Protocol Title: The role of estrogen in the neurobiology of eating disorders: A study of cognitive flexibility, and reward in eating disorders

Principal Investigator: Kamryn T. Eddy, Ph.D.

Site Principal Investigator: Poornima Kumar, Ph.D. (McLean Hospital)

Description of Subject Population: Female subjects between 14 and 35 years old with restrictive eating and/or athletes with irregular or missed periods

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.

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.

Key Information

We are asking you to be in a research study. This form will tell you what you should expect if you agree to be in the study. You will find more information about each of the following points later in this form.

It is your decision whether or not to join the study. We are asking you to be in this study because you have restrictive eating and/or engage in excessive exercise and have low estrogen.
We are doing the research to find out if replacing the estrogen levels in girls and young women with restrictive eating and/or athletes who have irregular or missed periods by using an estrogen

patch will help improve mental flexibility and reward responsiveness.
If you agree, you will participate in 4 study visits that include computer tasks, questionnaires, blood draws, and an fMRI scan where you will perform tasks inside the scanner. You will be in the study for 12 weeks if you decide to stay for the whole study.

The main risks of being in the study are discomfort, nausea, irritation at patch site, and a bruise from blood draws.

You might benefit from being in the study if you are in the active drug group because you may experience improvement in your eating disorder symptoms, mental and behavioral flexibility, and responsiveness to rewards.

You will be paid up to $525 via check for taking part in this research study. You will find more information about the payment amount for each visit and a plan if you do not complete all study visits later in this form.

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

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

Dr. Kamryn Eddy, Ph.D. can be reached at 617-724-1744 Monday through Friday 9am to 5pm. **Dr. Lauren Breithaupt-Langston, Ph.D.** can be reached at 913-439-8200 Monday through Friday 9am to 5pm. **Meghan Slattery, NP**, may be reached at 617-643-0267 or 24 hours a day/7 days a week by beeper at 617-726-7777 pager number 21788. You may contact any clinician 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 617-643-4034.

If you want to speak with someone **not** directly involved in this research study, please contact the Mass General Brigham IRB. 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
- Any pressure to take part in, or to continue in the research study

Detailed Information

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?

Eating disorders which involve restrictive eating and/or excessive exercise are common, and often start in adolescence. These eating disorders are associated with inflexibility (for example, having trouble doing things differently than usual) and lower response to rewards (for example, less interest in things or activities many people enjoy). Inflexibility and lower response to rewards are mental and behavioral patterns that can make eating disorders long-lasting and hard to treat.

Females with these eating disorders also often have lower levels of estrogen, leading to missed or irregular periods. Estrogen helps increase mental flexibility and reward responsiveness.

We are doing this study to find out if replacing the estrogen levels in girls and young women with restrictive eating and/or athletes who have irregular or missed periods by using an estrogen patch (so it is absorbed through your skin and gets your estrogen level to where it should be) will help improve mental flexibility and reward responsiveness.

This study will measure eating attitudes and behaviors, mental flexibility, and reward responsiveness before and after receiving 12 weeks of estradiol (estrogen) supplement or 12 weeks of placebo.

The U.S. Food and Drug Administration (FDA) has approved estradiol for use in children and adolescents with low estrogen levels. However, estradiol skin patches are not approved by the FDA to improve mental flexibility, or reward responsiveness. This means that using estradiol in this way can only be used for this purpose in research studies.

Prometrium (progesterone pill) is approved by the FDA to treat secondary amenorrhea (absence of menstrual periods in women who have previously had a menstrual period) and prevent endometrial hyperplasia (benign thickening of the uterine lining) during treatment with estrogen, but Prometrium is not approved by the FDA to improve mental flexibility, or reward responsiveness. Provera is an approved study substitute for Prometrium if you have a peanut allergy. You will be provided active Provera regardless of your estrogen randomization.

