INSTITUTE: National Cancer Institute

STUDY NUMBER: 16-C-0011 PRINCIPAL INVESTIGATOR: Mark Gilbert, M.D.

STUDY TITLE: BTTC09-01: A Phase I-II Trial of Everolimus and Sorafenib in Patients with Recurrent High-Grade Gliomas

Continuing Review Approved by the IRB on 07/28/20
Amendment Approved by the IRB on 08/20/18 (D) Date posted to web: 08/14/20

Standard

INTRODUCTION

We invite you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:

Taking part in NIH research is entirely voluntary**.**

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your NIH doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at NIH, or with family, friends or your personal physician or other health professional.

Why is this study being done?

This is an investigational study. Everolimus is FDA approved and commercially available for the treatment of kidney cancer and certain types of brain tumors. It is designed to block a special protein in tumor cells and block the formation of new blood vessels, which is important in tumor

growth. Sorafenib is FDA approved and commercially available for the treatment of kidney cancer. Sorafenib is designed to stop cell growth and to block the formation of new blood vessels (the tubes that carry blood around the body), which are involved in the growth and development of tumors. The combination of everolimus and sorafenib to treat brain tumors is investigational. At this time, this combination is only being used in research.

The goal of Phase 1 of this clinical research study is to find the highest tolerable dose and best schedule of the combination of everolimus and sorafenib that can be given to patients with malignant glioma.

The goal of Phase 2 of this study to learn if the combination of everolimus and sorafenib can help to control malignant glioma. The safety of this combination will also be studied in both phases.

Why are you being asked to take part in this study?

You are being asked to take part in this study because you have malignant glioma (such as glioblastoma multiforme, gliosarcoma, anaplastic astrocytoma, anaplastic oligodendroglioma, anaplastic mixed oligoastrocytoma, or malignant astrocytoma) that has returned after treatment.

How many people will take part in this study?

Up to 118 participants will take part in this multicenter study. Up to 30 will be enrolled at NCI.

Description of Research Study

Before you begin the study

Before starting the study, the Study Doctor will ask you about your health and your medical history. The doctor will examine you and measure your height, weight, blood pressure and heart rate. You will be asked about any medicines you have been taking. You will also have screening tests to help the doctor decide if you are eligible to take part in this study. If some of these tests have been performed within the past 14 days, they may not need to be repeated. These tests include routine blood and urine tests. You will also have tests done for hepatitis B and/or C if:

- You have a risk of having hepatitis B and/or C or;
- You live in or have lived in specific areas such as Asia, Africa, Central and South America, Eastern Europe and Spain, Portugal or Greece or;
- If your study doctor thinks it is appropriate.

If you test positive for hepatitis B, you may not be allowed into the study. If you test negative for hepatitis B, the study doctor may continue to monitor your blood for the hepatitis B virus and

to see if your liver is damaged or inflamed. Your study doctor will inform you if there is a need for treatment. This may mean you are given an anti-viral drug and you will stop taking the study drug.

If you test positive for hepatitis C, you will not be allowed into the study. If you test positive for hepatitis C while you are taking study drug, you will need to stop the study drug because the treatment for hepatitis C has serious side effects.

Other screening tests include CT scan or MRI of your brain, a CT scan or x-ray of your chest, an EKG and you will also complete a questionnaire about your quality of life. If you are a woman of childbearing potential (able to get pregnant), you will be tested to see if you are pregnant.

During the study

If you are found to be eligible to take part in this study, you will be assigned to a study phase based on when you join this study.

If you are enrolled in Phase 1, you will be assigned to 1 of 6 dose levels of the combination of everolimus and sorafenib based on when you join this study. You will remain on the same dose level for the entire study. Up to 3 participants will be enrolled at each dose level. The first 3 participants in each group will receive the lowest dose level. Each set of 3 new participants will receive a higher dose than the one before it, if no intolerable side effects were seen. This will continue until the highest tolerable dose of study drugs given in combination is found.

If you are enrolled in Phase 2, you will receive the combination of everolimus and sorafenib at the highest dose and on the same schedule that was tolerated in Phase 1.

Study Drug Administration

Each cycle is 28 days.

