haven't actually progressed. The word for tumors that change their appearance over time, first flaring up before becoming smaller is "pseudoprogression", with the first part, "pseudo", meaning false and the second part, "progression", meaning worsening. Since it takes time for the tumor to shrink and the appearance of 'false worsening' or pseudoprogression to improve, the imaging has been postponed from 8 weeks to 12 weeks on the basis that the longer the time between scans the greater the chance that the tumors will look smaller, if pseudoprogression is really taking place. Just in case 12 weeks is not enough time to tell the difference between true progression and pseudoprogression, the physician may decide to keep you

on RRx-001 for another 4 weeks before rescanning. If at this time (16 weeks) the tumors don't look any better or have even grown past a certain size limit, then your physician is required to stop or discontinue RRx-001 and re-start irinotecan therapy.

- 3-D (Dimensional) Contrast Enhanced Ultrasound (CEUS) is a procedure that observes the blood flow in a particular region of interest, in this case liver masses or metastases. Practically, CEUS consists of an injection of a microbubbles (small organic bubbles smaller than 1mm in size), prepared at the time of use, at the bedside, into a vein in the arm. This is followed by an injection of saline solution. These microbubbles, which travel through the whole body, eventually reaching the vessels of the tumor, irregularly reflect the ultrasound 'echoes' to form (with the help of a computer processor) 3-D images of the flow of blood through the tumor blood vessels. All the while the liver mass or metastasis is continuously observed on the monitor. There are very few risks practically speaking, so the injection of microbubbles can be repeated as often as needed. **This procedure is limited to RRx-001-treated subjects at Stanford University** with imageable liver metastases and will be performed *on selected subjects only* at the following timepoints:

    - Cycle 1 Day 1, both before and after dosing with RRx-001
    - Cycle 1 Day 8 before RRx-001 dosing
    - Cycle 1 Day 22 before RRx-001 dosing
    - Cycle 2 Day 22 both before and after RRx-001 dosing
    - At least 1 week after the start of irinotecan dosing

    Each imaging session will last approximately from 20 min to 1 hour. The purpose of 3-D CEUS is to both follow response to treatment and to learn whether blood flow to liver metastases may predict response to treatment.

- You will be asked to complete a Quality of Life (QOL) Questionnaire. This questionnaire may take between 10 to 15 minutes to complete.

Screening procedures for RRx-001 Patients only: If you are randomized (randomly assigned) to receive RRx-001 during the first (1st) stage of treatment, the following procedures will be performed:

- FDG-PET will be done only if you are assigned (randomized) to the RRx-001 'arm.' This is the same as a CT scan (see above) except that a different type of dye is used to make it easier to 'see' your tumor(s).

- Tumor biopsy - you will most likely be scheduled to have a sample of your tumor(s) collected (biopsy) unless you have a previous sample that can be collected. This sample will be sent to a lab and studied to better understand your tumor(s).

Optional Procedures to be conducted during the study:

- Approximately 2 teaspoons of blood will be taken to test for biomarkers. Biomarkers are proteins in your blood and tissue that can be measured to assess your disease and your body's response to the study drug. This blood collection will be used for research. This procedure is optional.

_____ **Yes,** you give permission to take part in these optional procedure.

_____ **No,** you do **not** give permission to take part in these optional procedure.

_____ _____
Signature of Participant Date

- With your consent, small pieces of cancer tissue will be removed by either by surgery or by a needle before treatment with RRx-001 and after four (4) weeks of treatment with RRx-001. The research biopsy is done in a similar way to biopsies done for diagnosis. The sample will be analyzed for different biomarkers to measure response to treatment.

- Common side effects of a biopsy are a small amount of bleeding at the time of the procedure, pain at the biopsy site, which can be treated with regular pain medications, and bruising. Rarely, an infection can occur. This procedure is optional.

_____ **Yes,** you give permission to take part in these optional biopsy procedures.

_____ **No,** you do **not** give permission to take part in these optional biopsy procedures.

_____ _____
Signature of Participant Date

TREATMENT PERIOD

If the exams, tests and procedures show that you can be in the study and you choose to take part, then you will be "randomized" into one of the study groups detailed below. Randomization means that you are put into a group by chance. A computer program will place you in one of the study groups. Neither you, your doctor, nor the study sponsor can choose the group you will be in. You will have a 66% chance (2 out of 3) of receiving RRx-001 and a 33 % chance (1 out of 3) of receiving regorafenib. Whether you are given RRx-001 or regorafenib, you will also receive best supportive care, which includes treatments to help manage side effects and symptoms of cancer. This is an open label study, which means you will know to which group you are assigned.

You will be scheduled to return to the study site for the Day 1 visit of the first (1st) stage of the Treatment Period. Additional study visits will occur for the RRx-001 subjects weekly. For the Regorafenib patients, additional study visits will occur every 2 weeks. You will be asked to continue the use of non-hormonal methods of birth control and to return to all required clinic visits during the entire Treatment Period of study.

RRx-001 Group

During Stage 1, if you are assigned to the RRx-001 group, you will be given the study drug once a week at a dose of 4 mg RRx-001 will be given to you while you are in the clinic through a vein in your arm over a period that will not be longer than 4 hours from the time that blood is withdrawn from a vein in your body. Approximately 30 minutes before the infusion, you will receive pre-medications such as dexamethasone, a corticosteroid, to help with any pain associated with the infusion. Sometimes it may be necessary to slow down the infusion and administer RRx-001 over a longer time. Based on any side effects you are experiencing, you and the Doctor will have the option to split the dose and deliver it on two separate days during the same week.

