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TITLE: Novel, Non-Hormonal Therapy for the Treatment of Chronic Pain Due to Endometriosis in Adolescent and Adult Women

PRINCIPAL INVESTIGATOR: Amy DiVasta, MD, MMSc

CONTRACTING ORGANIZATION: Boston Children's Hospital, Boston, MA

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Boston Children's Hospital
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13. SUPPLEMENTARY NOTES

14. ABSTRACT

Background: Endometriosis afflicts millions of women worldwide, resulting in the loss of academic, athletic, social, and professional success. Women can experience chronic pain, fertility challenges, and higher risk of cardiovascular disease. As no cure exists, patients require disease management across the lifespan. However, current therapies are suboptimal, and pain is often left untreated. Medications with favorable long-term safety, efficacy, and tolerability are desperately needed. As endometriosis is dependent on angiogenesis for its growth and maintenance, we believe that angiogenesis inhibitors are a promising option for treatment. However, these medications have not yet been studied since the currently approved angiogenesis inhibitors induce severe side effects and are teratogenic, making them inappropriate for use in reproductive-age women. We will overcome this obstacle by repurposing an existing drug (cabergoline) that has an acceptable safety profile as an angiogenesis inhibitor to treat chronic pelvic pain associated with endometriosis.

Hypothesis/Objectives: We propose to conduct a randomized, double-blind, placebo controlled trial to determine the efficacy of cabergoline as an adjunct treatment for persistent pain due to endometriosis.

Specific Aims: (1) To determine the extent to which cabergoline adjunct treatment alleviates persistent pelvic pain suffered by women with laparoscopically-proven endometriosis. We hypothesize that after 6 months, subjects randomized to cabergoline (n=40) will demonstrate decreased pain measures, improved functional disability scores, and increased quality of life scores compared to baseline and to subjects randomized to placebo (n=40). (2) To measure the impact of cabergoline on inflammation, angiogenesis, and cardiovascular risk in endometriosis. We hypothesize that cabergoline will significantly decrease angiogenic and inflammatory biomarkers over 6 months, while placebo therapy will have no effect on these same markers. We also hypothesize that clinical markers of cardiovascular risk will improve over 6 months in subjects receiving cabergoline. (3) To determine if the magnitude of central hypersensitization in women with endometriosis differs from healthy, age-matched controls, and whether 6 months of cabergoline therapy will alter these levels. We hypothesize that subjects with endometriosis will more frequently demonstrate central hypersensitization compared to healthy females, and that this increased frequency will decline with cabergoline therapy.

Study Design: The study is a randomized, double-blind, placebo controlled trial. Participants will be randomized to either cabergoline 0.5 mg by mouth twice weekly or placebo tablet by mouth twice weekly. Primary outcomes include validated measures of pain assessed in multiple dimensions, including physical pain, emotional symptoms, quality of life, sexual function, and ability to function in daily life. Secondary outcomes include angiogenic and inflammatory biomarkers, measures of vascular resistance, and a measurement of central hypersensitization to pain.

15. SUBJECT TERMS

Endometriosis; chronic pelvic pain; angiogenesis; cardiovascular risk; central hypersensitization

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1. INTRODUCTION:

Endometriosis is dependent on angiogenesis (the sprouting of new blood vessels) for its growth and maintenance, but the side effects of currently approved angiogenesis inhibitors make these agents inappropriate for use in reproductive-age patients. This obstacle will be overcome by performing a randomized, double-blind clinical trial aimed at repurposing an existing drug, cabergoline, as a safe, alternative angiogenesis inhibitor for adolescents and young women with endometriosis. This trial utilizes a novel, non-hormonal, non-surgical, therapeutic approach aimed at alleviating the pain and suffering associated with this common chronic disease that currently has limited treatment options.

2. KEYWORDS:

Endometriosis, Pelvic pain, Adjunct therapy, Angiogenesis, Cabergoline, Pulse Wave Velocity, Cardiovascular risk; Central hypersensitization

3. ACCOMPLISHMENTS:

What were the major goals of the project?

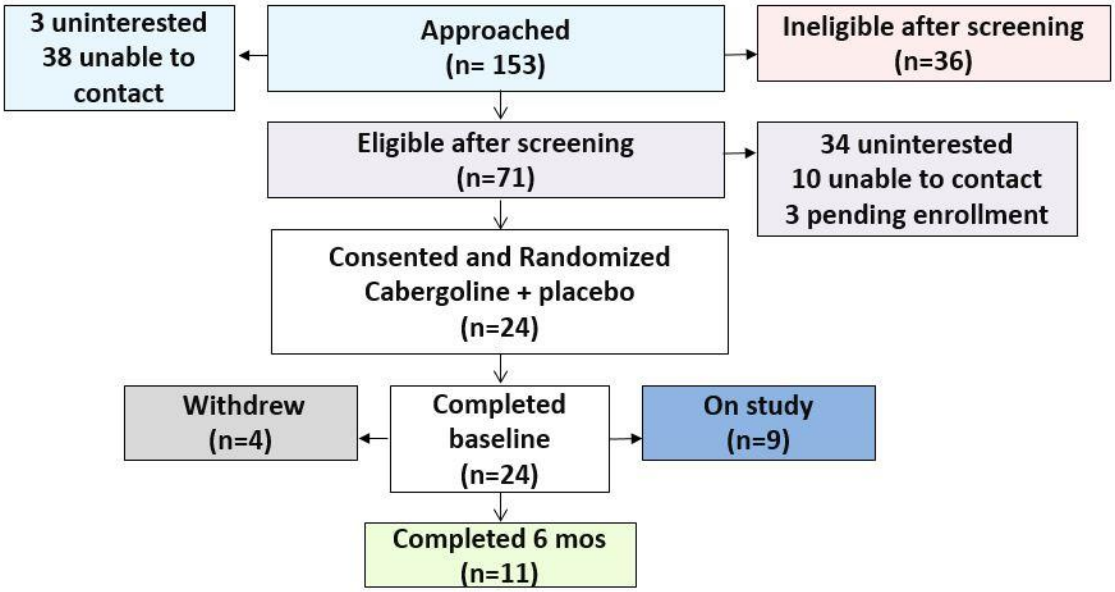
Major Task 1: Launch the randomized clinical trial
Major Task 2: Complete enrollment of n=80 study subjects
Major Task 3: Obtain data required to successfully complete Specific Aim 2
Major Task 4: Prospectively measure Quantitative Sensory Testing at baseline, 3 month, and 6 month study visits
Major Task 5: Complete study and analyze the data from the randomized controlled trial