This research study will compare estradiol (administered as a patch) to placebo. The placebo looks like the estradiol patch, but contains no estradiol. In addition, you will be given progesterone pills for two to three 10-day courses during the next 12 weeks. The placebo pill looks like the progesterone pill, but contains no progesterone. During this study, you may get a placebo instead of estradiol. Placebos are used in research studies to see if the results are due to the study drug or due to other reasons.

Who will take part in this research?

We are asking you to take part in this study because you have restrictive eating and/or engage in excessive exercise and have low estrogen.

We expect to enroll up to 130 subjects with restrictive eating and/or excessive exercise and who have low estrogen levels (as indicated by not getting their periods regularly) in this research study.

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

What will happen in this research study?

You will be in this study for up to a total of about 12 weeks (3 months). During this time, we will ask you to make 4 study visits. Visit 1 will take place at MGH; visits 2 and 3 will take place at McLean Hospital in Belmont, MA with an option to complete parts of these visits at MGH; and visit 4 will take place at MGH. We may complete some activities virtually/via phone if necessary. You may choose which virtual platform you prefer.

If you choose to take part in this study, we will ask you to sign this consent form before we do any study procedures. If you are eligible to continue taking part in this study, we will ask you to come back for 3 more study visits. The study visits are discussed in detail below.

Screening Visit (Visit 1)

The screening visit will take about 3.5 hours. During this visit, we will do some tests to see if you qualify to take part in this research study. The study doctor or nurse practitioner will review the results of these tests and procedures. We may complete some portions of this visit on separate days and/or at the baseline visit if need be.

At this visit, we will:

- Ask you questions about your health and menstrual history. We will measure your pulse, height, and weight. We may also perform a brief physical exam and/or measurement of height and/or vital signs (blood pressure, temperature, breathing rate).

- 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 or nurse practitioner 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 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.

- Draw a blood sample for routine tests. (We will not repeat the blood work for which we have records, if the records provided are less than two months old. This does not include the pregnancy test. Additionally, if blood cannot be drawn at the screen visit, we will draw these labs at baseline or you may have them drawn at an outside clinic. You will not begin study medication until these labs are checked and cleared by a study clinician.)

- Give you a psychiatric and eating disorder interview. The clinical interviews will be audio recorded.

- Ask you to complete three brief questionnaires about hand preference, eating disorders symptoms and exercise.

- Ask you to complete an MRI safety questionnaire to make sure it is safe for you to have an MRI scan.

- Give you a food diary. Study staff will give you instructions on how to fill it out and ask you to bring it back at the next visit.

- If you are less than 16 years old, we will take an x-ray of your left wrist to see how mature your bones are.

Baseline Visit (Visit 2)

If you are eligible and want to continue in the study, we will ask you to come to Massachusetts General Hospital and McLean Hospital. This visit will take about 7 hours.

At this visit, we will:

- Ask you questions about your health. We will measure your pulse, blood pressure and weight. We may also perform an optional brief physical exam and/or measurement of height and/or vital signs (temperature, breathing rate) at a study clinician's discretion.

- Ask for a urine sample to test for pregnancy and drug use or use serum from blood already being collected to test for pregnancy if a urine sample cannot be obtained. Information about drug use will not be stored electronically. If you test positive for illicit substances, you may not be able to complete the MRI scan.

- Draw blood to measure the amount of certain hormones like estrogen.

- Ask you to provide a small sample of hair.

- Ask you to grip a bar to measure your grip strength.

- Ask about your eating disorder symptoms. This clinical interview will be audio recorded.

- Ask you to fill out questionnaires about eating disorder symptoms, exercise, mood, anxiety, and experience of pleasure. We may ask you to complete the anxiety, mood, and hunger questionnaires at multiple points during the visit. We may ask your parent/guardian to complete a questionnaire.

