Protocol Title: Effects of Anorexia Nervosa on Peak Bone Mass

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Site Principal Investigator:

Description of Subject Population: Subjects between 14 and 22 years old diagnosed with anorexia nervosa

Effects of Anorexia Nervosa on Peak Bone Mass
NCT01301183
Version date: March 29, 2018
Consent Form

About this consent form

Please read this form carefully. It tells you important information about a research study. A member of our research team will also talk to you about taking part in this research study. People who agree to take part in research studies are called "subjects." This term will be used throughout this consent form.

Partners HealthCare System is made up of Partners hospitals, health care providers, and researchers. In the rest of this consent form, we refer to the Partners system simply as "Partners."

If you have any questions about the research or about this form, please ask us. Taking part in this research study is up to you. If you decide to take part in this research study, you must sign this form to show that you want to take part. We will give you a signed copy of this form to keep.

Some of the people who are eligible to take part in this study may not be able to give consent because they are less than 18 years of age (a minor). Instead we will ask their parent(s) to give permission for them to take part in the study and will ask them to agree (give their

assent) to take part. Throughout the consent form, "you" always refers to the person who takes part in the study.

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.

Why is this research study being done?

Anorexia nervosa is common in girls and young women. Anorexia nervosa can lead to decreased bone density and increased risk of broken bones. People with anorexia nervosa often have low levels of hormones called insulin like growth factor-1 (IGF-1) and estradiol (a form of estrogen). IGF-1 stimulates bone cells to build bone. Estradiol helps to build bone and also helps prevent bone breakdown. We are doing this study to find out if giving low doses of IGF-1 and estradiol will help increase bone density in girls and young women with anorexia nervosa.

This study will measure bone density and bone microarchitecture (tiny structures within bone) before and after receiving 12 months of estradiol (estrogen) supplement and placebo or 12 months of estradiol supplement along with IGF-1 supplement.

Recombinant human IGF-1 (rhIGF-1, the IGF-1 medication) and estradiol skin patches are not approved by the U.S. Food and Drug Administration (FDA) to improve bone strength. This means that IGF-1 can only be used in research studies.

The U.S. Food and Drug Administration (FDA) has approved IGF-1 to treat conditions of short stature (height) due to primary IGF-1 deficiency but the FDA has not approved IGF-1 to improve bone strength.

Estrogen has been approved by the FDA for use in children and adolescents with low estrogen levels. However, it has not been approved for improving bone strength in teenagers with anorexia nervosa.

This research study will compare rhIGF-1 to placebo. The placebo looks exactly like rhIGF-1, but contains no rhIGF-1. During this study, you may get a placebo instead of rhIGF-1. Placebos are used in research studies to see if the results are due to the study drug or due to other reasons. You will take the study drug, either rhIGF-1 or placebo, twice a day for 12 months by using a small needle to put the study drug under your skin.

We are asking you to take part in this study because you have anorexia nervosa.

Our approved target enrollment study wide is 272, with 222 subjects approved to be enrolled at Partners. We expect to enroll 200 subjects with anorexia nervosa in this research study, in order to find 100 subjects who can complete the entire study. We will enroll 72 subjects without anorexia nervosa in order to find 36 who can complete the entire study.

The National Institutes of Health are paying for this research to be done.

How long will I take part in this research study?

You will be in this study for up to a total of 14 months. During this time, we will ask you to make 10 study visits to MGH.

What will happen in this research study?

If you choose to take part in this study, we will ask you to sign this consent form before we do any study procedures. After signing the consent form you can decide not to participate in the study. We will first ask you to come to a Screening Visit. If you are eligible to continue taking part in this study, we will ask you to come back for 9 more study visits. The study visits are discussed in detail below.

Screening Visit (Visit 1)

The screening visit will take about 3 hours. During this visit, we will do some tests to see if you qualify to take part in this research study. The study doctor will review the results of these tests and procedures.

At this visit, we will:

- Ask you questions about your health and give you a brief physical exam, including finding out your stage of puberty and menstrual history. We will measure your vital signs (blood pressure, temperature, heart and breathing rates).

- Measure your height and weight with you standing backwards so you cannot see the numbers.

- Draw a blood sample for routine tests.