You will take everolimus by mouth 1 time a day every day while you are on study. You should take everolimus whole without chewing them. You should take everolimus without food (1 hour before or 2 hours after eating), with at least 1 cup (8 oz.) of water in the morning, at the same time each day.

You will take sorafenib by mouth 2 times each day on Days 1-7 and Days 15-21 of every cycle.

You should take sorafenib without food (1 hour before or 2 hours after eating), with at least 1 cup (8 oz.) of water.

You may take the study drugs at the same time. Your study doctor will tell you about any changes needed in the way you take the medicine.

It is very important for you to take the study drug just as the study doctor tells you. Do not skip any doses unless your study doctor tells you to skip doses. If you throw up after taking the study drug, you should NOT take another tablet that day. Let your study doctor know that you got sick. If you do forget to take the study drug one day, do not take any extra doses the next day. Call your study doctor and ask for advice.

During the study, you must talk to the study doctor before you take any drug other than the study drug. This includes homeopathic, alternative, or herbal medicines, and vitamins. Please avoid eating grapefruit, star fruit, and Seville oranges or drinking their juices while in the study. The juices in these fruits can change the way your body treats or breaks down everolimus (Afinitor®).

You will be given a study drug diary where you will write down the study drugs that you take at home. You should also bring the diary, study drug, and any empty bottles, with you to each study visit.

Study Visits

Every 2 weeks:

- Blood (about 1-2 teaspoons) will be drawn for routine tests.

Every 4 weeks:

- You will have a physical exam and neurologic exam.
- Routine blood and urine tests
- You will be asked about any drugs you may be taking and if you have had any side effects. (For the first cycle, this is every week if you are in Phase 1.)
- Your blood pressure will be recorded (For the first cycle, this is every week).

Every 4 weeks for the first 2 cycles or the first 4 cycles (if you received bevacizumab previously), then every 8 weeks:

- You will have a brain MRI scan or CT scans to check the status of the disease.
- You will complete the quality-of-life questionnaire which will take about 5 minutes.

At any time during the study, extra tests may be performed if the doctor thinks they are needed for your safety. The study doctor will tell you more about any extra tests.

When you are finished taking the drugs

At the end of the study, give any study medicine or empty containers you still have to your study doctor or nurse.

After you stopped taking the study drugs, the study staff will call you every 3 months to check how you are doing. Each phone call will take about 5 minutes.

Birth Control

If you are a woman who is breast feeding or pregnant, you may not take part in the study because we don't know how this medicine would affect your baby or your unborn child. If you are a woman who can become pregnant, or are the partner of a woman who can become pregnant, you will need to practice a highly effective method of birth control before starting study treatment, during study treatment, and for 8 weeks after you finish study treatment. Highly effective contraceptive methods are also required for female partners of male patients who are sexually active and may become pregnant. If you think that you or your partner is pregnant, you should tell your study doctor or nurse at once.

Please discuss with your Study Doctor the most appropriate birth control method for you that also respect your cultural and religious situation.

Highly effective contraception methods are one of the following:

- Total abstinence
- Use of oral (estrogen and progesterone), injected or implanted combined hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.
- Female sterilization: have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
- Male sterilization: The vasectomized male partner should be the sole partner for that subject with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate.

If you become pregnant or suspect being pregnant during study treatment or within 8 weeks after completing study treatment, you must inform the Study Doctor immediately, and you have to

stop ongoing study treatment immediately. You will not be allowed to continue study treatment if you are pregnant. Your Study Doctor will medically follow your pregnancy until delivery to monitor you and your child`s safety.

As a male participant in the study you must agree to use a condom during intercourse and not father a child during the study and for the period of 8 weeks following stopping of study treatment. In addition, it is advised that your female partner uses a highly effective form of birth control method (contraception) if she is sexually active and may become pregnant.

In case you father a child while in this study you will be asked to report the pregnancy to the Study Doctor. Consent from your partner will be needed to allow your Study Doctor to medically follow this pregnancy until delivery to monitor the mother`s and child`s safety.