Regorafenib Group

If you are assigned to the regorafenib group, you will receive the regorafenib pills with instructions to take four 40mg pills (160mg) by mouth once daily on Days 1 through 21 of each cycle. You should take the Regorafenib pill with a low fat (less than 30%) meal. On Days 22 through 28 you will not take any regorafenib pills. Each cycle is 28 days long. The dose of regorafenib that you take throughout the study may be continued, modified or interrupted according to treatment guidelines. You will be asked to complete a form called a 'Dose Diary' that records the time, day and number of tablets of regorafenib that you took and bring it with you when you come to the clinic. Typically, you will be asked to come to the clinic every two weeks during Stage 1.

Study Procedures – Stage 1

Day 1 (±1 day), Cycle 1, Stage 1

After you've completed the Screening Period, which will last approximately twenty-eight (28) days, you will be scheduled to return to the clinic for your first day of treatment with RRx-001 or regorafenib as part of Stage 1 of the Treatment Period. Each cycle is 4 weeks long. The study staff will discuss with you the scheduling of this visit, based upon how long it takes to complete all the Screening Procedures. The following tests and procedures will be performed:

- You will be asked to complete a Quality Of Life (QOL) Questionnaire
- A physical exam and measurement of your height, weight and vital signs (to include your sitting blood pressure, heart rate, breathing rate and oral temperature).
- An ESASr will be performed unless one was performed in the 48 hours prior to C1D1, as a part of screening.
- You will be asked about the medications you are currently taking ('Concomitant Medications') and any side effects you are experiencing.
- Approximately 2 teaspoons of blood will be taken to check your overall health and the health of your organs (i.e. liver and kidneys).
- Approximately 2 teaspoons of blood will be taken to examine and analyze the genes and proteins of circulating tumor cells. The blood will be collected from a vein in your arm
- A pregnancy test if you are a woman and able to get pregnant.
- If you are taking regorafenib, it will be dispensed to you on a monthly basis and you will receive instructions when and how often to take it. You will be asked to keep a diary of all the pills you take daily and to bring back the bottle of regorafenib pills with you to each clinic visit for a pill count by the clinic staff.
- Contrast Enhanced Ultrasound (CEUS) may be performed before and after dosing to measure the blood flow of your liver metastases provided: 1) you are at Stanford 2) you are receiving RRx-001 and 3) in the opinion of the doctor you are a good candidate.
- If you are receiving RRx-001, your doctor will administer pre-medications, such as dexamethasone, a corticosteroid (anti-inflammatory medications), approximately 30 minutes prior to RRx-001 administration. RRx-001 will be administered to you in the following way: 100 milliliters (mLs) or approximately 14 tablespoons will be removed from a vein in your arm or chest and collected in a bag. From there, a specific amount of RRx-001 (4 mg) is mixed with the collected blood. Afterward, the RRx-001 + blood mixture is re-injected back into a vein in the chest or the arm over a time period that will not be longer than 4 hours from the time that the 100 mLs of blood was first removed. Schedule your next visit to the clinic.

Day 8 (±1 day), Cycle 1, Stage 1

The day that you return to the clinic for your second (2nd) treatment with RRx-001 during Stage 1 is called Cycle 1, Day 8. At this visit the Doctor and/or study staff will do the following:

- Ask you about any side effects you are experiencing
- Contrast Enhanced Ultrasound (CEUS) may be performed before dosing to measure the blood flow of your liver metastases provided: 1) you are at Stanford 2) you are receiving RRx-001 and 3) in the opinion of the doctor you are a good candidate.
- If you are receiving RRx-001, your doctor will administer pre-medications, such as dexamethasone, a corticosteroid (anti-inflammatory medications), approximately 30 minutes prior to RRx-001 + blood administration.
- Schedule your next visit to the clinic.

Day 15 (±1 day), Cycle 1, Stage 1

The day that you return to the clinic for your third (3rd) treatment with RRx-001, or for the second (2nd) time if you are receiving regorafenib in Stage 1 is called Cycle 1, Day 15. The Doctor and/or study staff will do the following at this visit:

- You will be asked to complete a Quality Of Life (QOL) Questionnaire
- A physical exam and measurement of your height, weight and vital signs (to include your sitting blood pressure, heart rate, breathing rate and oral temperature).
- An ESASr assessment will be performed.
- You will be asked about the medications you are taking now ('Concomitant Medications') and any side effects you are experiencing.
- Approximately 2 teaspoons of blood will be taken to check your overall health and the health of your organs (i.e. liver and kidneys). This blood will be collected from a vein in your arm.
- Approximately 2 teaspoons of blood will be taken to examine and analyze the genes and proteins of circulating tumor cells. The blood will be collected from a vein in your arm.
- If you are taking regorafenib, you will be asked to keep a diary of all the pills you take daily and to bring back the bottle of regorafenib pills and the diary with you at this clinic visit for a pill count by the clinic staff.
- If you are receiving RRx-001, your doctor will administer pre-medications approximately

30 minutes prior to RRx-001 + blood administration. Schedule your next visit to the clinic.

Day 22 (±1 day), Cycle 1, Stage 1

The day that you return to the clinic for your fourth (4th) treatment with RRx-001 in Stage 1 is called Cycle 1, Day 22. This will be your last visit in the first (1st) four-week cycle. The Doctor and/or study staff will do the following at this visit:

- Ask you about any side effects you are experiencing.
- Contrast Enhanced Ultrasound (CEUS) may be performed before dosing to measure the blood flow of your liver metastases provided: 1) you are at Stanford 2) you are receiving RRx-001 and 3) in the opinion of the doctor you are a good candidate.
- If you are receiving RRx-001, your doctor will administer pre-medications approximately 30 minutes prior to RRx-001 + blood administration. Schedule your next visit to the clinic.
- If you have given consent, you will be scheduled to have a sample (biopsy) taken of your tumor(s). This procedure is optional and is being done for research.