- Ask for a urine sample to test for pregnancy, or use serum from blood already being collected to test for pregnancy if a urine sample cannot be obtained. If you are pregnant, you cannot take part in this study. If your test results show that you are pregnant, we will let you know. If you are age 14-17, we will tell your parent/guardian the results of this test if you agree to let us. Even if you don't agree, the study doctor may decide to tell your parent/guardian based on your age and maturity. If you are at least 18 years old, we will tell you and not your parents about the results of the test. This test result will not become part of your medical record. It will stay a part of your research record. Every effort will be made to protect this information. However, there are times when the study doctor or study staff will legally have to release this information.

- Give you a psychiatric interview after the screening visit. This interview will be done by a study psychiatrist or psychologist and it may be done over the telephone.

- Take a bone age x-ray of your left wrist. This is a special type of x-ray scan that helps us find out how mature your bones are.

- We will study your bone strength, body fat, and muscle content. To do this, we will use a special type of X-ray machine called a dual energy x-ray absorptiometry (DEXA) machine. During the DEXA scan, we will ask you to remove all metal items from your body including clothing fasteners, jewelry and accessories. We may ask you to wear a hospital gown if necessary. You will lie still on the scanning table while the arm of the DEXA machine passes over your body from head to toe. This will take about 20 minutes. DEXA scans are for research purposes only and the scans do not reliably show bone disorders such as tumors or other abnormalities. The results are not useful for your care and won't be put in your medical record.

- We may do the DEXA scan at the baseline visit (Visit 2)

- Give you a food diary. A nutritionist will give you instructions on how to fill it out and ask you to either mail it back to us or bring it back at the next visit.

Although it is hoped that you will complete the food diary, you can choose not to do so and still participate in the study.

- Give you a snack once you complete the visit

Study Drug (rhIGF-1):
You will be given information about the study drug, rhIGF-1, at this initial Screening Visit, but will not receive study drug until you have been found eligible for the study. We will give you instructions about how to give yourself rhIGF-1 injections at home. You will give yourself both rhIGF-1 and placebo injections exactly the same way. You will need to give yourself these injections twice a day using a syringe and needle. These injections will need to be given under your skin about 30 minutes after breakfast and dinner every day for 12 months. You may give yourself the injection under the skin of your arm, stomach, or thigh. We will give you emergency contact information for a member of the study staff, in case you experience trouble giving yourself the injections. The bottle containing rhIGF-1 needs to be stored in the bottom shelf of a refrigerator at all times (except when taken out for an injection).

Half of the subjects with anorexia nervosa will receive rhIGF-1. The other half will receive placebo. The placebo looks exactly like the rhIGF-1 but does not contain any rhIGF-1. You will have an equal chance (1 out of 2) of receiving either rhIGF-1 or placebo. The MGH research pharmacy will randomly decide (like flipping a coin) whether you will receive placebo or IGF-1. Only the pharmacy will know whether you will receive IGF-1 or placebo, but your study doctor can find out this information if needed.

We will ask you to write down the time at which you give yourself the injections at home in a logbook that we will give to you. You will need to bring the logbook with you to show the study doctor at each visit.

rhIGF-1 may rarely cause your blood sugar level to drop. We will give you instructions about how to recognize the symptoms of low blood sugar and what to do if you have low blood sugar. You should carry a juice box or glucose (sugar) pills with you at all times while you are taking part in the study. If you have any symptoms of low blood sugar, you should drink a juice box or take 2 glucose (sugar) pills and call a member of the study staff. Some symptoms of low blood sugar are weakness, dizziness, trembling, nausea, anxiety, hunger, and paleness.

Study Drug (estrogen patches and progesterone):
We will give you self-adhesive patches delivering estrogen (100 micrograms/day). Everyone taking part in this study will use patches with estrogen, not placebo. You will apply 1 patch twice a week (Sunday morning and Wednesday night of every week for the next 12 months).

These patches are less than ¾ inch across in size and may be applied on the lower belly or back. The patch should be applied on a clean, dry area that is not oily, bruised or irritated. You should avoid putting the patches around your waistline since tight clothing may rub the patch off.