- Perform an MRI scan. MRI is a way to measure the structure and activity in your brain using magnetic fields. We will use the MRI scans to see which parts of your brain are more active and which are less active while you are at rest and while you play three different brain games. For each task, you will be asked to look at different letters, pictures, or words on a screen and then make a choice by pressing a button. For all these MRI games, you will get to practice them outside the scanner before you do them in the scanner. Additionally, you will wear a non-invasive wireless monitor that clips on to your pointer finger to measure your heart rate and a respiratory cushion on a belt fastened to the lower chest to measure your respiratory rate. The total time for the MRI games, including instructions and breaks between tasks is about 90 minutes.

Since MRI uses a large magnet, people who have certain metal implants cannot have this scan. Also you will be asked to remove all metal items before the scan. The MRI scanner is a large machine shaped like a tube. You will lie on a narrow table and will be moved into the MRI tunnel. The tunnel is only a little larger than your body. You will be asked to lie still during the scan. As images are taken, the MRI makes loud noises. Earplugs will be offered to help reduce this noise. You will be able to hear and speak to the research staff at all times during the scan. We can stop the scan at any time, if needed.

If you would like to experience how being in an MRI would look, feel and sound like, you can come to McLean Hospital prior to Visit 2 to do a mock scan. This means that we will show you in a safe environment, how an MRI would look, feel, and sound like and what we would ask you to do.

- Give you computerized behavioral tasks of mental flexibility, decision-making, and reward, which takes about 20-30 minutes.

- Give you a brief assessment of vocabulary and mental reasoning, which takes about 20 minutes.

- Review your 4-day food diary. We will give you another food diary to bring back at your next study visit. We will also ask about what you ate the day before and the day of the visit.

- The nutritionist will ask you questions about your intake of foods and supplements that contain calcium and/or vitamin D as well your physical activity in the past week.

You may sometimes have the option of combining the first two visits, the screen and baseline. Alternatively, you may sometimes also have the option to split Visit 2 into two shorter visits, which could be done at McLean and MGH.

Study Drug (estrogen patch and progesterone pill or placebo patch and placebo pill):
We will give you self-adhesive patches delivering estrogen (100 micrograms/day) or placebo (no medicine). You will apply 1 patch twice a week (e.g., Sunday morning and Wednesday night of every week for the next 12 weeks) starting on the day of your Visit 2. These patches 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 patch. Pregnant women cannot take part in this study.

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

Those receiving estrogen will also take a pill containing 200 mg of Prometrium (Progesterone) or 5 mg of Provera for two to three 10-day courses during the next 12 weeks. We will provide you with detailed instructions on which dates you will be taking the pills during the 12 weeks of the study. Progesterone may cause you to have menstrual periods.

Those in the placebo patch group will take a placebo pill for 10 days in the evenings for two to three 10-day courses during the next 12 weeks.

If you have a peanut allergy, you will be given 5 mg of active Provera in place of Prometrium regardless of randomization.

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. You also have the option to receive electronic surveys that remind you when to take the different study drugs and how much. You can opt out of receiving surveys 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 and/or receive reminder surveys.

☐ Yes ☐ No Initials_____ Circle Preference: Phone Reminder or Survey

8 Week (Visit 3)

This visit will last about 4 hours, and will take place at McLean Hospital. You will need to come in around the same time of day as Visit 2.

- Ask you questions about your health. We will measure your pulse and weight. Review any side effects of medications. We may also perform a brief physical exam and/or measurement of height and/or vital signs (blood pressure, temperature, breathing rate).

- Ask for a urine sample to test for pregnancy and drug use, or use serum from blood already being collected to test for pregnancy if a urine sample cannot be obtained. Information about drug use will not be stored electronically. If you test positive for illicit substances, you may not be able to complete the MRI scan.

- Draw blood to measure the amount of certain hormones like estrogen. You may have blood collected at an external laboratory like Quest.

- Ask you to provide a small sample of hair.

- Ask you to grip a bar to measure your grip strength.