Risks or Discomforts of Participation

While on this study, you are at risk for side effects. These side effects will vary from person to person. The more commonly occurring side effects are listed in this form, as are rare but serious side effects. You should discuss these with the study doctor. You may also want to ask about uncommon side effects that have been observed in small numbers of patients but are not listed in this form. Many side effects go away shortly after treatment is stopped, but in some cases, side effects may be serious, long-lasting or permanent, and may even cause death.

Tell the study staff about any side effects that you may have, even if you do not think they are related to the study drugs.

Sorafenib and everolimus each may cause low blood cell counts (red blood cells, platelets, and/or white blood cells):

- A low red blood cell count (anemia) may cause difficulty breathing and/or fatigue. You may need a blood transfusion.
- A low platelet count increases your risk of bleeding (such as nosebleeds, bruising, stroke, and/or digestive system bleeding). You may need a platelet transfusion.
- A low white blood cell count increases your risk of infection (such as pneumonia and/or severe blood infection). Infections may occur anywhere and become life-threatening. Symptoms of infection may include fever, pain, redness, and difficulty breathing.

Sorafenib Side Effects

Likely (occurring in more than 20% of patients)		
• fatigue • skin rash • skin peeling • shedding of skin • hand-foot syndrome (palms of hands/soles of feet having pain, swelling, and blistering) • hair loss (partial or total)	• abnormal salts, minerals, and/or acids in the blood (possible weakness, swelling, fatigue, low blood pressure, organ failure, heart problems, changes in mental status, and/or seizure) • abnormal digestive blood tests (possible pancreas damage)	• diarrhea • abdominal pain • weight loss • loss of appetite • nausea • increased risk of bleeding • low blood cell counts (red/ white/platelets)

Less Likely (occurring in 3-20% of patients)		
• high blood pressure • decreased blood supply to the heart • heart attack • nerve damage (loss of feeling)	• headache • itching • dry skin • skin redness • vomiting • constipation	• liver problems • pain (muscle/joint) • weakness • difficulty breathing • cough

Exact frequency unknown but occurring in between 1 and 10% of patients:		
• flushing • depression • fever • acne • shedding and scaling of the skin (possible fatal loss of bodily fluids)	• loss of appetite • upset stomach • difficulty swallowing • tongue pain • inflammation of the mucous membranes • mouth blisters/sores (possible difficulty swallowing)	• dry mouth • impotence • low red blood cell counts • abnormal liver tests (possible liver damage) • kidney failure • hoarseness • flu-like symptoms

Rare but serious (occurring in fewer than 3% of patients)		
• irregular heartbeat • heart failure	• low blood levels of sodium (possible	• nosebleeds • build-up of fluid around

• heart attack • tear of the main artery of the heart • severe increase in blood pressure (possible stroke) • bleeding in the brain • brain damage that may be reversible (possible headache, confusion, seizures, and/or vision loss) • blood clot blocking a blood vessel (possibly in the heart and brain) • temporary stroke symptoms • very severe blistering skin disease (loss of large portion of skin) • very severe blistering skin disease (with ulcers of the skin and digestive tract) • tissue swelling • underactive thyroid gland (possible weight gain, heart failure, and/or constipation) • overactive thyroid gland (possible weight loss, heart rate changes, and/or sweating)	headache, confusion, seizures, and/or coma) • dehydration • bleeding in the digestive system • hole in the intestines (possibly leaking contents into the abdomen) • inflammation of the pancreas (possible abdominal pain) • gallbladder inflammation (possible abdominal pain) • jaundice (yellowing of skin and/or eyes • liver failure • liver damage due to inflammation • bone destruction (jaw bone) • breakdown of muscle tissue (possible kidney failure) • decreased kidney function (possible kidney failure • bleeding in the esophagus	the lungs • bleeding in the airways • lung inflammation (possible difficulty breathing) • allergic reaction (such as skin reaction and/or hives) • life-threatening allergic reaction (such as difficulty breathing, low blood pressure, and/or organ failure) • infection • preeclampsia-like syndrome (high blood pressure and increased proteins in the urine [possible kidney damage]) • pain at the tumor site • breakdown products of the cancer cells entering the blood stream (possible weakness, low blood pressure, muscle cramps, kidney damage, and/or other organ damage) • delayed wound healing

Sorafenib may cause you to develop another type of cancer (such as skin cancer and lung cancer).