You should apply the patch immediately after opening the package and removing the protective liner. It should be pressed firmly in place with the palm of the hand for about 10 seconds, making sure there is good contact, especially around the edges. If a patch falls off, it may be reapplied, or if necessary, a new patch may be applied. The location of application should be rotated, with at least 1 week between applying the patch again at the same location.

You will be able to swim and shower while wearing the patch.

If you are a woman who can become pregnant, we will give you a urine or serum pregnancy test before you start using the estrogen patch. Pregnant women cannot take part in this study.

We will continue to give you pregnancy tests during the entire study.

You will also take a pill containing 100 mg of Prometrium (Progesterone) for the first 10 days of every month for the next 12 months. Prometrium will cause you to have menstrual periods.

Study Drug Reminders:
You will receive a paper medication calendar to keep track of each dose taken and to return to study staff at each visit. Additionally, we can enter medication reminders on your or your parent/guardian's phone's calendar to remind you when to take the different study drugs and how much. You can change the settings and frequency, or discontinue the alarms at any time. All patient information will remain confidential, and no identifiers will be used. Please indicate below if you would like to receive reminders via your phone's calendar.

☐ Yes ☐ No Initials_____

Baseline Visit (Visit 2)

If you are eligible and want to continue in the study, we will ask you to come to MGH in the morning at about 8:00 a.m. This visit will take about 4 hours. You will need to come in fasting. Fasting means that you cannot have anything to eat or drink, except for water, after midnight.

At this visit, we will:

- Ask you questions about your health and give you a brief physical exam.

- Ask you to bring in your food diary and review it with the nutritionist. We will give you another food diary to bring back at your next study visit.
- Measure your height and weight.
- Ask you about your exercise schedule.
- Draw blood to measure the amount of certain chemicals in your blood. These include calcium, vitamin D, other chemicals important for bone formation, and glucose (sugar).
- We will perform the DEXA scan at this visit, if it was not performed at the initial Screening Visit.
- Teach you and your parents or guardians how to give yourself rhIGF-1 injections.
- Give you a breakfast of your choice to eat.
- Teach you how to give the IGF-1 injections. You will give the first rhIGF-1 shot under your skin about 30 minutes after you finish eating breakfast.
- Look at your bone structure by giving you an X-treme CT. The X-treme CT is an X-ray machine that can take detailed pictures of your bones.
- Ask you to take calcium and vitamin D supplement pills daily. These pills will help your bones grow while you are taking part in the study. Not getting enough calcium and vitamin D through food or through supplements may prevent your bones from growing well. We will give you 6 months worth of pills at this visit.
- Ask for a urine sample to test for pregnancy, or use serum from blood already being collected to test for pregnancy if a urine sample cannot be obtained.
- Ask you to complete an eating disorder questionnaire. This will take you about 10 minutes.
- Ask you to complete two questionnaires regarding your mood. These will take you about 10 minutes total.
- Ask you to complete questionnaires that assess cognition (if time and circumstances allow during the visit).

- Give you a snack once you complete the visit

You may sometimes have the option of combining the first two visits, the screen and baseline.

1-month (Visit 3), 4.5-month (Visit 5), 7.5-month (Visit 7), and 10.5-month (Visit 9)

These visits will last about 30 minutes. You will need to come in fasting. At these visits, we will:

- Ask you questions about your health and give you a brief physical exam
- Measure your height and weight
- Draw some blood to measure the amount of glucose and IGF-1 in your blood.

  If you do not live close to the study center, you will be able to have your blood drawn offsite. If you choose this option, you will also have questions about your history and your physical exam done by a local doctor for each offsite visit. Some of the tests will be done at these offsite locations, and the results will be mailed to us. Otherwise, the samples themselves will be mailed to us. If you are a Hasbro patient, you can conduct these visits and the blood draws with your treatment team at Hasbro.

- Ask for a urine sample to test for pregnancy, or use serum from blood already being collected to test for pregnancy if a urine sample cannot be obtained.

3-month (Visit 4) and 9-month (Visit 8)

These visits will last about 30 minutes. You will need to come in fasting. If you are a Hasbro patient, you can also conduct these visits and the blood draws with your treatment team at Hasbro.
At these visits, we will:

- Ask you questions about your health and give you a brief physical exam
- Ask for a urine sample to test for pregnancy, or use serum from blood already being collected to test for pregnancy if a urine sample cannot be obtained.
- Measure your height and weight

- Ask you to bring in your food diary and review it with the nutritionist. We will give you another food diary to bring back at your next study visit.