- Perform an MRI scan. MRI is a way to measure the structure and activity in your brain using magnetic fields. We will use the MRI scans to see which parts of your brain are more active and which are less active while you are at rest and while you play three different brain games, measuring mental flexibility and reward responsiveness. For each task, you will be asked to look at different letters, pictures, or words on a screen and then make a choice by pressing a button. For all these MRI games, you will get to practice them outside the scanner before you do them in the scanner. Additionally, you will wear a non-invasive wireless monitor that clips on to your pointer finger to measure your heart rate and a respiratory cushion on a belt fastened to the lower chest to measure your respiratory rate. The total time for the MRI games, including instructions and breaks between tasks is about 90 minutes.

  Since MRI uses a large magnet, people who have certain metal implants cannot have this scan. Also you will be asked to remove all metal items before the scan. The MRI scanner is a large machine shaped like a tube. You will lie on a narrow table and will be moved into the MRI tunnel. The tunnel is only a little larger than your body. You will be asked to lie still during the scan. As images are taken, the MRI makes loud noises. Earplugs will be offered to help reduce this noise. You will be able to hear and speak to the research staff at all times during the scan. We can stop the scan at any time, if needed.

  If you would like to see experience how being in an MRI would look, feel and sound like, you can come to McLean Hospital prior to Visit 2 to do a mock scan. This means that we will show you in a safe environment, how an MRI would look, feel, and sound like and what we would ask you to do.

- Give you computerized behavioral tasks of mental flexibility and reward, which takes about 20-30 minutes.

- Ask you to fill out questionnaires about mood, anxiety, and experience of pleasure. We may ask you to complete the anxiety, mood, and hunger questionnaires at multiple points during the visit.

- We will also ask about what you ate the day before and the day of the visit.

You may sometimes also have the option to split Visit 3 into two shorter visits, which could be done at McLean and MGH.

If you are unable to physically present for your 8-week visit, we will administer all measures except for the fMRI virtually. The fMRI will then be completed during the 12-week visit along with typical study activities. If the fMRI is delayed to 12-weeks, you will continue to wear the estrogen/placebo patch and take the progesterone/placebo as instructed by study staff for an additional 4-5 weeks. You may be asked to take an additional course of progesterone/placebo at a study clinician's discretion. Measures collected during the 12-week visit will be collected around 16-weeks. All reasonable attempts will be made to complete the second fMRI. If you ultimately do not complete the second fMRI, but do complete other 8-week study activities, you will be paid $75. You will then proceed with the 12-week visit as normal.

12 Week (Visit 4)

This visit will last about 3.5 hours.

- Ask you questions about your health. We will measure your pulse and weight. Review any side effects of medications. We may also perform a brief physical exam and/or measurement of height and/or vital signs (blood pressure, temperature, breathing rate).

- 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.

- Draw blood to measure the amount of certain hormones like estrogen. You may have blood collected at an external laboratory like Quest.

- Ask you to provide a small sample of hair.

- Ask you to grip a bar to measure your grip strength.

- Ask about your eating disorder symptoms. This clinical interview will be audio recorded.

- Ask you to fill out questionnaires about eating disorder symptoms, exercise, mood, anxiety, and experience of pleasure. We may ask you to complete the anxiety, mood, and hunger questionnaires at multiple points during the visit. We may ask your parent/guardian to complete a questionnaire.

- Give you computerized behavioral tasks of mental flexibility, decision-making, and reward, which takes about 20-30 minutes.

- Review your 4-day food diary. We will also ask you about what you ate the day before and the day of the visit. We will also ask you about your physical activity in the past week. If not previously asked, we may ask you questions about your intake of foods and supplements that contain calcium and/or vitamin D.

- If you are unable to complete study measures by the 12-week timepoint due to scheduling needs (i.e. COVID-19 quarantine), you may remain on the study drug up until 20 weeks post-baseline. We may collect final study measures up until 20 weeks post-baseline, and you will stop taking the study medication and cease study participation once these measures are collected.

