CREST-2

1. General Information About This Research Study

Study Title: CREST-2

CREST-2 Principal Investigator: Thomas Brott, MD, Mayo Clinic, Jacksonville, FL

Clinical Site Principal Investigator: Matthew Flaherty, MD

Clinical Study Site: University of Cincinnati Medical Center, Cincinnati, Ohio

A. Study Eligibility and Purpose

You are being asked to take part in this research study because one of your carotid arteries is narrowed. Carotid arteries are the main arteries feeding your brain. This narrowing increases your risk of having a stroke. The narrowing is caused by a thickened area called a plaque.

Current procedures for treating narrowed carotid arteries include carotid endarterectomy (CEA) or carotid artery stenting (CAS). During CEA the plaque is removed through a surgical cut in the neck. During CAS a metal device called a stent is placed in the narrowed part of the artery to hold it open.

This study will test a novel intensive medical management plan to treat your narrowed carotid artery. The plan targets multiple risk factors for carotid artery disease such as high blood pressure, high cholesterol, diabetes, and smoking cessation. Your local doctor and national experts will develop your plan. You will also be enrolled in a risk factor management program.

Participants in this study will receive the novel intensive medical management plan alone, or in combination with CEA or CAS.

The main purpose of the study is to find out if the incidence of stroke or death is different or the same between subjects that receive medical management alone compared to subjects that receive medical management in combination with CEA or CAS. The occurrence of stroke and death may be higher, lower, or the same between groups

As you read this form describing the study, ask any questions you have. Take your time to decide. Feel free to discuss the study with your family, friends, and healthcare provider before you decide. Your participation is voluntary. You may decide not to participate and you may stop participating at any time during the study. If so, none of your current benefits or normal health care will be affected in any way. When you feel comfortable that all your questions have been answered, and you wish to take part in this study, sign this form in order to begin your participation. Your signature means you have been told about the study and the risks. Your signature on this form also means that you want to take part in this study.

B. Number of Participants

Overall, there will be about 2,480 people enrolled in this study across North America and internationally.

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C. Additional Information You Should Know

The National Institute of Neurological Disorders and Stroke (NINDS), a branch of the US National Institutes of Health (NIH) is funding the study. The NINDS will pay your study doctor or the institution to cover costs related to running the study.

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

Conflict of Interest

Your doctor may be referring you to this study and if your doctor is also an Investigator in this study, he or she has a potential conflict by having two sets of interests (your well-being, and the scientific conduct of the study). If you are uncomfortable with your doctor working with you as part of this research study, but still wish to participate in the research, you may request to work with a different member of the research team.

2. What Will Happen To You While You Are In This Research Study?

The study team will describe the treatment options for the narrowing of the artery feeding your brain. The options include the novel intensive medical management plan with or without opening the artery.

Intensive medical management includes treatments for lifestyle risk factors such as high blood pressure, high cholesterol, diabetes, and smoking cessation. Your local doctor will work with you to control these risk factors. The study will also involve your doctor working with national experts. These experts will review your progress to see if there are changes that could be made to better control your risk factors.

The other options for treating the narrowed artery include carotid endarterectomy (CEA) or carotid artery stenting (CAS). Both of these procedures have been used by doctors across the nation for many years to treat the narrowing of arteries.

CEA is a surgical procedure. During CEA the thickened area (plaque) of the artery is removed through an incision (surgical cut) in the neck.

CAS consists of placing a metal device called a stent in the narrowed part of the artery to hold it open.

You and your local doctor will then decide whether CEA or CAS would be the best option to open your carotid artery.

After you have decided on the best option for you, you will receive one of the options below by chance (as in the flip of a coin):

- Intensive medical management alone
- Intensive medical management plus either CEA or CAS

You will have a 1 out of 2 chance of being in either group. Neither you nor your doctor will be able to choose which group you are placed into.

Intensive Medical Management:
All participants in the study will receive intensive medical management.

You will take an aspirin tablet (between 70-325 mg) once a day. If you are unable to take aspirin 70-325 mg daily, your study physician will discuss a suitable alternative.

You may take other medications to control various risk factors such as high blood pressure or high cholesterol. Your doctor will be reviewing your progress with national experts, and together they will work with you on approaches to manage your blood pressure and cholesterol.

The study doctor will also work with your primary care doctor on a program for weight loss, smoking cessation, exercise, and diabetes management, depending on your individual health needs.