- Draw some blood to measure the amount of glucose and IGF-1 in your blood, as well as the amount of some chemicals that show how your bones have grown.

- Ask you about your exercise schedule.

6-month (Visit 6) and 12-month (Visit 10)

These visits will include all of the procedures done at the baseline visit (Visit 2) listed above, including the DEXA scan.

Taking You out of the Study Early

The study doctor may take you out of the study without your permission. This may happen because:

- The study doctor thinks it is best for you to stop taking the study drug
- You are unable to attend the required study visits
- You are unable to give the study drug
- The Sponsor decides to stop the study
- We stop doing the study for other reasons
- You become pregnant

If this happens, the study doctor will explain why you need to stop taking part in the study.

Review of Medical Records from Hospital Admissions or Emergency Department Visits

MGH has an electronic system that lets your study doctors know if you are admitted to a Partners Hospital, or if you visit a Partners Hospital Emergency Department for any reason. This alert will let the study doctors know why you are there. We want to make sure the study doctors know about any possible problems or side effects you experience while you are taking part in the study.

Sending Study Information to Research Collaborators Outside Partners

We may need to send your study samples to research collaborators at different labs. We will label all your study materials with a code instead of your name. The key to the code connects your name to your study information and samples. The study doctor will keep the key to the code here at Partners and will not share it with our research collaborators. No one outside of Partners will know which study information or samples are yours.

Storing Samples at MGH for Future Use

We would like to store some of your samples and health information for future research related to eating disorders. We will label all your samples and health information with a code instead of your name. The key to the code connects your name to your health information and samples. The study doctor will keep the key to the code in a password protected computer.

About 28 tablespoons of blood will be drawn throughout the entire course of the study.

Do you agree to let us store your samples and health information for future research related to eating disorders?

☐ Yes ☐ No Initials_____

If later you change your mind and want your samples destroyed, contact the study doctor.

Future Studies:

We would like to contact you about future research studies. Please indicate below whether or not we may contact you about future research studies:

Yes: _____ No: _____ Initials: _____

<u>If you turn 18 during this Study</u>

If you turn 18 years of age while you are taking part in this study, we will ask you to sign a new consent form at that time.

What are the risks and possible discomforts from being in this research study?

Risks of rhIGF-1:

RhIGF-1 (recombinant human IGF-1) is FDA approved for treating children with short stature. It has been used successfully in children with short stature (height) and in children with very low levels of IGF-1 in order to increase growth rate and adult height. In these children, rhIGF-1 is given in higher doses than what you will receive in this study with very few side effects. IGF-1 is not FDA approved to improve bone strength. However, rhIGF-1 has been successfully used in adult women with anorexia nervosa to increase bone density with very few side effects. Takign rhIGF-1 may cause you to have one or more of the side effects listed below.

Common side effects:

- Mild or moderate hypoglycemia (low blood sugar). Low blood sugar occurs in a number of people receiving rhIGF-1. This is avoided by giving rhIGF-1 30 minutes after a meal or snack

- The most commonly seen side effects include some redness and pain at the injection site, which goes away on its own.

Less common side effects:

- Severe hypoglycemia (low blood sugar). Some symptoms of low blood sugar include weakness, dizziness, nausea, trembling, paleness, and hunger. Untreated low blood sugar (below 40 mg/dl) may cause confusion, drowsiness, changes in behavior, coma, and seizures.

  Although this is very unlikely to happen, if by any chance your glucose levels remain low and you feel you may pass out, please call 911. If you have a severe and long-lasting headache with nausea and vision changes, and you cannot reach a member of the study staff right away, please go to the nearest emergency room.

- In children receiving rhIGF-1 or growth hormone to increase growth rate, too rapid growth can rarely cause the growth plate at the upper end of the long bone of the thigh to slip. This may cause a limp, and pain at the hip and knee. RhIGF-1 and growth hormone can also cause some worsening of a pre-exisitng curvature of the spine.

  Increased pressure within the brain may sometimes occur that may cause headaches, nausea and vision changes.