- We are interested in the composition of microbial communities present in the human body. These bacteria are present in your digestive system, and we are looking to investigate how they might be affected by hormones and potentially connect to distant organs like the brain. If you consent to this portion of the study, we will ask that you provide a stool sample during the baseline and 12-week study visit. If you are unable to provide a stool sample during the visit, a collection kit will be provided to you to complete at home before your visit. You may then bring the completed kit to your baseline and/or 12-week visit. Additionally, you will be asked to report any recent antibiotic or probiotic use as well as foods consumed in the last 24 hours prior to stool collection. You will be compensated up to $75 ($25 at Baseline and $50 at 12-week visit) for providing a stool sample. Providing stool samples is optional.

  Do you agree to participate in this additional component of the baseline and 12-week visits?
  ☐ Yes ☐ No Initials_____

- We are interested in understanding whether physiologic estrogen replacement has an impact on cortisol secretion. Collecting hair samples in this study will allow us to study

this. If you consent to this portion of the study, we will collect a small hair sample during the baseline, 8-week, and 12-week study visits. Providing hair samples is optional.

Do you agree to participate in this additional component of the baseline and 12-week visits?
☐ Yes ☐ No Initials_____

- We are interested in understanding whether physiological estrogen replacement has an impact on inflammation in the blood and brain. Collecting cerebrospinal fluid (CSF) by performing a CSF draw via lumbar puncture procedure will allow us to study this. If you are interested in taking part in the CSF sub-study, you will be asked to sign a separate consent form for the procedure. If you agree to participate in the sub-study the CSF draw will be performed at, or near, your Week 12 visit. You may be asked to take an additional course of progesterone/placebo in order to participate in this visit.

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 or complete study activities within the allotted time window
- 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 or nurse practitioner 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.

How may we use and share your samples and health information for other research?

At the completion of this research study, we would like to store and be able to use and share your identifiable samples and health information with researchers at Mass General Brigham for other research related to eating disorders. If we share your samples and/or health information with other researchers outside of Mass General Brigham, we will label the samples and information with a code instead of your name or other directly identifying information. The key to the code connects your name or other identifiers to your sample and/or information. We will keep the code in a password protected computer.

Because these samples and/or health information are identifiable, we are asking your permission to store, use and share them for other research. You can still take part in the research study whether or not you give permission for the storage, use, and sharing of the samples and health information for other research.
Do you agree to let us store and use your samples and health information for other research related to eating disorders?

☐ Yes ☐ No Initials _____

If later you change your mind and want your samples destroyed, contact the study doctor. About 9 tablespoons of blood will be drawn throughout the entire course of the study.

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 _____

If you turn 18 during this Study

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.

Will you get the results of this research study?

You and your doctor should not expect to get information about the results of the research study or the results of your individual participation in the research study. We will study samples and

information from many people. It could take many years before anyone knows whether the results have any meaning. There is a small chance that we find out something from the study that might be important to your health. If this happens, we may contact you to find out if you would like to learn more. However, even if we find something important to your health, we cannot guarantee that you will be contacted.

You can choose to get a newsletter that will tell you about the research studies we are doing. This newsletter will not announce your results or anyone else's, but it will tell you some information about what we are learning about eating disorders. We will also publish what we learn in medical journals. In the future, when research results are published, they may show that certain groups (for example, racial or ethnic groups, or men/women) have genes that are associated with increased risk of a disease. If this happens, you may learn that you are at increased risk of developing a disease or condition.

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

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 two 10 day courses, 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.
• If you remain on the study drug for longer than the typical 12-week window, the overall risks associated with continued study drug use will be similar to those stated above, commensurate with the amount of additional time you take the study drug. Study clinicians will monitor your safety throughout your entire duration on the study drug.

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.
- Current 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 (either Prometrim or Provera) by mouth include:

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

- headaches,
- insomnia,
- nervousness,
- drowsiness,
- 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. Elderly post-menopausal females were diagnosed with a higher rate of dementia with prescribed combined estrogen/Provera, but it is not known if the findings apply to a younger population. As progesterone can cause drowsiness, we recommend taking the progesterone pill in the evening.

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 or nurse practitioner right away. If you are having trouble breathing, call 911 immediately.

