

<b>MEDICAL RECORD</b>	<b>CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY</b> <ul style="list-style-type: none"> <li>• Adult Patient or</li> <li>• Parent, for Minor Patient</li> </ul>
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INSTITUTE: National Cancer Institute

STUDY NUMBER: 13-C-0120 PRINCIPAL INVESTIGATOR: Tim Greten, M.D.

STUDY TITLE: A Pilot Study of Tremelimumab - A Monoclonal Antibody Against CTLA-4 in Combination with either Trans-Arterial Catheter Chemoembolization (TACE), Radiofrequency Ablation (RFA), or Cryoablation in Subjects with Hepatocellular Carcinoma (HCC) or Biliary Tract Carcinomas (BTC)

Continuing Review Approved by the IRB on 06/10/19

Amendment Approved by the IRB on 09/14/17 (J)

Date posted to web: 06/19/19

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 research is being done to study the effectiveness of the combination of the drug Tremelimumab with trans-arterial catheter chemoembolization (TACE), radiofrequency ablation (RFA) or cryoablation.

Tremelimumab is an experimental drug that has not been approved by the U.S. Food and Drug Administration (FDA). TACE, RFA and cryoablation are standard procedures that are used to treat tumors.

PATIENT IDENTIFICATION	<b>CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY</b> <ul style="list-style-type: none"> <li>• Adult Patient or</li> <li>• Parent, for Minor Patient</li> </ul> NIH-2514-1 (07-09) P.A.: 09-25-0099 File in Section 4: Protocol Consent (1)
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**MEDICAL RECORD****CONTINUATION SHEET for either:**

NIH 2514-1, Consent to Participate in A Clinical Research Study  
NIH 2514-2, Minor Patient's Assent to Participate In A Clinical Research Study

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STUDY NUMBER:13-C-0120

CONTINUATION: page 2 of 12 pages

If you receive TACE a small catheter will be placed into the artery at the groin and chemotherapy will be injected directly into the liver. A material which closes off the vessels supplying blood to the tumor is also injected. If you receive RFA you will be put to sleep and a needle will directly be placed into the tumor and your tumor will be burnt (or part of it). If you receive Cryoablation you will be put to sleep and a needle will be put directly into the tumor and the tumor will be frozen (or part of it). Once it is determined which procedure you will receive your doctor will explain the procedure in full detail.

Although Tremelimumab is not approved by the FDA, it has been evaluated in a number of clinical studies, and over 1000 patients, most of whom had melanoma. Tremelimumab is similar in how it works to another drug (called ipilimumab) which was recently approved by the FDA. Tremelimumab has been tested in a small group of patients with liver cancer or hepatocellular cancer (HCC) and in general was well tolerated. It has not been tested however in combination with TACE, RFA or cryoablation, which is the main goal of this study.

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

You are being asked to take part in this study because you have advanced hepatocellular cancer (HCC) or biliary tract cancer that has not responded to other types of therapy, and your doctor has determined that you are not a candidate for liver transplantation.

**How many people will take part in this study?**

About 90 people will take part in this study.

**Description of Research Study****Before you begin the study**

Before you begin this study, you will have several exams and tests to make sure you are eligible for this study. The exams and tests are part of regular cancer care and may be done even if you do not join the study. If you recently had some of the tests, they may not need to be repeated. The research team will explain these exams and tests to you. You will have:

- History and physical exam
- Review of current medications and past treatments
- Blood work
- Urine laboratory tests
- Tumor measurements using special x-rays called computerized tomography (CT or CAT scans) or magnetic resonance imaging (MRI) of your chest, stomach, and pelvis areas

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PATIENT IDENTIFICATION**CONTINUATION SHEET for either:**

NIH-2514-1 (07-09)

NIH-2514-2 (10-84)

P.A.: 09-25-0099

File in Section 4: Protocol Consent

---

**MEDICAL RECORD****CONTINUATION SHEET for either:**NIH 2514-1, Consent to Participate in A Clinical Research Study  
NIH 2514-2, Minor Patient's Assent to Participate In A Clinical Research Study

---

STUDY NUMBER:13-C-0120

CONTINUATION: page 3 of 12 pages

- A heart test called an electrocardiogram or ECG to check your heart
- Urine or blood pregnancy test

**During the study**

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will begin treatment.