You will also be enrolled in a risk factor management program called INTERVENT. This is a program that is used around the country and in other parts of the world that helps patients manage their risk factors.

Help in managing your risk factors will be done through telephone calls with one of the INTERVENT staff members. These staff members, or coaches, are healthcare workers who are not physicians. These coaches have been specially trained to follow the medical management plan your study doctors have recommended for you and help you figure out ways to follow them as completely as possible.

You will have 6 telephone conversations with your coach in the first 3 months of the program and then 1 every 3 months until you have been in the study for 1 year. After that you will have a telephone conversation with your coach every 6 months for the rest of the time you are in the study. Each call will last from 15-20 minutes. You will not have to pay anything for these telephone calls. Reports will be sent to your study doctor and study coordinator about how well you are doing in the program, and also be reviewed by the national experts who work with your doctor. Your study doctor or coordinator will talk with you about how you are doing and if you should change anything.

It is important that you participate in the INTERVENT coaching. Patients enrolled in the program tend to have better results in controlling their risk factors than those who were not enrolled in the program. It is important that each participant in this study use the same program to manage their risk factors.

<u>Follow-up assessments</u>
You will have an in-person visit with a member of the study staff at the 44-day visit after you have been placed into one of the groups. You will have a follow-up visit at 4 months, 8 months, 12 months and then every six months thereafter for up to 4 years. At your 12-, 24-, 36-, and 48-month visit, you will have blood drawn to monitor your risk factors and the effectiveness of the medication you are taking. If you are a diabetic, it is recommended that you have a blood test

every 4 months to measure how well your diabetes is being controlled. If your blood tests are not meeting treatment goals, your study doctor may have additional blood tests repeated. You will be asked questions about your health status and any changes in your health since your last visit.

Your blood pressure will be measured at each visit. You may be asked to return for more visits if your blood pressure is higher than standard-of-care guidelines. At this time, you may need to change your blood pressure medications and return every 30 days until it is under better control.

If circumstances arise that make it difficult for you to come into the clinic for a follow-up visit, we will try to arrange to do a telephone interview or a virtual visit with you to collect some information.

An important part of this study is to see how treating the narrowing of your carotid artery might affect your thinking (cognition). This assessment will be done by a telephone interview with research staff at the University of Alabama at Birmingham. This interview will last about 20 minutes. You will be called at baseline and annually for the next 4 years. Patients who do not fluently speak English will not take part in this testing.

You will also have a test that will measure how much your artery is narrowed (a carotid duplex ultrasound) performed at the 12-, 24-, 36-, and 48-month visit. A carotid duplex ultrasound is done using a probe that is placed against the outside of your neck, over the carotid artery. Sound waves from the probe produce an image of the blood flowing through the artery.

It is possible that during follow-up, a small proportion of patients may develop a stroke. Under these circumstances, your carotid artery may be considered to be "symptomatic." The standard of care is to undergo either surgery or stenting to open the "symptomatic" carotid artery, and we will recommend the same approach for you. The final decision will remain with you and your treating physician. You will continue medical management and we will continue to follow your progress as planned in the study.

If you will undergo **Carotid Endarterectomy (CEA)**:

The study doctor will review the entire procedure with you. You will sign a separate consent form for the CEA surgery. A general description of what will be done during the procedure is described below.

Before the procedure

You will need to take aspirin in preparation for your procedure. This medication is intended to prevent your blood from clotting and will be prescribed by your doctor. You will also be started on medications for lowering cholesterol, blood sugar, and blood pressure as necessary and appropriate for you. You will have blood tests to evaluate your risk factors.

You will be given fluids and medicines to help you relax and keep you from feeling pain through a needle inserted into a vein. The procedure may be performed under general anesthesia (while you are asleep) or local anesthesia (medication injected into your neck like that used by dentists). Your doctor and anesthesiologist will decide which form of anesthesia is best for you.

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After the procedure
After your surgical procedure, you will take aspirin (70-325 mg tablet) daily indefinitely. In addition to this, your doctor may ask you to take other medications, such as medicine to control blood pressure, blood sugar, and cholesterol, as necessary for you. Your stroke risk factors will be managed as they are for the patients assigned to receive medical management alone.

If you will undergo **Carotid Artery Stenting (CAS):**

The study doctor will review the entire procedure with you. You will sign a separate consent form for the CAS procedure. A general description of what will be done during the stenting procedure is described below.