Day 1 (±1 day), Cycle 2, Stage 1

Like Cycle 1, above, Cycle 2 is also 4 weeks The day that you return to the clinic for your fifth (5th) treatment with RRx-001, or for the third (3rd) time if you are receiving regorafenib, in Stage 1 is called Cycle 2, Day 1. The Doctor and/or study staff will do the following at this visit:

- You will be asked to complete a Quality Of Life (QOL) Questionnaire
- A physical exam and measurement of your height, weight and vital signs (to include your sitting blood pressure, heart rate, breathing rate and oral temperature).
- An ESASr assessment will be performed.
- You will be asked about the medications you are taking now ('Concomitant Medications') and any side effects you are experiencing.
- Approximately 2 teaspoons of blood will be taken to check your overall health and the health of your organs (i.e. liver and kidneys). This blood will be collected from a vein in your arm.
- Approximately 2 teaspoons of blood will be collected to examine and analyze the genes and proteins of circulating tumor cells. The blood will be collected from a vein in your arm
- Approximately 2 teaspoons of blood will be collected from a vein in your arm to test for certain exploratory indicators, or 'biomarkers.' This blood collection will be used for research.

- If you are taking regorafenib, it will most likely be dispensed to at this visit (based on your insurance) and you will receive instructions when and how often to take it. You will be asked to bring the prior bottle of regorafenib pills, and your dosing diary with you to this clinic visit for a pill count by the clinic staff.

- If you are receiving RRx-001, your doctor will administer pre-medications approximately 30 minutes prior to RRx-001 + blood administration. Schedule your next visit to the clinic.

Day 8 (±1 day), Cycle 2, Stage 1

The day that you return to the clinic for your sixth (6^{th}) treatment with RRx-001 in Stage 1 is called Cycle 2, Day 8. The Doctor and/or study staff will do the following at this visit:

- Ask about side effects you are experiencing

- If you are receiving RRx-001, your doctor will administer pre-medications approximately 30 minutes prior to RRx-001 + blood administration. Schedule your next visit to the clinic.

Day 15 (±1 day), Cycle 2, Stage 1

The day that you return to the clinic for your seventh (7^{th}) treatment with RRx-001, or for the fourth (4^{th}) time if you are receiving regorafenib in Stage 1, is called Cycle 2, Day 15. The Doctor and/or study staff will do the following at this visit:

- You will be asked to complete a Quality Of Life (QOL) Questionnaire
- A physical exam and measurement of your height, weight and vital signs (to include your sitting blood pressure, heart rate, breathing rate and oral temperature).
- An ESASr assessment will be performed.

- You will be asked about the medications you are taking now ('Concomitant Medications') and any side effects you are experiencing.

- Approximately 2 teaspoons of blood will be taken to check your overall health and the health of your organs (i.e. liver and kidneys). The blood will be collected from a vein in your arm.
- Approximately 2 teaspoons of blood will be taken to examine and analyze the genes and proteins of circulating tumor cells. The blood will be collected from a vein in your arm

- If you are taking regorafenib, you will be asked to bring back the 'Dosing Diary' of all the pills you take daily, along with the bottle of regorafenib pills, with you to this clinic visit for a pill count by the clinic staff.

- If you are receiving RRx-001, your doctor will administer pre-medications approximately 30 minutes prior to RRx-001 + blood administration. Schedule your next visit to the clinic.

Day 22 (±1 day), Cycle 2, Stage 1

The day that you return to the clinic for your eighth (8^{th}) treatment with RRx-001 in Stage 1, is called Cycle 2, Day 1. This will be your last visit in the second (2^{nd}) four-week cycle. The Doctor and/or study staff will do the following at this visit:

- Ask you about any side effects you are experiencing.
- Contrast Enhanced Ultrasound (CEUS) may be performed before and after dosing to measure the blood flow of your liver metastases provided: 1) you are at Stanford 2) you are receiving RRx-001 and 3) in the opinion of the doctor you are a good candidate.
- If you are receiving RRx-001, your doctor will administer pre-medications approximately 30 minutes prior to RRx-001 + blood administration. Schedule for you to receive a CT or MRI scan (see below).

Day 1 (±1 day), Cycle 3, Stage 1

The day that you return to the clinic for your ninth (9^{th}) treatment with RRx-001, or for the fifth (5^{th}) time if you are receiving regorafenib in Stage 1 is called Cycle 3, Day 1. The Doctor and/or study staff will do the following at this visit:

- You will be asked to complete a Quality Of Life (QOL) Questionnaire
- A physical exam and measurement of your height, weight and vital signs (to include your sitting blood pressure, heart rate, breathing rate and oral temperature).
- An ESASr assessment will be performed.
- You will be asked about the medications you are currently taking ('Concomitant Medications') and any side effects you are experiencing.
- Approximately 2 teaspoons of blood will be taken to check your overall health and the health of your organs (i.e. liver and kidneys).
- Approximately 2 teaspoons of blood will be taken to examine and analyze the genes and proteins of circulating tumor cells. The blood will be collected from a vein in your arm
- If you are taking regorafenib, it will be dispensed to you at this visit. You will be asked to keep a diary of all the pills you take daily and to bring back the bottle of regorafenib pills with you to each clinic visit for a pill count by the clinic staff.
- If you are receiving RRx-001, your doctor will administer pre-medications approximately 30 minutes prior to RRx-001 + blood administration.