Everolimus Side Effects

Likely (occurring in more than 20% of patients)		
• swelling (arm/leg) • high blood pressure • fatigue	• low blood sugar • abnormal salts, minerals, and/or acids in the blood	• abnormal taste • low blood cell counts (red, white, platelets)

• fever • headache • seizure • anxiety • aggression • behavioral disturbance • skin rash and/or itching • acne • nail changes • high blood levels of fat (possible heart disease and/or stroke) • high blood sugar (possible diabetes)	(possible weakness, swelling, fatigue, low blood pressure, organ failure, heart problems, changes in mental status, and/or seizure) • mouth blisters/sores • loss of appetite • weight loss • diarrhea • constipation • abdominal pain • nausea • vomiting	• increased risk of bleeding • abnormal liver test (possible liver damage and/or yellowing of the skin and/or eyes) • weakness • abnormal kidney test (possible kidney damage) • cough • nosebleed • difficulty breathing • infection

Less Likely (occurring in 3-20% of patients)		
• chest pain (possibly due to heart trouble) • fast heartbeat • chills • migraine • dizziness • difficulty sleeping • depression • dry skin • skin peeling, redness, and/or sores • breaking of nails • eczema (skin inflammation) • hair loss (partial or total) • hand-foot syndrome (palms of hands/soles of feet having pain, swelling, and blistering)	• diabetes • abnormal blood levels of fat • dry mouth • upset stomach • inflammation of the stomach and/or intestines • hemorrhoids • difficult and/or painful urination • blood in the urine • uterine and/or vaginal bleeding • changed, painful, heavy, or stopped menstrual cycle • pain (jaws/joint/arm/leg/ back) • muscle spasms	• tremors • abnormal sensation (such as pins and needles) • swelling (eyelid) • red eyes • kidney failure • build-up of fluid around the lungs • lung inflammation (possible difficulty breathing) • stuffy/runny nose • difficulty swallowing • sore throat • life-threatening allergic reaction (such as difficulty breathing, flushing, chest pain, and/or tissue swelling)

Frequency unknown but possibly occurring in 1-10% of patients		
• low blood pressure	• high blood levels of uric	• weakening or loss of bone

(possible dizziness/fainting) • irregular heartbeat • swelling • blood clots in a vein (possible pain, swelling, and/or redness) • fainting • agitation • hallucinations (seeing or hearing things that are not there) • weakness on one side of the body • hair growth • opening of a wound • dehydration • sweating/night sweats • change in body appearance due to high levels of steroid hormone • overactive thyroid gland (possible weight loss, heart rate changes, and/or sweating)	acid (possible painful joints and/or kidney failure) • vomiting of blood • paralysis of the intestines • swelling of the scrotum • abdominal pain • gas • heartburn • thickened gums • abdominal wall inflammation • inability to urinate • frequent urination • urge to urinate • impotence • ovarian cysts (fluid-filled lump) • increase in • infection-fighting cells • lymph node swelling • high blood platelet count (possible increased clotting) • bone destruction	strength (possible broken bones) • inflammation of bone in the spine • painful joint inflammation • pain (muscle/joint) • joint swelling • blurry vision • cataracts (clouding of the lens of the eye) • back-up of urine into the kidney • kidney inflammation (possible kidney damage/failure) • blood clot in an artery to the kidney (possible kidney damage or loss of function) • decreased kidney function • fluid in the lung (possible difficulty breathing) • wheezing

Rare but serious (occurring in fewer than 3% of patients)		
• heart failure • sudden stopping of the heart • multiple blood clots possible organ dysfunction and/or failure) • blood clot at the site of a graft	• decreased brain function (possible paralysis and/or coma) • wound healing problems • abnormal blood clotting in small blood vessels (possible stroke and/or other organ damage) • inflammation of the pancreas (possible abdominal pain)	• low sperm count • slowing or stoppage in the normal flow of bile (possible body yellowing • and/or abdominal pain) • severe life-threatening infection (possible low blood pressure, kidney failure, and/or heart failure

Everolimus may rarely cause you to develop another type of cancer (such as lymphoma [a type of lymph node cancer] and/or skin cancer [such as melanoma]). It could also cause thickening in the lining of the uterus and uterine fibroids.