Treatment involves receiving Tremelimumab through a vein (IV) once every 4 weeks and then once every 12 weeks for 2 years' total. Treatment can be stopped before completion of 2 years' therapy if your disease shows clear evidence of growth or your body is no longer tolerating the treatment. A 4-week time-period is called a cycle. In this study, there are six initial cycles followed by maintenance.

**On the first day of every cycle you will receive the following:**

- History and physical exam
- Review of current medications and treatments
- Routine and research blood tests. The purposes of the research blood tests will be to see if there is evidence that your immune system has become 'activated' by the treatment.
- Urine laboratory tests
- Receive Tremelimumab

**On the first day of every week during cycles 1 through 6 you will receive the following:**

- Routine blood tests
- History and physical exam
- Review of current medications and treatments

During your second cycle (within 4 days of Day 36), you will receive the TACE, RFA, SBRT or cryoablation procedure. The procedure that you will receive at this time is based on the size and location of your tumor as well as other conditions that will be discussed by the study doctors.

Every 8 weeks, you will have tumor measurements using special x-rays called computerized tomography (CT or CAT scans) or magnetic resonance imaging (MRI) of your chest, stomach, and pelvis.

While you are in the maintenance phase of the study if it is confirmed that your disease has progressed you may be eligible to receive re-induction therapy using Tremelimumab. This option will be discussed with you by your study doctor.

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**PATIENT IDENTIFICATION****CONTINUATION SHEET for either:**

NIH-2514-1 (07-09)

NIH-2514-2 (10-84)

P.A.: 09-25-0099

File in Section 4: Protocol Consent

---

**MEDICAL RECORD****CONTINUATION SHEET for either:**NIH 2514-1, Consent to Participate in A Clinical Research Study  
NIH 2514-2, Minor Patient's Assent to Participate In A Clinical Research Study

---

STUDY NUMBER:13-C-0120

CONTINUATION: page 4 of 12 pages

**When you are finished taking the drugs (treatment)**

After you have finished taking the study drugs, you will be asked to return to clinic within 4 weeks for a safety follow up visit. At this visit, you will be asked questions about your health, get a physical exam and undergo routine and research blood and urine tests. If you have any unresolved drug related health issues, you will be followed until you feel better. If you are unable to return for this visits, we will obtain the information from you by telephone. After that we will contact you by phone once a year.

**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 an effective form of birth control before starting study treatment, during study treatment, and for 3 months after you finish study treatment. In addition, male subjects should not donate sperm during the study and for 3 months after the last dose of study therapy. If you think that you or your partner is pregnant, you should tell your study doctor or nurse at once.

Effective forms of birth control include:

- abstinence
- intrauterine device (IUD)
- hormonal [birth control pills, injections, or implants]
- tubal ligation
- vasectomy

**Risks or Discomforts of Participation**

If you choose to take part in this study, there is a risk that:

- You may lose time at work or home and spend more time in the hospital or doctor's office than usual
- You may be asked sensitive or private questions which you normally do not discuss.

There is also a risk that you could have side effects from the study drug. Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may interfere with your ability to have children.

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PATIENT IDENTIFICATION**CONTINUATION SHEET for either:**

NIH-2514-1 (07-09)

NIH-2514-2 (10-84)

P.A.: 09-25-0099

File in Section 4: Protocol Consent

---

**MEDICAL RECORD****CONTINUATION SHEET for either:**

NIH 2514-1, Consent to Participate in A Clinical Research Study  
NIH 2514-2, Minor Patient's Assent to Participate In A Clinical Research Study

---

STUDY NUMBER:13-C-0120

CONTINUATION: page 5 of 12 pages

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having any symptoms.
- The study doctor may be able to treat some side effects.

Below we show the most common and the most serious side effects that researchers know about. There might be other side effects that researchers do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

**Risks from study therapy****All Participants***Tremelimumab:*

The following are side effects that have been associated with Tremelimumab:

- Diarrhea
- Rash
- Pruritus (itching)
- Fatigue
- Nausea
- Vomiting
- Anorexia (loss of appetite)
- Headache
- Abdominal Pain
- Auto-immune changes to the pituitary gland leading to hormonal changes.
- Inflammation of the part of the intestine known as the colon which can lead to infection, blood in the stools and abdominal pain. This is also known as 'colitis'. Colitis has the potential to be life threatening and require prolonged hospitalizations. As part of its management it may require treatment with steroids which may place you at increased risk for severe infections.
- Inflammation of the liver which is also known as hepatitis. In extreme cases this may result in liver failure and death.
- Occasionally you can also get a skin rash related to the treatment and this can also result in severe and life threatening symptoms.
- Problems related to Tremelimumab infusion
- There is a remote chance that you may have a serious allergic reaction (anaphylaxis) to Tremelimumab. Anaphylaxis may cause a serious drop in blood pressure, difficulty in breathing, severe hives, and sometimes death. Your doctor will monitor you very closely after you receive the Tremelimumab, and will have medications available to treat any