Risks from study procedures:

Blood draws: 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. If you want, we can place a numbing cream on your arm to reduce any pain you may have from having your blood drawn.

MRI Risks: MRI scanners 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. 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. The MRI has the potential, during normal routine use, to cause localized warming of your skin and the underlying tissues. You should immediately inform us if you experience discomfort due to warming and the procedure will be stopped.

Some people experience dizziness or rarely nausea when going into an MRI scanner and these sensations may be more common in scans with higher magnetic fields. In most cases, these symptoms only last a short time. However, some people may experience them throughout the scan and/or continue to experience them for a short period of time after; generally, less than half an hour. No case of permanent problems is known.

This project is for research purposes only and is not intended for clinical diagnosis. The MRI scans that are being used in this study are not made to find abnormalities in your brain. You should not expect that the pictures of your brain will be looked at individually or examined in a way that could find an abnormality. You should not participate in this study in order to get a clinical diagnosis, or to get pictures of your brain that could be used for a clinical diagnosis. The information created by this study will not usually become part of your hospital record. This MRI is not the same as one that your own doctor would order. It may or may not show problems that would be found on a standard MRI. You will have a clinical MRI exam of your brain, which will be read by a board-certified Neuroradiologist, these findings will be entered into your hospital record. If any abnormality is detected, you will be notified immediately and given appropriate referrals for follow-up examinations if indicated. Being told about something like this may cause you anxiety and might suggest the need for additional tests and financial costs. Deciding whether to go ahead with any further examination or treatment would be entirely up to you.

Radiation: As a result of your participation in this study, if you are less than 16 years old you will be exposed to radiation from the x-ray of your hand. 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 taking part in this study is equal to a whole-body exposure of about 0.2 microSieverts (μSv). A μSv is a unit of radiation dose. This amount of radiation is about the same as you would normally get in less than one day from natural background sources from the earth and the sky.

Scientists disagree on whether radiation doses at these low levels are harmful. A possible effect that could occur at doses used in this study is a slight increase in the risk of developing cancer later in life.

Risks to an Embryo or Fetus, or to a breastfeeding Infant:
The effect of radiation from an x-ray on an embryo (baby developing in the womb) or on a nursing infant is unknown and may be harmful. If you are pregnant or think you may be pregnant, tell a member of the study staff immediately. Because of these unknown risks, you cannot take part in this study if you are pregnant, trying to become pregnant, or breastfeeding.

You may be pregnant if you miss your periods, are nauseous, vomiting, unusually tired, dizzy, or experience unusual breast fullness or tenderness

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. 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.

If you miss a period, or think you might be pregnant during the study, you must tell the study doctor or nurse practitioner 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 other mental health issues. The study staff is sensitive to this discomfort. Although we hope that you will answer all the questions, you may skip any that you choose not to answer. Taking the hair sample may make you feel uncomfortable or concerned about how you look. You can choose not to give a hair sample.

Concerns about your Safety and Learning Information that Indicates Intent to Seriously Harm Others or Yourself: If there are any concerns about your immediate safety, we will take appropriate action. This may include contacting treatment providers, and/or arranging for emergency evaluation and treatment. If we learn information from you during this study that indicates intent to seriously harm others or yourself, we may be required by law to share that information with third parties, including public safety or law enforcement authorities, and may take other precautions to protect against such harm.

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

Test Results: Some of our research test results may be useful to your doctor. If these tests show abnormalities, we will notify you and, with your permission, your doctor.

Data Sharing

Data from this study may be submitted to the National Institute of Mental Health Data Archive (NDA). The NDA is a data repository run by the National Institute of Mental Health (NIMH) that allows researchers studying mental health and substance use to collect and share deidentified information with each other. A data repository is a large database where information from many studies is stored and managed. Deidentified information means that all personal information about research participants such as name, address, and phone number is removed and replaced with a code number. However, identifiable information such as the date of study visits may remain in the database. With an easier way to share, researchers hope to learn new and important things about mental illnesses more quickly than before.