Day 8 (±1 day), Cycle 3, Stage 1

The day that you return to the clinic for your tenth (10th) treatment with RRx-001 during Stage 1 is called Cycle 3, Day 8. At this visit the Doctor and/or study staff will do the following:

- Ask you about any side effects you are experiencing
- If you are receiving RRx-001, your doctor will administer pre-medications, such as dexamethasone, a corticosteroid (anti-inflammatory medications), approximately 30 minutes prior to RRx-001 + blood administration.
- Schedule your next visit to the clinic.

Day 15 (±1 day), Cycle 3, Stage 1

The day that you return to the clinic for your eleventh (11th) treatment with RRx-001, or for the sixth (6th) time if you are receiving regorafenib in Stage 1 is called Cycle 3, Day 15. The Doctor and/or study staff will do the following at this visit:

- You will be asked about the medications you are taking now ('Concomitant Medications') and any side effects you are experiencing.
- If you are taking regorafenib, you will be asked to keep a diary of all the pills you take daily and to bring back the bottle of regorafenib pills and the diary with you at this clinic visit for a pill count by the clinic staff.
- If you are receiving RRx-001, your doctor will administer pre-medications approximately 30 minutes prior to RRx-001 + blood administration.
- Schedule your next visit to the clinic.

Day 22 (±1 day), Cycle 3, Stage 1

The day that you return to the clinic for your twelfth (12th) treatment with RRx-001, or for the seventh (7th) time if you are receiving regorafenib in Stage 1 is called Cycle 3, Day 22. This will be your last visit in the third (3rd) four-week cycle. The Doctor and/or study staff will do the following at this visit:

- Ask you about any side effects you are experiencing.
- CT or MRI imaging of your tumor(s) (for both RRx-001 and regorafenib patients)
    - Depending on the results of this scan, you may have a second "confirmatory" scan performed four (4) weeks later as part of Cycle 4, Day 22
- If you are receiving RRx-001, your doctor will administer pre-medications approximately 30 minutes prior to RRx-001 + blood administration.

- Schedule your next visit to the clinic.

Day 1 (±1 day), Cycle 4, Stage 1

The day that you return to the clinic for your thirteenth (13th) treatment with RRx-001, or for the eighth (8th) time if you are receiving regorafenib, in Stage 1 is called Cycle 4, Day 1. The Doctor and/or study staff will do the following at this visit:

- You will be asked to complete a Quality Of Life (QOL) Questionnaire
- A physical exam and measurement of your height, weight and vital signs (to include your sitting blood pressure, heart rate, breathing rate and oral temperature).
- An ESASr assessment will be performed.
- You will be asked about the medications you are taking now ('Concomitant Medications') and any side effects you are experiencing.
- Approximately 2 teaspoons of blood will be taken to check your overall health and the health of your organs (i.e. liver and kidneys). This blood will be collected from a vein in your arm.
- Approximately 2 teaspoons of blood will be collected to examine and analyze the genes and proteins of circulating tumor cells. The blood will be collected from a vein in your arm
- Approximately 2 teaspoons of blood will be collected from a vein in your arm to test for certain exploratory indicators, or 'biomarkers.' This blood collection will be used for research.
- If you are taking regorafenib, it will most likely be dispensed to at this visit (based on your insurance) and you will receive instructions when and how often to take it. You will be asked to bring the prior bottle of regorafenib pills, and your dosing diary with you to this clinic visit for a pill count by the clinic staff.
- If you are receiving RRx-001, your doctor will administer pre-medications approximately 30 minutes prior to RRx-001 + blood administration. Schedule your next visit to the clinic.

Day 8 (±1 day), Cycle 4, Stage 1

The day that you return to the clinic for your fourteenth (14th) treatment with RRx-001 in Stage 1 is called Cycle 4, Day 8. The Doctor and/or study staff will do the following at this visit:

- Ask about side effects you are experiencing
- If you are receiving RRx-001, your doctor will administer pre-medications approximately 30 minutes prior to RRx-001 + blood administration. Schedule your next visit to the clinic.

Day 15 (±1 day), Cycle 4, Stage 1

The day that you return to the clinic for your fifteenth (15^{th}) treatment with RRx-001, or for the ninth (9^{th}) time if you are receiving regorafenib in Stage 1, is called Cycle 4, Day 15. The Doctor and/or study staff will do the following at this visit:

- You will be asked about the medications you are taking now ('Concomitant Medications') and any side effects you are experiencing.
- If you are taking regorafenib, you will be asked to bring back the 'Dosing Diary' of all the pills you take daily, along with the bottle of regorafenib pills, with you to this clinic visit for a pill count by the clinic staff.
- If you are receiving RRx-001, your doctor will administer pre-medications approximately 30 minutes prior to RRx-001 + blood administration. Schedule your next visit to the clinic.

Day 22 (±1 day), Cycle 4, Stage 1

The day that you return to the clinic for your sixteenth (16^{th}) treatment with RRx-00, or for the tenth (10^{th}) time if you are receiving regorafenib in Stage 1 is called Cycle 4, Day 1. This will be your last visit in the fourth (4^{th}) four-week cycle. The Doctor and/or study staff will do the following at this visit:

- Ask you about any side effects you are experiencing.
- If you are receiving RRx-001, your doctor will administer pre-medications approximately 30 minutes prior to RRx-001 + blood administration. Schedule for you to receive a CT or MRI scan (see below).