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PATIENT IDENTIFICATION**CONTINUATION SHEET for either:**

NIH-2514-1 (07-09)

NIH-2514-2 (10-84)

P.A.: 09-25-0099

File in Section 4: Protocol Consent

**MEDICAL RECORD****CONTINUATION SHEET for either:**

NIH 2514-1, Consent to Participate in A Clinical Research Study  
 NIH 2514-2, Minor Patient's Assent to Participate In A Clinical Research Study

STUDY NUMBER:13-C-0120

CONTINUATION: page 6 of 12 pages

allergic reactions that might occur. Less serious allergic reactions, such as skin rash with or without itching and swelling, may also occur within hours to days after receiving the Tremelimumab. These effects usually get better without treatment.

- There is a remote chance that you may develop new allergies to previously exposed substances, other than Tremelimumab. For example, it is possible that you could develop an allergy to shellfish or IV contrast while taking Tremelimumab. These allergies may be severe and life threatening.

*Risks from Blood Collection*

Side effects of blood draws include pain and bruising in the area where the needle was placed, lightheadedness, and rarely, fainting. When large amounts of blood are collected, low red blood cell count (anemia) can develop.

*Risks from Biopsy*

This procedure usually causes only brief discomfort at the site from which the biopsy is taken. Rarely, infection or bleeding may occur at the needle site.

Tumor biopsies will be done by a specialist using the CT scanner or ultrasound machine to guide the biopsy needle into the tumor to ensure accuracy. To collect the research biopsies, you will be exposed to 3 CT scans. This radiation exposure is not required for your medical care and is for research purposes only. The amount of radiation you will receive in this procedure is 2.3 rem which is below the guideline of 5 rem per year allowed for research subjects by the NIH Radiation Safety Committee. The average person in the United States receives a radiation exposure of 0.3 rem per year from natural sources, such as the sun, outer space, and the earth's air and soil. If you would like more information about radiation, please ask the investigator for a copy of the pamphlet, An Introduction to Radiation for NIH Research Subjects.

*TACE Procedure (Cohort A/B)*

<b>Likely</b>	<b>Less Likely</b>	<b>Rare but Serious</b>
<ul style="list-style-type: none"> <li>• Abdominal pain</li> <li>• Fever</li> <li>• Nausea and/or vomiting</li> </ul>	<ul style="list-style-type: none"> <li>• Abdominal fluid buildup (Ascites)</li> <li>• Bleeding (at catheter insertion site)</li> <li>• Allergy to iodine contrast agent</li> </ul>	<ul style="list-style-type: none"> <li>• Liver failure</li> <li>• Kidney failure</li> <li>• Liver abscess formation</li> <li>• Stomach or duodenal ulcer</li> <li>• Pancreatitis</li> <li>• Cholecystitis (irritation of the gall bladder)</li> <li>• Arterial injury at catheter insertion site</li> </ul>

PATIENT IDENTIFICATION

**CONTINUATION SHEET for either:**

NIH-2514-1 (07-09)  
 NIH-2514-2 (10-84)  
 P.A.: 09-25-0099  
 File in Section 4: Protocol Consent

---

**MEDICAL RECORD****CONTINUATION SHEET for either:**NIH 2514-1, Consent to Participate in A Clinical Research Study  
NIH 2514-2, Minor Patient's Assent to Participate In A Clinical Research Study

---

STUDY NUMBER:13-C-0120

CONTINUATION: page 7 of 12 pages

*RFA Procedure (Cohorts A/B/E)*

The risks from the radiofrequency or microwave ablation procedure itself include a small chance of bleeding, injury to the normal liver tissue, and re-growth of the tumor. An infection, called an abscess, can develop in the treated tumor, and may require antibiotics and/or putting a temporary tube in the abscess to drain it. There should be minimal discomfort from the ablation procedure itself during the ablation procedure, because you will be "asleep" under general anesthesia. The length of time you will need to be in the hospital will vary but will be estimated by your doctors. This will be discussed with you in greater detail prior to the procedure.