During and after the study, the researchers will send identifiable information about your health and behavior and in some cases, your genetic information, to NDA. Other researchers nationwide can then file an application with the NIMH to obtain access to your deidentified study data for research purposes. Experts at the NIMH who know how to protect health and science information will look at every request carefully to minimize risks to your privacy.

You may not benefit directly from allowing your information to be shared with NDA. The information provided to NDA may help researchers find better treatments and outcomes. NIMH will also report to Congress and on its web site about the different studies that researchers are conducting using NDA data. However, you will not be contacted directly about the data you contributed to NDA.

You may decide now or later that you do not want to share your information using NDA. If so, contact the researchers who conducted this study, and they will tell NDA, which can stop sharing the research information. However, NDA cannot take back information that was shared before you changed your mind. If you would like more information about NDA, this is available on-line at https://nda.nih.gov.

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

You may not benefit from taking part in this study. If you are assigned to the active study drug group, it is possible that you may experience improvement in your eating disorder symptoms, mental and behavioral flexibility, and responsiveness to rewards. However, this is not guaranteed.

We hope that what we learn in this study may benefit others with eating disorders in the future.

Can you still get medical care within Mass General Brigham if you don't take part in this research study, or if you stop taking part?

Yes. Your decision won't change the medical care you get within Mass General Brigham 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.

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 you do if you 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 you be paid to take part in this research study?

We will pay a total maximum of $525 if you complete the entire study. However, if you do not finish the full study, you will be paid for the visits you attend as follows.

- You will receive up to $200 for Visit 2.
- You will receive up to $200 for Visit 3.
- You will receive up to $125 for Visit 4.
- Subjects do not get paid for Visit 1 (the screening visit).

Visits may be compensated on a prorated basis depending on completion of study components.

We will pay for your parking in the hospital garage during study visits (including Visit 1 [the screening visit]).

We will reimburse you for the cost of your transportation up to $50 per visit (including Visit 1 [the screening visit]). Please provide the study staff with any receipts you incur from transportation costs.

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.

In addition, you will receive monetary rewards from two of the tasks you complete. The tasks will be completed at baseline and Week 8, and for each completion of the first task, you can get between $20 and $85; for each completion of the second task, you can get between $10 and $20. This is in addition to the study reimbursement. For these extra payments, we will use an approved, outside vendor (Forte Research) make these payments to you via a reloadable credit card-based system, called Forte Payments. This secure system is similar to a gift card or credit card.

If you are paid by this system, you will be given a Forte Payments Visa card when you enroll in the study. Once the card is activated, the study team will add a payment after each paid visit you complete. The payment should be available to you within a day. You may use the card anywhere Visa cards are accepted, such as at a grocery store.

If you complete the optional stool collection at both timepoints, you will be paid an additional $75. If you only complete the optional stool collection at Baseline, you will be paid an additional $25.

We will need to collect your Social Security number in order to make these payments, and it will be shared securely with the company that runs the card-based system. Payments like this are considered taxable income. If you receive more than $600, the payment will be reported to the IRS as income by the hospital.

If you provide a receipt for something like travel expenses and we can cover that, that is not considered taxable income. Reimbursement of expenses will not be made using the Forte Payments card.

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

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

Charges for any ongoing or routine medical care you receive outside this study will be billed to you or to your insurance company in the usual way. You will be responsible for any deductibles or co-payments required by your insurer for your routine medical 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 you are 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 beginning of this consent form.

If you take part in this research study, how will we protect your privacy?

Federal law requires Mass General Brigham 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:

- Mass General Brigham 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 Mass General Brigham ethics board or an ethics board outside Mass General Brigham that oversees the research
- A group that oversees the data (study information) and safety of this study
- Non-research staff within Mass General Brigham 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 Mass General Brigham, 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 Mass General Brigham, 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 identifiable 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 the 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 Adult:

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

Adult	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: 11.05.2025