Before the stent procedure
About two days before the procedure, you will need to take aspirin and one other medication in preparation for your procedure. These medications are intended to prevent your blood from clotting and will be prescribed by your doctor. You will also be started on medications for lowering cholesterol, blood sugar, and blood pressure as necessary and appropriate for you. You will have blood tests to evaluate your risk factors.

After the stent procedure
You will take 75 mg of clopidogrel daily for 4 weeks. If you are allergic to clopidogrel, you will take either 90 mg of ticagrelor or10 mg of prasugrel twice daily for 4 weeks. You will also take one or two regular strength aspirin tablets (325 mg) daily for 4 weeks. The combination of these two medicines will help prevent blood clots from forming. After the 4 week period you will continue to take aspirin 70-325 mg every day indefinitely. Your local doctor may also ask you to take other medications to control blood pressure, blood sugar, or cholesterol. Your stroke risk factors will be managed as they are for the patients assigned to receive medical management alone.

3. How Long Will You Be in This Research Study?

You will be in the study for up to four years.

4. Why You Might Want To Take Part In This Research Study

This study may not make your health better. However, information learned in this trial will help to better care for patients with asymptomatic carotid disease in the future.

5. What Are the Risks Of This Research Study?

The risks of this study fall into three broad categories:

1. Risks of opening the artery. The main risks of opening the artery for CEA and CAS include stroke, heart attack, and death.
2. The risks of not opening the artery. The risk of not opening the artery is that patients might be at a higher risk of stroke than if they underwent opening the artery.
3. The risks of medical intervention. Medical intervention for risk factor control has risks associated with specific drug therapies.

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Risks of Intensive Medical Intervention Drug Therapies

The only drug that is specifically required on this study is aspirin. All subjects in this study will take aspirin.

Aspirin Side Effects

Aspirin may cause side effects. Tell your doctor if any of these symptoms are severe or do not go away:

- nausea
- vomiting
- stomach pain
- heartburn

Risks of Carotid endarterectomy (CEA)

The most important risks associated with the CEA procedure include:

- minor stroke (symptoms go away in 30 days) (occurs in less than 5% or 5 out of 100 patients)
- major stroke (occurs in less than 5% or 5 out of 100 patients)
- death (occurs in less than 1% or 1 out of 100 patients)
- long-term discomfort at the site of the surgical incision (occurs in less than 5% or 5 out of 100 patients)
- surgery may cause damage to the blood vessels resulting in bleeding or vessel narrowing. This may cause problems with neurological (nerve) function, depending on the severity. (occurs in less than 5% or 5 out of 100 patients)

Risks of Carotid Artery stenting (CAS)

The stenting part of this trial may be considered investigational by the FDA. All of the stents and their components that will be used in this trial have been approved by the FDA and are commercially available. However, there is a chance that the devices may be used off-label depending on your level of stenosis and what combination of devices your surgeon feels is best for your care.

The risks associated with the stent procedure include:

- minor stroke (symptoms go away within 30 days) (occurs in less than 4% or less than 4 out of 100 patients)
- major stroke (occurs in less than 1% or less than 1 out of 100 patients)
- death (occurs in less than 1% or less than 1 out of 100 patients)
- bleeding (occurs in less than 1% or 1 out of 100 patients)
- blockage to the artery in the leg requiring surgical repair (occurs in less than 1% or 1 out of 100 patients)

There may be discomfort or bleeding at the site of insertion of the catheter into the artery.

Risks that may be associated with the embolic protection device are:

- thrombosis (clot) of the filter (occurs in less than 1% or 1 out of 100 patients)

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- filter entanglement on the stent or other damage to the stent (occurs in less than 1% or 1 out of 100 patients)
- mechanical failure of the device (occurs in less than 1% or 1 out of 100 patients)

On very rare instances, filter entanglement with the stent or failure to recover the filter could result in the filter coming off and remaining inside the vessel. In such a case, your doctor would use additional measures to remove the filter or stabilize it in the vessel so that it does not block blood flow. The enlarging of the carotid artery may cause damage to the blood vessels resulting in bleeding or vessel narrowing. This may cause problems with neurologic (nerve) function or death, depending on the severity.

Some research participants may be allergic to the contrast material (x-ray dye) or other medications used during the procedure. Stenting involves exposure to radiation through the use of fluoroscopy, an x-ray camera that allows real-time moving images of the arteries.