Prior to the start of Cycle five (5), your doctor will order a CT or MRI "confirmatory scan" if your prior scan, at Cycle 3, Day 22, showed that your tumor(s) are progressing (growing larger).

If the tumor is stable (hasn't grown bigger and/or spread) or has decreased in size then you may remain on the study in Stage 1 and continue to receive RRx-001 or regorafenib; whichever treatment you were randomized (assigned to). All future visits will be nearly the same as the first four (4) cycles (above).

Progressive Disease Study Procedures:

If the scan shows that your tumor(s) has gotten larger in size, or is spreading, then you will be scheduled to return to the clinic to determine if, based on your overall health, you are eligible to enter '**Stage 2' of the treatment period**. At this visit, the Doctor and/or study staff will do the following:

- A physical exam and measurement of your height, weight and vital signs (to include your sitting blood pressure, heart rate, breathing rate and oral temperature).

- You will be asked about the medications you are taking now ('Concomitant Medications') and any side effects you are experiencing.
- Approximately 2 teaspoons of blood will be collected from a vein in your arm to test for certain exploratory indicators, or 'biomarkers.' This will be done for research.
- A pregnancy test if you are a woman and able to get pregnant.
- FDG-PET (for RRx-001 patients only)
    - FDG-PET will be done only if you are assigned (randomized) to the RRx-001 'arm.' This is the same as a CT scan except that a different type of dye is used to make it easier to 'see' your tumor(s).
- Schedule your next visit to the clinic to **start Stage 2 of the Treatment Period** (if applicable).

Study Procedures – Stage 2:

Irinotecan + bevacizumab (Stage 2)

During the second (2^{nd}) stage of the Treatment Period (known as 'Stage 2'), you will receive irinotecan 180 mg/m^2 given intravenously over 30-90 min infusion every two (2) weeks until your cancer is no longer responding. The Doctor will determine, based on your best interest and any side effects you are experiencing, the dose (how much) and frequency (how often) for this treatment. Like Stage 1 above, each cycle is 4 weeks (28 days) long, and you will receive best supportive care in addition to having imaging scans (CT or MRI) of your tumors done every two (2) cycles (or 8 weeks). Laboratory blood draws will be performed every two (2) weeks for the first eight (8) weeks and then every 4 weeks thereafter to test for your overall health and the health of your cells and your organs (i.e. liver and kidneys) as well as the level of the CEA biomarker. Approximately 2 teaspoons of blood will be collected from a vein in your arm. In addition, a quality of life questionnaire is required at each visit—to be filled out before the start of treatment. At each visit you will also be asked about other medications you are taking (concomitant medications) and any side effects you are experiencing.

For patients assigned to the RRx-001 treatment 'arm,' a PET-CT will also be performed during the first imaging study during treatment with irinotecan + bevacizumab as part of 'Stage 2.'

Contrast Enhanced Ultrasound (CEUS) may be performed after the first week of dosing with irinotecan to measure the blood flow of your liver metastases provided: 1) you are at Stanford 2) you have previously received RRx-001 and 3) in the opinion of the doctor you are a good candidate.

If you and doctor decide that it is no longer in your best interest to continue to receive treatment, or you discontinue the study for any reason, you will be asked to return to the study site (clinic) for the Off-Study Visit. At this visit you the clinic staff will perform assessments based on the institutions best standard of supportive care. An imaging study, such as an MRI, FDG-PET or CT scan may be performed as well.

Post-Treatment Survival Follow-up Period:

After your last treatment with RRx-001, regorafenib, or irinotecan + bevacizumab, you will be followed every eight (8) weeks until you are unable to be followed or withdraw your consent in writing, as described below on page 14. During this period, the clinic staff will check to see what additional treatments you are receiving and may contact you by phone or in person as well.

General Discussion of Genetics

EpicentRx Inc. will be responsible for deciding how your samples will be used. Blood and tissue taken from you may be used to establish products that could be patented and licensed. There are no plans to provide you with financial compensation should this occur. This blood and tissue and its derivatives may have significant therapeutic or commercial value. You consent to such uses. Your study doctor has no personal or financial interest in this research. If you decide later that you do not want the specimens collected from you to be used for future research, you may tell this to [INSERT PI], who will use his or her best efforts to stop any additional studies. However, in some cases, such as if your specimens have already undergone testing, it may be impossible to locate and remove the data collected from those tests because the data collection is no longer linked to you directly.

EpicentRx Inc. will be responsible, have control over the long-term storage location and will keep your DNA specimen and/or the information derived from it indefinitely.

There will be no direct benefit to you from this study since you will not be provided with any results or information regarding your DNA test. The investigator, however, may learn more about colon cancer.

Instances are known in which a subject in research has been required to furnish genetic information as a precondition for in applying for health insurance and/or a job. Participation in this study does not mean that you have had genetic testing. Genetic testing means having a test performed and the results provided to you and your doctor. If you are interested in having genetic testing performed you should consult your doctor, as some commercial tests are available. Your doctor can provide you with the necessary information to determine if such a test would be appropriate for you.

Some people involved in genetic studies have felt anxious about the possibility of carrying an altered gene that they could possibly pass on to their children. Even though we will do our best to keep your information confidential, there is the possibility that your genetic risk for certain diseases is accidently divulged to the wrong source, if that happens you might be discriminated against obtaining life or health insurance, employment or ability to adopt children.

Federal and State laws generally make it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:

a) Health insurance companies and group health plans may not request your genetic information that we get from this research.

b) Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.

c) Employers with 5 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

Be aware that these laws **do not** protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

RISKS OF PARTICIPATION

Participation in this study may involve some added risks or discomforts. While you are on this study, you are at risk for the side effects listed below. You should discuss these with your doctor. There may also be other side effects that we cannot predict. Other drugs will be given to make side effects less serious and uncomfortable. Many side effects go away shortly after the study drug is stopped, but in some cases, side effects may be serious, long lasting, and may even cause death.