  Because you will receive rhIGF-1 in a smaller dose than children with low IGF-1 levels, and for a very short period of time, these side effects should not happen.

Rare side effects include:

- Enlargement of lymph nodes
- Snoring
- Fat deposits at the injection site (a lump of fat which forms at the injection site)
- Ear problems (fluid in ear or ear pain)
- Joint pain
- Heart murmur or heart failure
- Allergic reaction
- Development of antibodies to IGF-1. Antibodies are proteins that are produced by the body to help fight infection and other foreign substances in the body. However, based on earlier studies, they do not appear to have any medical effect.

There may be other risks of rhIGF-1 that are currently unknown.

Risks of Estrogen:

Taking estrogen is associated with occasional side effects

Common side effects:

- Mild headaches

- Abnormal bleeding patterns, changes in nature and quantity of vaginal discharge
- Tenderness and enlargement of breasts
- Nausea and vomiting

Less common side effects:

- Abdominal pain and bloating

Rare side effects:

- Gall bladder disease
- Rashes
- Intolerance to contact lenses
- Migraines
- Dizziness
- Depression
- Abnormal movements
- Changes in weight
- Hypertension (high blood pressure) and clotting disorders (this includes clotting in large veins and strokes). These are more commonly seen in older women and in women with a family history of clotting disorders

- Continuously taking estrogen without taking progesterone might lead to cancer of the uterus. Because we will be giving you progesterone for only 10 days every month, this should not be a concern.

- Taking estrogen during pregnancy can be harmful to the unborn baby.

- Estrogen may cause you to stop growing earlier than expected. This is unlikely with the small doses of estrogen you will take in this study.

Reasons not to use estrogen

- Known or suspected pregnancy
- Undiagnosed abnormal uterine bleeding
- History of clotting disorders such as clots in superficial and deeply located veins in the body
- Known or suspected cancer of the breasts , uterus or ovaries.
- History of smoking

If you have a history of any of these disorders, you will be withdrawn from this study for your own safety. If you have a family history of clotting disorders, such as those mentioned above, or a family history of stroke or heart attack happening before the age of 50 years in a first or second degree relative, we will check your blood for clotting disorders. If are identified as having an abnormal result that makes you more likely to develop clotting disorders, this information will be made available to you at your request.

Risk of Progesterone:

Risks of taking progesterone by mouth include:

- clotting abnormalities,
- dizziness,
- nausea,
- abdominal pain,
- fatigue,
- headaches,

- insomnia,
- nervousness,
- sleepiness and
- breast tenderness and secretion.

Rare cases of breast cancer have been reported in women taking combined estrogen and progesterone. Rare instances of abnormal liver function have also been reported. The doses of progesterone that will be given with the estrogen patch used in this study are very small and are less likely to cause these side effects.

Risk of Calcium and Vitamin D:

Calcium taken by mouth can cause constipation and a metallic taste in the mouth.
Vitamin D in the dose you will take does not cause any side effects.

Risks of an Allergic Reaction:

As with any drug, an allergic reaction can occur. Allergic reactions can be mild or more serious, and can even result in death. Common symptoms of an allergic reaction are rash, itching, skin problems, swelling of the face and throat, or trouble breathing. If you think you are having an allergic reaction, call the study doctor right away. If you are having trouble breathing, call 911 immediately.

Risks of Fasting:

Fasting for long periods of time can cause your blood sugar levels to fall below normal. If this occurs, it may cause weakness, dizziness, sweating, headaches, or hunger. Because fasting will only occur between midnight and about 8 a.m. the following morning, we do not expect you to have any of these side effects.

Risks from study procedures:

There is a risk of superficial bruising and discomfort at the site where we draw blood from. Infection, lightheadedness, and fainting are risks involved with blood draws.

As a result of your participation in this study you will be exposed to radiation from x-ray studies of your bones, including the bone age x-ray of the wrist, the X-Treme CT scans and the DEXA

scans. Please note that this radiation is not necessary for your medical care and is for research purposes only. The total amount of radiation exposure you will receive from participation in this study is equal to a whole body exposure of about 0.16 milliSieverts (mSv). The dose that you will receive from participation in this research study is about the same as you would normally receive in about 20 days from background radiation from the earth and the sky.