Subjects who undergo CAS will receive aspirin combined with clopidogrel, ticagrelor or prasugrel. Clopidogrel and prasugrel are blood thinning medications routinely given to patients undergoing CAS to help the stent stay open. If you are already taking these medications, you will be asked to continue them. If you are not taking these medications, they will be started by your doctor with your CAS procedure.

Side effects of clopidogrel, ticagrelor and prasugrel:

- Bleeding may occur in up to 1 out of 10 patients. Bleeding can be serious and sometimes lead to death.
- Thrombotic Thrombocytopenic Purpura (TTP): TTP is rare occurring in 1 in 250,000 people taking clopidogrel. TTP is a blood clotting problem where blood clots form in blood vessels; and can happen anywhere in the body. TTP may cause death. Symptoms of TTP include:
- Purplish spots (called purpura) on the skin or in the mouth
- Yellowing of the skin or the whites of your eyes

Other risks

Side effects of 'statin' medications
There are many ‘statin’ medications. Your doctor will choose one of these medications.
Common (occur in 1 out of 10 people)

- Nausea
- Sore throat
- Diarrhea

Rare (occur in less than 1 out of 100 people)

- Muscle pain or damage that could cause kidney damage

Blood draws

The risks of drawing blood include pain, bruising, and rarely, infection at the site of the needle stick.

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Narrowing of the treated artery
Even with a successful procedure, CEA or CAS, there is a chance that the treated area could become narrow again. This may require additional treatment, such as repeat angioplasty and/or surgery to reduce the chance of stroke that can be caused by the re-narrowing.

Pregnancy and Birth Control
The study may involve unforeseeable risks to you or your fetus if you are pregnant. Therefore, pregnant women are excluded from this study. Should you become pregnant while taking part in this study, you must immediately notify your doctor.

1) Will women of child-bearing-potential be allowed to participate in this study?
   Yes: Women of child-bearing-potential will be able to participate in this study if they have a negative pregnancy test and agree to use acceptable birth control (see #5) since the risks to an unborn child are either unknown or potentially serious.

2) Will pregnant and/or nursing women be allowed to participate in this study?
   No: There is not enough medical information to know what the risks might be to an unborn child carried by a woman who takes part in this study.

3) Do you need to have a pregnancy test done to be part of the study?
   No: A pregnancy test will be done as part of your normal clinical care and not part of the study.

4) Will men who are able to father a child be allowed to participate in this study?
   Yes: Men who are able to father a child are allowed to take part in this study.

5) What types of birth control are acceptable?
   Surgical sterilization
   Approved hormonal contraceptives (such as birth control pills, Depo-Provera)
   Barrier methods (such as a condom or diaphragm) used with a spermicide
   An intrauterine device (IUD)

Risk summary

- Many side effects go away shortly after the medication or surgical procedure is stopped, but in some cases side effects can be serious, long lasting, or may never go away.
- Some side effects may not be known.
- Side effects may range from mild to life-threatening. There may be a risk of death.
- Other drugs may be given to make side effects less serious and less uncomfortable.
- Talk to the researcher and/or your healthcare provider about side effects and ask any other questions.

6. What Other Choices Do You Have If You Don't Take Part In This Research Study?

You do not have to be in this study to receive treatment for your condition. Your other choices may include other procedures or medications which will be discussed by the physician with you.

You should talk to the researcher and your regular physician about each of your treatment options before you decide if you will take part in this study.

7. Are There Reasons You Might Leave This Research Study Early?

Taking part in this research study is voluntary. You may decide to stop at any time. You should tell the researcher if you decide to stop and you will be advised whether any additional tests may need to be done for your safety.

In addition, the researchers may stop you from taking part in this study at any time:

- if it is in your best clinical interest,
- if you do not follow the study procedures,
- if the study is stopped.

8. Will You Need To Pay For Any Of The Tests And Procedures?

You and/or your health plan will need to pay for all tests and procedures that are part of this study, including CEA or CAS, and the blood tests to monitor your risk factors because they are part of regular medical care for patients with carotid artery disease. If your insurance does not cover the costs of the blood pressure and cholesterol medications required by this study to control your vascular risk factors, then the study will provide these medications at no additional cost to you. If study staff recommend that you take Praluent (alirocumab) to lower your cholesterol to the treatment goal of the study, the drug will be supplied at no cost to you while you are participating in the study. After your participation in the study, if your doctor decides you need to continue taking Praluent (alirocumab), you or your insurance company will be responsible for the cost of that medication.