There may be other risks associated with participation in this study that are currently unforeseeable.

In the initial clinical trial of RRx-001 in which 25 patients with various different types of cancers, including colorectal cancer, received RRx-001 intravenously, the main side effect in 84% of patients was temporary pain and/or a stinging, burning sensation at the injection site in the forearm and along the length of the vein as well as swollen veins (vasodilation). Pain and swollen veins, when they occurred, lasted during the entire time of infusion of RRx-001 and, generally, both of these side effects went away almost immediately (within minutes) of stopping the infusion of RRx-001.

Your doctor has several methods to manage and control the pain, should it occur. These methods include:

- Administering pain relievers before and during the infusion, including ibuprofen, corticosteroids (anti-inflammatory medications) and narcotics.
- Slowing down the infusion.

Other common side effects (≥10%) observed in the initial study, many of which may have been related to the pain at the injection site or the medications used to control it, included:

- Arm swelling (reported in 8/25 patients; 32%)
- Vein hardening (reported in 7/25 patients; 28%)
- Shortness of breath (reported in 5/25 patients; 20%)

- Mouth tingling/burning (reported in 4/25 patients; 16%)
- Anxiety (reported in 3/25 patients; 12%)
- Chest discomfort (reported in 3/25 patients; 12%)
- Cough (reported in 3/25 patients; 12%)
- Fatigue (reported in 3/25 patients; 12%)
- Skin discoloration (reported in 3/25 patients; 12%)

Less common side effects (<10%) observed in the initial study, many of which may have been related to the pain at the injection site or the medications used to control it, included:

- Flushing (reported in 2/25 patients; 8%)
- Throat discomfort (reported in 2/25 patients; 8%)
- Vein swelling (vasodilation) (reported in 2/25 patients; 8%)
- Vein blockage (reported in 2/25 patients; 8%)
- Weakness (reported in 2/25 patients; 8%)

Rare side effects (<5%) observed in 1 out of 25 patients in the initial study, many of which may have been related to the pain at the injection site or the medications used to control it, included:

- Abdominal pain (reported in 1/25 patients; 4%)
- Hand numbness (reported in 1/25 patients; 4%)
- Bloody mucus (reported in 1/25 patients; 4%)
- Decreased respirations (reported in 1/25 patients; 4%)
- Dizziness (reported in 1/25 patients; 4%)
- High blood pressure (reported in 1/25 patients; 4%)
- Infusion reaction (reported in 1/25 patients; 4%)
- Discomfort in the nose (reported in 1/25 patients; 4%)
- Runny nose (reported in 1/25 patients; 4%)
- Involuntary leakage of urine (reported in 1/25 patients; 4%)
- Vision changes (reported in 1/25 patients; 4%)
- Vomiting (reported in 1/25 patients; 4%)

There were no serious side effects that were thought to be related to RRx-001 during the initial study which were life-threatening or required hospitalization of the patient.

Because RRx-001 is an investigational drug and not a lot of patients have received the drug, not all of the side effects are known at this time. It is not known if additional side effects will be seen with this drug. For this reason, if you receive RRx-001, you will be watched closely for known and other unknown, possibly serious side effects.

Your doctor will describe the side effects of regorafenib to you in more detail, which may include peeling of the skin on your hands and feet (hand-foot skin reaction), swelling of the lining of the mouth and throat (mucositis), diarrhea, and high blood pressure (hypertension).

Risks of Regorafenib

The most common adverse reactions (≥20%) are:

- Asthenia/fatigue
- Hand Foot and Skin Reaction (HFSR)
    - Numbness
    - Tingling, or a "pins and needles" feeling
    - Increased skin sensitivity
    - Sensitivity to hot objects
    - Burning sensation
    - Redness, swelling
    - Calluses (hard layers of skin) on the palms of your hands or on the balls or heels of your feet
    - Blisters on your skin
    - Dry, cracked, peeling, or flaking skin
- Diarrhea- frequent or a loose bowel movement
- Decreased appetite/food intake
- Hypertension
- swelling, pain, and redness of the lining of your mouth, throat, stomach, and bowel (mucositis)
- Voice changes or hoarseness (Dysphonia)
- Infection
- Pain (not otherwise specified)
- Decreased weight
- Gastrointestinal and abdominal pain
- Rash
- Fever
- Nausea

Infrequent side-effects (occurring in 5-10% of patients):

- Bleeding which can be sever sometimes and lead to death
    - vomiting blood or if your vomit looks like coffee grounds
    - pink or brown urine
    - red or black (looks like tar) stools

    - coughing up blood or blood clots
    - menstrual bleeding that is heavier than normal
    - unusual vaginal bleeding
    - nosebleeds that happen often
- Dizziness
- Fever
- Impaired blood supply to the heart muscle, which may cause heart attack
- Infection, which may become severe and generalized
- Itching
- Kidney failure
- Loss of weight
- Reduced numbers of the cells that help the blood to clot

Rarely observed (single or few cases, not exceeding 5% of patients):

- Impaired blood supply to parts of the brain, which may cause a stroke or mini-stroke
- Dehydration
- Feeling unwell
- temporary disturbance of the liver function
- Severe liver problem:
    - yellowing of your skin or the white part of your eyes (jaundice)
    - nausea or vomiting
    - dark "tea-colored" urine
    - change in sleep pattern
- Severe allergic reaction
- Reduced numbers of bacteria-fighting white blood cells
- Clots in the lung blood vessels
- Transient loss of consciousness
- Hives
- A tear in your stomach or intestinal wall (bowel perforation)
    - severe pain in your stomach area (abdomen)
    - swelling of the abdomen
    - high fever
- A condition called reversible posterior leukoencephalopathy syndrome (RPLS)
    - severe headaches
    - seizure
    - confusion
    - change in vision
    - problems thinking

Other Study-Related Risks

***Allergic Reactions*:** As with any drug, there is the chance of an allergic reaction, which may include difficulty breathing, rash, flushing, weakness, dizziness, lightheadedness, and swelling.