Risks to an Embryo or Fetus, or to a breastfeeding Infant

If you are sexually active and able to become pregnant, you must agree to use one of the birth control methods listed below.

Acceptable birth control methods for use in this study are:

- Barrier methods (such as a condom or diaphragm) used with a spermicide (a foam, cream, or gel that kills sperm)
- Copper-containing intrauterine device (IUD) a device that is placed inside your uterus through the vagina by a doctor and can prevent pregnancy
- Abstinence (no sex)

We will complete a pregnancy test at every visit, so the likelihood of receiving any ionizing radiation from study procedures while pregnancy is extremely low. There is no known evidence of harm due to using the estrogen patch during early pregnancy but because the risks are not fully understood, it should not be worn during pregnancy. The effect of IGF-1 on early pregnancy has not yet been studied.

If you miss a period, or think you might be pregnant during the study, you must tell the study doctor immediately. If you become pregnant, you must stop taking the study drug and stop taking part in the study**.**

Emotional Risks

You may feel uncomfortable discussing issues related to eating problems, depression or anxiety, or substance use. The study staff is sensitive to this discomfort. If you share symptoms of depression, suicidality, or substance use, the study psychiatrist or psychologist will communicate with your existing treatment team and/or help to provide you with treatment referrals.

For your safety during this study, call your study doctor and your treating doctor BEFORE you take any new medication.

OPTIONAL SUB-STUDY - Regional Fat Distribution and Bone Marrow Fat Assessment with MRI/MRS:

In this sub-study, we will study the fat content of your bone marrow. This has been shown to be related to bone mineral density. The fat content of your bone marrow will be studied with magnetic resonance imaging/magnetic resonance spectroscopy (MRI/MRS). You will get these tests at the baseline and 12 month visits. This will take an additional 40-45 minutes.

Risk of MRI:

You will have an MRI scan of your body to quantify regional fat depots and thigh muscle area at baseline and again at 12 months. MRIs use powerful magnets to make images. There are no known radiation risks associated with MRI. However, persons with metal implants, such as surgical clips, or pacemakers should not have an MRI. All credit cards and other items with magnetic strips should also be kept out of the MRI room. Any loose metal object may cause damage or injury if it gets pulled toward the magnet. You will need to remove these devices when getting the scan. People who feel uncomfortable in confined spaces (claustrophobia) may feel uncomfortable in the narrow tube. The MRI makes loud banging noises as it takes images. Earplugs can be used to reduce the noises. The MRI can be stopped at any time at your request. If you are or suspect you are pregnant, you should not participate in this study.

MRI/MRS
The magnetic resonance spectroscopy techniques that we will use with the MRI study have the potential to cause localized and mild warming of your skin and the underlying tissues. For your safety and comfort, the use of these methods is restricted to prevent any excessive local warming. You should immediately inform us if you experience discomfort due to warming and the procedure will be stopped.

You will get additional $50 remuneration after the baseline and 12-month visits for participating in this sub-study.

Do you agree to take part in the optional MRI/MRS imaging for bone marrow fat assessment?
Yes: _____ No: _____ Initials: _____

What are the possible benefits from being in this research study?

You may not benefit from taking part in this study. However, you may have improved bone density and bone structure after taking part in this study.

Others with anorexia nervosa may benefit in the future from what we learn in this study.

What other treatments or procedures are available for my condition?

Other treatments for low bone density in anorexia nervosa include:

- Regaining and maintaining your normal body weight is the best treatment for prevention of further and continued bone loss. However, this may not normalize bone density.

- Adequate daily intake of calcium and vitamin D. Recent studies have shown that this may not be sufficient alone.

- Bisphosphonates. These medications are successful in improving bone density in certain groups of women. Bisphosphonates are typically avoided in young girls and women of reproductive age because they may be harmful during pregnancy.

- PTH (Teriparatide). PTH increases bone density in post-menopausal women, however, PTH is not recommended in young people at this time given reports of bone cancers when PTH has been given to animals.

Talk with the study doctor if you have questions about any of these treatments or procedures.

Can I still get medical care within Partners if I don't take part in this research study, or if I stop taking part?