The central oversight of medical management and the INTERVENT lifestyle program will be provided to you by the study at no cost whether you have health insurance or not.

9. Will You Be Paid For Participating In This Research Study?

You will receive $95 for each scheduled visit you complete. These scheduled visits include the baseline visit, and the subsequent visits at 44-days, 4-months, 8-months, and then at 12-months, 18-months, 24-months, 30-months, 36-months, 42-months, and 48-months. You will be paid following each visit.

Payments will be made to you with a prepaid debit card.

Every effort will be made to have the payment loaded on to your card within one business day of your visit.

Details of the system are explained on an additional information sheet.

If you receive payments for being a part of this research study, you may be asked to complete an Internal Revenue Service (IRS/W-9) form. The amount you receive may count as income and may affect your income taxes. Your social security number will be required to complete the IRS (W-9) form.

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If you are able to be seen by the CREST-2 team at all eleven visits, your total reimbursement could be up to $1,045.

You may also receive an additional $95.00 for other study visits.

10. What Happens If You Are Injured Or Become Ill Because You Were In This Research Study?

If you have side effects from the study treatment, you need to report them to the researcher and your regular physician, and you will be treated as needed. Your hospital will bill you or your insurer for these services at the usual charge. You or your health plan might also have to pay for other drugs or treatments which are given to help you control side effects. There are no plans to pay you or give you other compensation for an injury, should one occur. However, you are not giving up any of your legal rights by signing this form.

Before you take part in this study, you should call your health insurer to find out if the cost of these tests and/or procedures will be paid for by the plan. Some health insurers will not pay for these costs.

You will have to pay for any costs not covered by your health insurer.

In the event that you become ill or injured from participating in this research study, emergency medical care will be provided to you. The University of Cincinnati will decide on a case by case basis whether to reimburse you for your out of pocket health care expenses.

11. What Are Your Rights If You Are In This Research Study?

Taking part in this research study will not change your rights and benefits. Taking part in this research study does not give you any special privileges. If you decide to not participate in this study, or stop in the middle of the study, no benefits are taken away from you. You do not have to be in this research study to receive or continue to receive medical care.

You will be told of important new findings or any changes in the study or procedures that may affect you or your willingness to continue in the study.

12. What About Your Privacy?

We have obtained a **Certificate of Confidentiality** from the Department of Health and Human Services. The Certificate is designed to prevent us from being forced to disclose identifying information for use in any federal, state, or local civil, criminal, administrative, legislative, or other court proceeding, even if faced with a court subpoena. You should understand, however, 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. We may not withhold information if you give your insurer or employer or a law enforcement agency permission to receive information about your participation in this project. This means that you and your family must also actively protect your own privacy.

The Certificate does not prevent us from taking steps, including reporting to authorities, to prevent serious harm to yourself or others. Such disclosures will be made as described below.

The research team may share your information with:

- The Department of Health and Human Services (HHS), to complete federal responsibilities for audit or evaluation of this project;
- Public health agencies, to complete public health reporting requirements;
- Hospital or university representatives, to complete hospital or university responsibilities for oversight of this study
- Your primary care physician if a medical condition that needs urgent attention is discovered; Appropriate authorities to the extent necessary to prevent serious harm to yourself or others.

Authorization to Use and Disclose Health Information

A federal regulation known as the Privacy Rule gives you certain rights concerning the privacy of your health information. Researchers covered by this regulation are required to get your authorization (permission) to use and disclose (share with others) any health information that could identify you. You should have received a Notice of Privacy Practices when you received health care services here. If not, let us know and a copy will be given to you.

If you sign this informed consent form, you are giving permission for the use and disclosure of your health information for purposes of this research study. You do not have to give this permission. Your health care outside of the study, payment for your health care, and your health care benefits will not be affected if you choose not to sign this form. However, if you do not sign this form, you will not be able to participate in the study.

Who Will Use and Disclose My Health Information? The study doctor and research staff (the study team) may use your health information to conduct, review, and determine the results of the study. The study team may also use your information to prepare reports or publications about the study. However, your name will not appear in any report or publication without your permission.

What Health Information will be Used and Disclosed? The study team will record your medical history, the treatment you receive, and the results of examinations and tests done during the study on study forms. The study team will send the completed study forms to the study sponsor. Representatives from the groups identified below may need to look at your medical records to make sure that the information on the study forms is correct or that the study was conducted properly. Your medical records may include other health information about you and may include documents that directly identify you. Reviews like that will take place at the study center or where the medical records are stored and can take place after the study is over.