Intravenous (IV) Injection Side Effects: If the drug leaks from the vein the shot is given into, it may cause skin irritation at the needle site.

Risks of blood draws: There is a risk of discomfort or pain, bleeding, swelling and a small arm bruise and swelling when blood is drawn. Rarely, a clot or infection may occur at the site of the blood draw. Some people also become faint, dizzy, or light-headed during or immediately after the blood draw.

Risks and Side Effects of a Central Line: Subjects may be required to have placement of a "central line." A central line is a catheter that is placed under your skin and into a large vein. It will allow easy administration of the chemotherapy drugs. Risks of placement of a central line include bleeding or lung collapse when the catheter is placed, as well as inflammation at the site of the catheter, and infection.

Reproductive Risks: You should not become pregnant or father a baby while on this study and for a period of time following your last dose of RRx-001 or regorafenib because the drugs in this study can affect a fetus and cause serious birth defects. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study. If you are female and capable of childbearing, a pregnancy test will be done before the study begins in order to be as sure as possible that you are not pregnant. Your participation requires that you use non-hormonal contraception methods (such as abstinence, diaphragm, condom, or intrauterine device) to prevent pregnancy for the duration of the study and for 30 days following your last dose of RRx-001 or regorafenib. Ask about counseling and more information about preventing pregnancy.

Risks from CT Scans: During your participation in this research study, you will be exposed to radiation from scheduled CT scans. The total exposure resulting from these imaging studies is calculated to be approximately 91 mSv the first year and 78 mSv each additional year. This amount is *more* than you would receive from one year of natural exposure in the [INSERT CITY OF SITE] area, which is approximately 1.6 mSv. Cumulative exposure from radiation may increase your risk of developing certain types of cancer in the future.

The principal investigator for this research study has determined and verified that all of the CT scans prescribed for this study would typically be performed as part of the standard medical care required to adequately monitor your current illness. You will have a CT scan of your chest, abdomen and pelvis at Screening and every 8 weeks thereafter. Additional imaging may be performed if clinically indicated. Radiation exposure may be decreased if non-radiation imaging is used, such as MRI. If you are especially concerned with radiation exposure, or you have had a lot of x-rays or imaging scans already, you should discuss this with the principal investigator for this study, [INSERT PI], or your regular doctor.

Risks of MRI Scans: As part of this study, Magnetic Resonance Imaging (MRI) may be done. The imager makes a loud, banging noise while it is taking pictures. You will be given a set of earplugs to help with the noise. You may experience feelings of claustrophobia or anxiety. You may also experience some discomfort and tiredness from lying still in a confined space during the imaging. There are no known effects from exposure to magnetic fields (MRI). However,

some subjects undergoing this procedure become anxious. If this happens to you, you can stop the procedure at any time. If you have metal clips or plates in your body or a pacemaker, you should tell your doctor about it. MRI may not be appropriate under some of the following conditions: a cardiac pacemaker; metal fragments in eyes, skin, or body; heart valve replacement; brain clips; venous umbrella; being a sheet-metal worker or welder; aneurysm surgery; intracranial bypass; renal or aortic clips; prosthetic devices such as middle ear, eye, joint, or penile implants; joint replacements; hearing aid; neurostimulator; insulin pump; I.U.D.; being pregnant or trying to become pregnant; shunts/stents; metal mesh/coil implants; metal plate/pin/screws/wires, or any other metal implants; and permanent eyeliner and/or eyebrows.

Risks of CEUS: Microbubble contrast agents are safe with a low incidence of side effects. They are not toxic to the kidney and severe allergic reactions (anaphylaxis) are extremely rare on the order of 0.001%. Subjects with severe heart and lung disease are not good candidates for CEUS.

Risks of IV Contrast: As part of this study a CT scan may be done. There may be some reactions related to the contrast dye used in CT scans. Contrast dye is usually administered when you get a CT scan. Contrast dye may also be used in MRI scans. Some people may develop hives and itching or other allergic symptoms from this dye, swelling of the heart, cramps of the voicebox, breathing distress caused by narrowing of the airways in lungs, low blood pressure, with loss of consciousness, and in rare cases, severe loss of blood and fluids leading to shock and death, fainting, seizures, and irregular heartbeats. In addition, if you have low kidney function, this dye can temporarily or permanently decrease your kidney function.

Risks of Loss of Confidential Information: There is also a small risk that information from your health records will be released to an unauthorized party. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small. An identification code assigned by the study team to each patient will be used in place of your name to protect your identity when reporting trial-related data.

BENEFITS OF PARTICIPATION

If you agree to take part in this study, there may not be direct medical benefit to you. Others, however, may benefit from the information learned from this research study, and the investigators may learn more about RRx-001.

ALTERNATIVES TO PARTICIPATION

If you choose not to take part in or stop participating in this research study, there may be other treatments. Refusal to take part in this study will not cause penalty or loss of benefits to which you are otherwise entitled.