If you have had hepatitis (liver inflammation) in the past, taking everolimus may rarely cause the hepatitis to come back, which may cause death.

You must not drink grapefruit juice or eat grapefruit products while taking everolimus.

For those patients receiving Everolimus in combination with Sorafenib, there is a rare complication of muscle weakness, muscle cramps, stiffness and spasm, muscle pain in the shoulders, thighs, or lower back; trouble moving arms and legs; and dark red or brown urine or decreased urination. Symptoms may occur in one area of the body or affect the whole body. This complication may occur in both early and later stages of treatment. The severity of the symptoms will vary and in rare cases, it can lead to death.

Using the **study drugs together** may cause side effects that are not seen when each is given alone. The study drug combination may also increase the frequency and/or severity of the side effects listed above.

Other Risks

Blood draws may cause pain, bleeding, and/or bruising. You may faint and/or develop an infection with redness and irritation of the vein at the site where blood is drawn. Frequent blood collection may cause anemia (low red blood cell count), which may create a need for blood transfusions.

Questionnaires may contain questions that are sensitive in nature. You may refuse to answer any question that makes you feel uncomfortable. If you have concerns about completing the questionnaire, you are encouraged to contact your doctor or the Principal Investigator.

This study may involve unpredictable risks to the participants.

Potential Benefits of Participation

Are there benefits to taking part in this study?

The aim of this study is to determine a safe dose and to see if this experimental treatment will cause your tumors to shrink. We do not know if you will receive personal medical benefit from taking part in this study. These potential benefits could include shrinking of your tumor or lessening of your symptoms, such as pain, that are caused by the cancer. Because there is not much information about the drug's effect on your cancer, we do not know if you will benefit from taking part in this study, although the knowledge gained from this study may help others in the future who have cancer.

Alternative Approaches or Treatments

Instead of being in this study, you have these options**:**

- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly. Instead, it tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Please talk to your doctor about these and other options.

Stopping Therapy

Your doctor may decide to stop your therapy for the following reasons:

- if your disease comes back during treatment
- if you become pregnant while on study therapy
- if you have side effects from the treatment that your doctor thinks are too severe

In this case, you will be informed of the reason therapy is being stopped.

You can stop taking part in the study at any time. However, if you decide to stop taking part in the study, we would like you to talk to the study doctor and your regular doctor first.

If you decide at any time to withdraw your consent to participate in the trial, we will not collect any additional medical information about you. However, according to FDA guidelines, information collected on you up to that point may still be provided to Brain Tumor Trials Collaborative (BTTC), Novartis (drug supplier) and its authorized agents, and Bayer Pharmaceuticals or designated representatives. If you withdraw your consent and leave the trial, any samples of yours that have been obtained for the study and stored at the NCI can be destroyed upon request. However, any samples and data generated from the samples that have already been distributed to other researchers or placed in the research databases cannot be recalled and destroyed.

Research Subject's Rights

What are the costs of taking part in this study?

If you choose to take part in the study, the following will apply, in keeping with the NIH policy:

- You will receive study treatment at no charge to you. This may include surgery, medicines, laboratory testing, x-rays or scans done at the Clinical Center, National Institutes of Health (NIH), or arranged for you by the research team to be done outside the Clinical Center, NIH if the study related treatment is not available at the NIH.
- There are limited funds available to cover the cost of some tests and procedures performed outside the Clinical Center, NIH. You may have to pay for these costs if they are not covered by your insurance company.
- Medicines that are not part of the study treatment will not be provided or paid for by the Clinical Center, NIH.
- Once you have completed taking part in the study, medical care will no longer be provided by the Clinical Center, NIH.

Will your medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), which are involved in keeping research safe for people.
- National Cancer Institute Institutional Review Board
- Brain Tumor Trials Collaborative (BTTC), Novartis (drug supplier) and its authorized agents, and Bayer Pharmaceuticals
- Governmental agencies in other countries where the study drug may be considered for approval

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

Research Related Injury

If you are injured while participating in this study, principal investigator will provide you with treatment per the NIH Clinical Center Research Injury Policy (Item # 2 on page 16). Novartis (drug supplier) will not pay any money to you or your medical bills.