Who Will Receive My Health Information? Your study information or medical records (as described above) or both may be shared with the following people or groups:

- The study sponsor or its representatives, including companies it hires to provide study-related services
- Researchers who are conducting this study at other study centers
- UC Institutional Review Board and any other committees responsible for overseeing the research

- Staff of the UC Human Research Protection Program
- Mayfield Clinic employees and UC Health, LLC on behalf of itself and affiliate entities providing service or care to you
- Federal and State agencies, such as the U.S. Food and Drug Administration
- (FDA), Department of Health and Human Services (DHHS), the National Institutes of Health (NIH), and other US and non-US government bodies that oversee or review research

Will My Information Be Protected by the Privacy Rule After it is Disclosed to Others? Mayfield Clinic employees and UC Health, LLC on behalf of itself and affiliate entities providing service or care to you are required by the Privacy Rule to protect your health information. After your information is shared with others, such as the study sponsor, it may no longer be protected by the Privacy Rule. The people who receive this information could use it in ways not discussed in this form and could disclose it to others. The sponsor will use and disclose your information only for research or regulatory purposes or to prepare research publications. In addition to using it for this study, the sponsor may reanalyze the study data at a later date or combine your information with information from other studies for research purposes not directly related to this study. The goal of any such research would be to learn more about drugs, devices or diseases or to help design better studies in the future. When using your information in these ways, the sponsor may share it with regulatory authorities, other researchers, its business partners, or companies it hires to provide research-related services.

What Happens if I Leave the Study Early? If you stop participating in the study early for any reason, the study team will tell the sponsor why. If the study team asks you to come to any more study visits and you agree, the study team will send the sponsor information from those visits as well. All information collected about you may continue to be used and disclosed.

Will My Authorization Ever Expire? This Authorization does not have an expiration date. The study team may need to correct or provide missing information about you even after your study participation is over and a review of your medical records may also take place after the study is over.

May I Take Back My Authorization? You have the right to take back (revoke) your Authorization at any time by writing to the person in charge of this research study whose information is listed on the front of this form. If you revoke your Authorization, the study team will not collect any new health information about you. However, they can continue to use and disclose any already-collected information if that is necessary for the reliability of the study. The sponsor can also still keep and use any information that it has already received. If you revoke your Authorization, you can no longer continue to participate in the study.

May I Look At My Study Information? You have a right to see and make copies of your medical records. However, to ensure the reliability of the study, you will need to wait to see your study records until the study is completed.

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Information Disclosed to Study Sponsor
If this information is given out to anyone outside of the study sponsor, the information may no longer be protected by federal privacy regulations and may be given out by the person or entity that receives the information. However, the sponsor will take steps to help other parties understand the need to keep this information confidential.

This authorization lasts until the end of the study. The study does not end until all data has been collected, checked (or audited) and analyzed. Sometimes this can be years after your study visits have ended. For example, this could happen if the results of the study are filed with a regulatory agency like the Food and Drug Administration.

If you stop authorization, the sponsor may continue to use your information already collected as part of this study, but will not collect any new information. Also, you will no longer be able to participate in the study.

If you sign this informed consent form, you are giving permission for the use and disclosure of your health information for purposes of this research study. You do not have to give this permission. Your health care outside of the study, payment for your health care, and your health care benefits will not be affected if you choose not to sign this form. However, if you do not sign this form, you will not be able to participate in the study.

Your name and telephone number will be provided to the University of Alabama at Birmingham Survey Research Unit and the INTERVENT program to conduct the telephone assessments required as part of this study.

The researchers in this study would like to have your social security number on file. This number will be kept in a password-protected, encrypted database separate from the rest of the study data. The purpose of keeping participants social security numbers on file is to potentially link them in the future with national or regional health-related databases for research purposes only. The file containing any social security numbers will be destroyed at the end of the study.

Please initial one of the following:

_____ I agree to allow the research staff to use my social security number only as described in this study.
_____ I do not wish to disclose my social security number.