Yes. Your decision won't change the medical care you get within Partners now or in the future. There will be no penalty, and you won't lose any benefits you receive now or have a right to receive.

Taking part in this research study is up to you. You can decide not to take part. If you decide to take part now, you can change your mind and drop out later. We will tell you if we learn new information that could make you change your mind about taking part in this research study.

What should I do if I want to stop taking part in the study?

If you take part in this research study, and want to drop out, you should tell us. We will make sure that you stop the study safely. We will also talk to you about follow-up care, if needed.

Also, it is possible that we will have to ask you to drop out of the study before you finish it. If this happens, we will tell you why. We will also help arrange other care for you, if needed.

Will I be paid to take part in this research study?

We will pay $910 dollars if you complete the entire study and the MRI sub-study. If you do not complete the study, we will pay you $90 dollars for each visit you complete and $50 dollars for each MRI. Subjects do not get paid for Visit 1 (the screening visit).

We will pay for your parking in the hospital garage during study visits.

We will pay for the cost of your transportation up to $25 per visit.

We may use your samples and information to develop a new product or medical test to be sold. The Sponsor, hospital, and researchers may benefit if this happens. There are no plans to pay you if your samples are used for this purpose.

What will I have to pay for if I take part in this research study?

Study funds will pay for all of the study visits, labs, procedures, or medications.

Study funds will pay for certain study-related items and services. We may bill your health insurer for, among other things, routine items and services you would have received even if you did not take part in the research. You will be responsible for payment of any deductibles and co-payments required by your insurer for this routine care or other billed care. If you have any

questions about costs to you that may result from taking part in the research, please speak with the study doctors and study staff. If necessary, we will arrange for you to speak with someone in Patient Financial Services about these costs

What happens if I am injured as a result of taking part in this research study?

We will offer you the care needed to treat any injury that directly results from taking part in this research study. We reserve the right to bill your insurance company or other third parties, if appropriate, for the care you get for the injury. We will try to have these costs paid for, but you may be responsible for some of them. For example, if the care is billed to your insurer, you will be responsible for payment of any deductibles and co-payments required by your insurer.

Injuries sometimes happen in research even when no one is at fault. 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.

If you think you have been injured or have experienced a medical problem as a result of taking part in this research study, tell the person in charge of this study as soon as possible. The researcher's name and phone number are listed in the next section of this consent form.

If I have questions or concerns about this research study, whom can I call?

You can call us with your questions or concerns. Our telephone numbers are listed below. Ask questions as often as you want.

Anne Klibanski, MD is the doctor in charge of this research study. You can call her at 617-726-3870 Monday through Friday 9am to 5pm. You can also call **Dr. Madhu Misra** at 617-724-5602 Monday through Friday 9am to 5pm. Dr. Misra may also be reached at any time by calling 617-724-5700 and asking to have her paged at ID#32383. You may contact either physician for questions about the consent in addition to questions about the study.

If you have questions about the scheduling of appointments or study visits, call the study coordinator at 617-643-0266.

If you want to speak with someone **not** directly involved in this research study, please contact the Partners Human Research Committee office. You can call them at 857-282-1900.

You can talk to them about:

- Your rights as a research subject
- Your concerns about the research
- A complaint about the research

Also, if you feel pressured to take part in this research study, or to continue with it, they want to know and can help.

If I take part in this research study, how will you protect my privacy?

Federal law requires Partners to protect the privacy of health information and related information that identifies you. We refer to this information as "identifiable information."

In this study, we may collect identifiable information about you from:

- Past, present, and future medical records
- Research procedures, including research office visits, tests, interviews, and questionnaires

Who may see, use, and share your identifiable information and why:

- Partners researchers and staff involved in this study
- The sponsor(s) of the study, and people or groups it hires to help perform this research or to audit the research
- Other researchers and medical centers that are part of this study
- The Partners ethics board or an ethics board outside Partners that oversees the research
- A group that oversees the data (study information) and safety of this study
- Non-research staff within Partners who need identifiable information to do their jobs, such as for treatment, payment (billing), or hospital operations (such as assessing the quality of care or research)
- People or groups that we hire to do certain work for us, such as data storage companies, accreditors, insurers, and lawyers

- Federal agencies (such as the U.S. Department of Health and Human Services (DHHS) and agencies within DHHS like the Food and Drug Administration, the National Institutes of Health, and the Office for Human Research Protections) state agencies, and foreign government bodies that oversee, evaluate, and audit research, which may include inspection of your records
- Public health and safety authorities, if we learn information that could mean harm to you or others (such as to make required reports about communicable diseases or about child or elder abuse)
- Other researchers within or outside Partners, for use in other research as allowed by law.