Certificate of Confidentiality

To help us protect your privacy, we have obtained a Certificate of Confidentiality. The researchers can use this Certificate to legally refuse to disclose information that may identify you

in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if there is a court subpoena. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

You should also know that there are several circumstances in which the Certificate does not provide coverage. These include when information:

- will be used for auditing or program evaluation internally by the NIH; or
- must be disclosed to meet the legal requirements of the federal Food and Drug Administration (FDA).
- is necessary for your medical treatment and you have consented to this disclosure;
- is for other research.

In addition, identifiable, sensitive information protected by this Certificate cannot be admissible as evidence or used for any purpose in any action, suit, or proceeding without your consent.

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers will not use the Certificate to withhold that information.

The Certificate of Confidentiality will not protect against the required reporting by hospital staff of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others.

Conflict of Interest

The National Institutes of Health (NIH) reviews NIH staff researchers at least yearly for conflicts of interest. This process is detailed in a Protocol Review Guide. You may ask your research team for a copy of the Protocol Review Guide or for more information. Members of the research team who do not work for NIH are expected to follow these guidelines but they do not need to report their personal finances to the NIH.

Members of the research team working on this study may have up to $15,000 of stock in the companies that make products used in this study. This is allowed under federal rules and is not a conflict of interest.

The National Institutes of Health and the research team for this study are using drugs developed by Novartis (drug supplier) and by Bayer Pharmaceuticals through a joint study with your researchers and the company. The company also provides financial support for this study.

Use of Specimens and Data for Future Research

To advance science, it is helpful for researchers to share information they get from studying human samples. They do this by putting it into one or more scientific databases, where it is stored along with information from other studies. A researcher who wants to study the information must apply to the database and be approved. Researchers use specimens and data stored in scientific databases to advance science and learn about health and disease.

We plan to keep some of your specimens and data that we collect and use them for future research and share them with other researchers. We will not contact you to ask about each of these future uses. These specimens and data will be stripped of identifiers such as name, address or account number, so that they may be used for future research on any topic and shared broadly for research purposes. Your specimens and data will be used for research purposes only and will not benefit you. It is also possible that the stored specimens and data may never be used. Results of research done on your specimens and data will not be available to you or your doctor. It might help people who have cancer and other diseases in the future.

If you do not want your stored specimens and data used for future research, please contact us in writing and let us know that you do not want us to use your specimens and/or data. Then any specimens that have not already been used or shared will be destroyed and your data will not be used for future research. However, it may not be possible to withdraw or delete materials or data once they have been shared with other researchers.

OTHER PERTINENT INFORMATION

1. Confidentiality. When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or authorized hospital accreditation organizations.

2. Policy Regarding Research-Related Injuries. The Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the National Institutes of Health, the Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

3. Payments. The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, patients are not paid for taking part in research studies at the National Institutes of Health. Reimbursement of travel and subsistence will be offered consistent with NIH guidelines.

4. Problems or Questions. If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Mark Gilbert, M.D., Building 82, Room 235A, Telephone: 240-760-6023. You may also call the Clinical Center Patient Representative at 301-496-2626. If you have any questions about the use of your specimens or data for future research studies, you may also contact the Office of the Clinical Director, Telephone: 240-760-6070.

5. Consent Document. Please keep a copy of this document in case you want to read it again.

COMPLETE APPROPRIATE ITEM(S) BELOW:

A. Adult Patient's Consent

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

Signature of Adult Patient/ Legal Representative | Date

Print Name

B. Parent's Permission for Minor Patient.

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study.

(Attach NIH 2514-2, Minor's Assent, if applicable.)

Signature of Parent(s)/ Guardian | Date

Print Name

C. Child's Verbal Assent (If Applicable)

The information in the above consent was described to my child and my child agrees to participate in the study.

Signature of Parent(s)/Guardian | Date | Print Name

THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM JULY 28, 2020 THROUGH JULY 27, 2021.

Signature of Investigator | Date | Signature of Witness | Date

Print Name | Print Name