13. Who Can Answer Your Questions?

You can call …	At …	If you have questions or concerns about:
CREST-2 Principal Investigator: Dr. Thomas Brott	**Phone:** 904-953-2000	Questions about the study tests and procedures
Clinical Site Principal: Dr. Matthew Flaherty	**Phone:** 513-558-6609	Research-related injuries or emergencies Any research-related concerns or complaints
University of Cincinnati IRB	Phone: 513-558-5259	Rights of a research subject
Research Subject Advocate	Toll-Free: 800-889-1547	Use of Protected Health Information or any research-related concerns or complaints

14. Summary and Enrollment Signatures

You have been asked to take part in a research study. The information about this study has been provided to you to inform you about this study.

- I have read the whole consent form, and all of my questions have been answered to my satisfaction.
- I have been given the information about the use and disclosure of my health information for this research study
- I am satisfied that I have been given enough information about the purpose, methods, risks, and possible benefits of the study to decide if I want to join.
- I know that joining the study is voluntary, and I agree to join the study.
- I know that I can call the investigator and research staff at any time with any questions or to tell them about side effects.
- I know that I may withdraw from the study at any time.
- A copy of this form will be put in my medical records and I will be given a copy of this completed form. Please sign and date to show that you have read all of the above guidelines. Please do not sign unless you have read this entire consent form. If you do not want to sign, you don't have to, but if you don't you cannot participate in this research study.

_____ _____

(Date / Time) (Printed Name of Participant)

_____

(Signature of Participant)

_____ _____

Date/Time (Printed Name of Next of Kin/Legally Authorized Representative)

_____

(Signature of Next of Kin/Legally Authorized Representative)

_____ _____

(Date / Time) (Printed Name of Individual Obtaining Consent)

_____

(Signature of Individual Obtaining Consent)

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Addendum to the CREST-2 Informed Consent Document for Optional Research MRIs at the beginning and end of the Study

CREST-2 Principal Investigator: Thomas Brott, MD, Mayo Clinic, Jacksonville, FL

Clinical Site Principal Investigator: Matthew Flaherty, MD

Clinical Study Site: University of Cincinnati Medical Center, Cincinnati, Ohio

The following information should be read as an addition to the information in the above informed consent document.

The purpose of this form is to see if you will agree to have optional research MRIs (Magnetic Resonance Imaging) scan at the beginning and end of the study.

The MRI at the beginning of the study will be done to look at plaque in your carotid arteries. At the end of the study a MRI scan will be done of your brain.

The MRI scanner is a larger machine with a tunnel or hole in the center.

You will be asked to lie down on the table of the MRI scanner, which slides in and out of the tunnel. You may feel the table vibrate and/or move slightly during the scan. The MRI machine makes loud knocking sounds. Because of this you will be given earplugs that you will be required to wear. A little microphone and loudspeaker is placed inside the MRI scanner so that you can talk to the scanner operator at any time. If you experience any discomfort, you can tell the scanner operator through the intercom. You may experience a localized twitching sensation due to the magnetic field changes during the scan. This is not unexpected and should not be painful. The entire MRI scan will last about 45 to 60 minutes.

Risks associated with MRI: The MRI uses a powerful magnet to examine blood vessels in key area of the body. MRI does not involve x-rays. People who have certain types of metal objects in their bodies cannot have a MRI. The force of the magnet could move these objects within the body and cause serious injury. You will be asked to complete a MRI screening form to check for the presence of metallic implants and materials. People with pacemakers, aneurysm clips, and cochlear implants, or metal/foreign objects in their eyes cannot have the MRI. You need to tell your doctor or MRI technician if you have any of these things inside you, or even if you only suspect that you might and/or you are not sure where they are.

Possible Claustrophobia (Fear of Small Spaces): Some people with claustrophobia and others may feel too closed in and may not be able to tolerate MRI scanning. If you feel too confined in the MRI scanner, you can ask that the scan be stopped after you enter the MRI scanner.

CREST-2

Possible Discomfort/Hearing Damages from Noise: The MRI machine makes loud knocking sounds when it is scanning. Because of this you will be asked to wear earplugs while having your MRI scan. The earplugs minimize discomfort from noise and keep the MRI noise within the safety range for hearing.

I agree to have an MRI of my carotid arteries to look at plaque at the beginning of the study.

☐ Yes ☐ No

I agree to have a brain MRI at the end of the study.

☐ Yes ☐ No

_____ _____
(Date / Time) (Printed Name of Participant)

_____
(Signature of Participant)

_____ _____
(Date / Time) (Printed Name of Individual Obtaining Consent)

_____
(Signature of Individual Obtaining Consent)