*Cryoablation (Cohort D only)*

The risks from cryoablation procedure itself include a small chance of bleeding, injury to the normal liver tissue, and re-growth of the tumor. Nerve damage may result. Completely frozen nerves can cause motor weakness or numbness in the area supplied by the nerves. There should be minimal discomfort from the cryoablation procedure itself during the procedure, because you will be "asleep" under general anesthesia. Following percutaneous cryotherapy, you should be able to resume your usual activities within one to three days. If you have had open cryoablation, you should be able to resume your usual activities within seven to 10 days. You should avoid lifting heavy objects for at least 72 hours. This will be discussed with you in greater detail prior to the procedure.

**Potential Benefits of Participation****Are there benefits to taking part in this study?**

The aim of this study is 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**

*What other choices do I have if I do not take part in this study?*

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

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PATIENT IDENTIFICATION**CONTINUATION SHEET for either:**

NIH-2514-1 (07-09)

NIH-2514-2 (10-84)

P.A.: 09-25-0099

File in Section 4: Protocol Consent

---

**MEDICAL RECORD****CONTINUATION SHEET for either:**

NIH 2514-1, Consent to Participate in A Clinical Research Study  
NIH 2514-2, Minor Patient's Assent to Participate In A Clinical Research Study

---

STUDY NUMBER:13-C-0120

CONTINUATION: page 8 of 12 pages

- 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.

**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.
- Qualified representatives from MedImmune, Inc., the pharmaceutical company who produces Tremelimumab.

**Stopping Therapy**

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

- if he/she believes that it is in your best interest

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PATIENT IDENTIFICATION**CONTINUATION SHEET for either:**

NIH-2514-1 (07-09)

NIH-2514-2 (10-84)

P.A.: 09-25-0099

File in Section 4: Protocol Consent

---

**MEDICAL RECORD****CONTINUATION SHEET for either:**NIH 2514-1, Consent to Participate in A Clinical Research Study  
NIH 2514-2, Minor Patient's Assent to Participate In A Clinical Research Study

---

STUDY NUMBER:13-C-0120

CONTINUATION: page 9 of 12 pages

- if your disease comes back during treatment
- if you have side effects from the treatment that your doctor thinks are too severe
- if new information shows that another treatment would be better for you
- if you become pregnant

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 MedImmune, Inc. 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.

**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 Tremelimumab developed by MedImmune, Inc. through a joint study with your researchers and the company. The company also provides financial support for this study.

**Optional Biopsy**

An optional tumor biopsy may be performed at baseline and at the time of the RFA or TACE and, if applicable, prior to re-induction. These are optional biopsies which you do not have to undergo. If performed, the tissue will be studied to see if any immune cells have entered the tumor. The biopsy to be performed is exclusively for research purposes and will not benefit you. It might help other people in the future. The decision to participate in this part of the research is optional, and no matter what you decide to do, it will not affect your care. You will be given the opportunity to sign a separate consent at the time of the biopsy.

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PATIENT IDENTIFICATION**CONTINUATION SHEET for either:**

NIH-2514-1 (07-09)

NIH-2514-2 (10-84)

P.A.: 09-25-0099

File in Section 4: Protocol Consent

---

**MEDICAL RECORD****CONTINUATION SHEET for either:**

NIH 2514-1, Consent to Participate in A Clinical Research Study

NIH 2514-2, Minor Patient's Assent to Participate In A Clinical Research Study

STUDY NUMBER:13-C-0120

CONTINUATION: page 10 of 12 pages

**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.

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**PATIENT IDENTIFICATION****CONTINUATION SHEET for either:**

NIH-2514-1 (07-09)

NIH-2514-2 (10-84)

P.A.: 09-25-0099

File in Section 4: Protocol Consent

STUDY NUMBER: 13-C-0120

CONTINUATION: page 11 of 12 pages

**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, Tim Greten, M.D., Building 10, Room 12N226, Telephone: 240-760-6114. 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.

STUDY NUMBER: 13-C-0120

CONTINUATION: page 12 of 12 pages

**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 JUNE 10, 2019 THROUGH JUNE 24, 2020.**

\_\_\_\_\_  
Signature of Investigator      Date      Signature of Witness      Date

\_\_\_\_\_  
Print Name

\_\_\_\_\_  
Print Name