Certificate of Confidentiality

A federal Certificate of Confidentiality (Certificate) has been issued for this research to add special protection for information and specimens that may identify you. With a Certificate, unless you give permission (such as in this form) and except as described above, the researchers are not allowed to share your identifiable information or identifiable specimens, including for a court order or subpoena.

Certain information from the research will be put into your medical record and will not be covered by the Certificate. This includes records of medical tests or procedures done at the hospitals and clinics, and information that treating health care providers may need to care for you. Please ask your study doctor if you have any questions about what information will be included in your medical record. Other researchers receiving your identifiable information or specimens are expected to comply with the privacy protections of the Certificate. The Certificate does not stop you from voluntarily releasing information about yourself or your participation in this study.

Even with these measures to protect your privacy, once your identifiable information is shared outside Partners, we cannot control all the ways that others use or share it and cannot promise that it will remain completely private.

Because research is an ongoing process, we cannot give you an exact date when we will either destroy or stop using or sharing your identifiable information. Your permission to use and share your information does not expire.

The results of this research may be published in a medical book or journal, or used to teach others. However, your name or other identifiable information **will not** be used for these purposes without your specific permission.

Your Privacy Rights

You have the right **not** to sign this form that allows us to use and share your identifiable information for research; however, if you don't sign it, you can't take part in this research study.

You have the right to withdraw your permission for us to use or share your identifiable information for this research study. If you want to withdraw your permission, you must notify the person in charge of this research study in writing. Once permission is withdrawn, you cannot continue to take part in the study.

If you withdraw your permission, we will not be able to take back information that has already been used or shared with others, and such information may continue to be used for certain purposes, such as to comply with law or maintain the reliability of the study.

You have the right to see and get a copy of your identifiable information that is used or shared for treatment or for payment. To ask for this information, please contact the person in charge of this research study. You may only get such information after the research is finished.

Informed Consent and Authorization

Statement of Person Giving Informed Consent and Authorization

- I have read this consent form.
- This research study has been explained to me, including risks and possible benefits (if any), other possible treatments or procedures, and other important things about the study.
- I have had the opportunity to ask questions.
- I understand the information given to me.

Signature of Subject:

I give my consent to take part in this research study and agree to allow my identifiable information to be used and shared as described above.

Subject	Date	Time (optional)

Signature of Parent(s)/Guardian for Child:

I give my consent for my child to take part in this research study and agree to allow his/her identifiable information to be used and shared as described above.

Parent(s)/Guardian for Child	Date	Time (optional)

Assent

Statement of Person Giving Assent

- This research study has been explained to me, including risks and possible benefits (if any), other possible treatments or procedures, and other important things about the study.
- I have had the opportunity to ask questions, and my questions have been answered.

Signature of Child:

I agree to take part in this research study and agree to allow my identifiable information to be used and shared as described above.

Child, Ages 14-17	Date	Time (optional)

Signature of Study Doctor or Person Obtaining Consent:

Statement of Study Doctor or Person Obtaining Consent

- I have explained the research to the study subject.
- I have answered all questions about this research study to the best of my ability.

Study Doctor or Person Obtaining Consent	Date	Time (optional)

Consent of Non-English Speaking Subjects Using the "Short Form" in the Subject's Spoken Language

Statement of Hospital Medical Interpreter

As someone who understands both English and the language spoken by the subject, I interpreted, in the subject's language, the researcher's presentation of the English consent form. The subject was given the opportunity to ask questions.

Hospital Medical Interpreter	Date	Time (optional)

OR

Statement of Other Individual (Non-Interpreter)

As someone who understands both English and the language spoken by the subject, I represent that the English version of the consent form was presented orally to the subject in the subject's own language, and that the subject was given the opportunity to ask questions.

Name	Date	Time (optional)

Consent Form Version Date: 6.22.2018