You do not have to participate in this study to receive treatment for your cancer. Other possible treatments could include treatment with other drugs or drug combinations, participation in other research studies, or supportive care only (no cancer treatment).

Regorafenib is available commercially, meaning you do not need to participate in this research study to be prescribed regorafenib to treat your cancer.

Please talk to your doctor about these and other options.

COSTS/COMPENSATION

The study drug, RRx-001, will be supplied at no cost while you take part in this study. The cost of getting the study drug, RRx-001, ready is also provided at no cost. The study drug administration is not paid for by the study sponsor, so you or your health plan/insurance company may have to pay for this.

It is possible the study drug, RRx-001, may not continue to be supplied while you are on the study. Although not likely, if this occurs, your study doctor will talk to you about your options.

You and/or your health plan/insurance company will need to pay for all of the other costs of caring for your cancer while in this study, including the costs of tests, procedures, or medicines to manage any side effects, unless you are told that certain tests are supplied at no cost. Before you decide to be in the study, you should check with your health plan/insurance company to find out exactly what they will pay for.

Examples of procedures and drugs that may be billed include the following: routine clinic visits, routine laboratory tests, CT and MRI imaging, pre-medications (ibuprofen and dexamethasone), and FDA-approved chemotherapy, regorafenib.

There will be no payment to you for participating in this study.

The sponsor, EpicentRx, Inc., is paying the institution, [INSERT SITE], to do this study.

COMPENSATION FOR RESEARCH-RELATED INJURY

If you are injured as a direct result of being in this study, treatment will be available. The costs of such treatment will be covered by [INSERT SITE] or the study sponsor, EpicentRx, Inc., depending on a number of factors. The University and the study sponsor, EpicentRx, Inc., do not normally provide any other form of compensation for injury. You may call the [INSERT SITE] Human Research Protections Program Office at (xxx) xxx-xxxx for more information about this, to inquire about your rights as a research subject, or to report research-related problems.

VOLUNTARY PARTICIPATION

Participation in this study is entirely voluntary. If you choose not to participate or wish to withdraw your consent to participate in these study procedures at any time, it will in no way affect your regular treatments or medical care at this institution or loss of benefits to which you are entitled.

You will be informed of any new findings that might affect your willingness to continue participating in the study.

The study doctor may stop your participation in this study without your consent. If you have any side effects that are very serious or if you become ill during the course of the research study you may have to drop out even if you would like to continue. The study doctor will make the decision and let you know if it is not possible for you to continue. The decision that is made is to protect your health and safety, or because it is part of the research plan that people who develop certain conditions or do not follow the instructions from the study doctor may not continue to participate. In addition, EpicentRx Inc. may end your participation in the study at any time without your consent.

If you withdraw from the study for any reason, you must notify your study doctor, [INSERT PI] at (xxx) xxx-xxxx. You will be asked to return to the clinic so that the study doctor may perform a final evaluation, which includes laboratory tests. Additional details can be found in the Procedures section of this document.

DO YOU HAVE ANY QUESTIONS?

[INSERT PI] and/or_____ has explained this study to you, and answered your questions. You may contact [INSERT PI] at (xxx) xxx-xxxx. You may also call the hospital 24-hour paging system at (xxx) xxx-xxxx and ask for the oncologist on-call. If you have other questions or research-related problems, you may call the [INSERT SITE] Clinical Trials Office at (xxx) xxx-xxxx.

If you have questions about your rights as a research participant, your participation in this study, and/or concerns about this study, you may call the [INSERT SITE] Human Research Protections Program (a group of people who review the research study to protect your rights and welfare) at (xxx) xxx-xxxx.

A description of this clinical trial will be available on 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.

CONFIDENTIALITY

The confidentiality of your research records will be maintained to the extent permitted by law. Your medical information will not be made publicly available unless disclosure is required by law or regulation.

Study data is labeled with a code instead of your name or other information that can easily identify you. Your identity will remain confidential.

Data obtained from this study, including your protected health information, will be given to the sponsor of this study, EpicentRx Inc., and/or its representatives, and may be used by and/or disclosed to the Food and Drug Administration (FDA), Department of Health and Human

Services (DHHS) agencies, the [INSERT SITE] Institutional Review Board, and other governmental agencies in the United States or other countries in which regulatory approval of RRx-001 may be sought. Once your personal health information is released it may be re-disclosed and no longer protected by privacy laws.

As a rule, the researchers will not continue to use or disclose information about you, but will keep it secure until it is destroyed. Sometimes, it may be necessary for information about you to continue to be used or disclosed, even after you have canceled your permission or the study is over. Examples of reasons for this include:

- To avoid losing study results that have already included your information
- To provide limited information for research, education, or other activities (This information would not include your name, social security number, or anything else that could let others know who you are.)
- To help [INSERT SITE] and government officials make sure that the study was conducted properly.

Your permission allowing the researches and study staff to access your health information expires at the end of the study, unless you cancel it sooner. You may cancel your permission at any time by writing to:

[INSERT PI NAME AND APPROPRIATE ADDRESS]

You will be asked to sign a separate HIPAA authorization form to allow the study team to access and share information from your medical record.

SIGNATURE AND CONSENT

Your participation in this study is voluntary, and you may refuse to participate or withdraw from the study at any time without prejudice or loss of benefits to which you are otherwise entitled. You will receive a signed copy of this consent document and a copy of "The Experimental Subject's Bill of Rights" to keep.

You agree to participate.

_____
Printed Name of Participant

_____ _____
Signature of Participant Date

_____
Printed Name of Person Obtaining Consent

_____ _____
Signature of Person Obtaining Consent Date