What was accomplished under these goals?

<u>Major Task 1: Launch the randomized clinical trial (completed)</u>
The trial was successfully launched in Year 1.

<u>Major Task 2: Complete enrollment of the n=80 subjects (in progress)</u>
Subject recruitment, screening, and enrollment continued in Year 2, after a COVID-related shutdown for the second half of Year 1. We are experiencing continued participant hesitancy around coming into the hospital, and continue to make efforts to improve recruitment methods.

Recruitment history to date is displayed in the graphic below:



Two Data and Safety Monitoring Board (DMSB) meetings occurred during Year 2, in January 2021 and June 2021. At the suggestion of a DSMB member in the January meeting, we added a questionnaire to capture data from our study participants about the COVID-19 pandemic, including symptoms, testing, and vaccination status. This questionnaire will allow the study statistician to differentiate symptoms of COVID-19 from possible medication-related symptoms. The questions were developed in collaboration with Dr. Stacey Missmer, Scientific Director of the Boston Center for Endometriosis. The questionnaire is now being administered at each study visit. No safety concerns or recommendations were raised at the third DSMB meeting in June 2021.

The independent study monitor conducted two visits in Year 2, in November 2020 and March 2021. No significant concerns were identified by the study monitor. In advance of our next monitoring visit in October 2021, we have been notified that our current monitor Brenda Barton, BSN, RN, CCRP is leaving Boston Children's Hospital and will be replaced by Jessica Serino-Cipoletta, MSN, RN, CPN, from the same ICCTR Office of Research Regulatory Support, Education and Quality (ORRSEQ) group.

Major Task 3: Obtain data required to successfully complete Specific Aim 2 (in progress)
Study outcome measures have been collected at all in-person visits. Pulse Wave Velocity measurements were collected at all baseline and 6 month visits. One 3-month visit was completed in part as a virtual visit because the participant had temporarily relocated out of the state. The participant determined that she was going to remain out of state, and withdrew from the study before completing the in-person portion of the visit.

Collection of specimens for inflammatory and angiogenic biomarkers has occurred at each in-person visit. In our Year 2, Quarter 2 report, we described the high volume of laboratory errors that occurred in the first 11 months of the study. After working closely with the Experimental Therapeutics Unit (ETU), we created safeguards to minimize the risk of laboratory errors including

double-checks and having only senior lab staff process our samples. Since this intervention, no laboratory errors affecting laboratory tests, either safety or experimental labs, have occurred.

Major Task 4: Prospective measure Quantitative Sensory Testing at baseline, 3 month, and 6 month visits (in progress)
Our research assistants have been trained in the proper conduct of the Quantitative Sensory Testing protocol developed by our co-investigator, Dr. Sieberg. The Quantitative Sensory Testing has been collected at all in-person completed visits with the exception of one visit in Year 2 Quarter 1 where QST was not performed due to participant time constraints.

Major Task 5: Complete study and analyze the data from the trial (in progress)
The data are being prospectively entered into our REDCap database. A systematic data double-checking protocol was completed by research assistants during Year 2 Quarter 1 and will continue periodically throughout the trial. In addition, the independent study monitor reviews every entered value for every fifth participant as part of study monitoring visits.

We are holding regular meetings with our biostatistician to continually review and clean the data. Given the blinded nature of the study and the limited number of trial completers to date, we have not yet explored any of the study outcome measures. Safety measures are analyzed in an unblinded fashion before all DSMB meetings. These analyses are conducted by the statistician and shared only with the unblinded DSMB members. No safety concerns were raised to the investigators after review.

What opportunities for training and professional development has the project provided?
The research assistants involved in the study received mentorship from Ms. Jenny Sadler Gallagher regarding the conduct of study visits, techniques for obtaining informed consent, and the maintenance of the REDCap database. With the departure of Miss Anna Kapral to pursue nursing school, Miss Esther Kim took over her research assistant role in June 2021. Miss Kim's training is ongoing. Miss Emma Singleton has taken on a mentorship role while training Miss Kim on all study protocols. The study team has also taken advantage of training and educational opportunities provided by Boston Children's Hospital, including training on Part 11 compliant databases. The research assistants, coordinator and PI meet at least monthly for ongoing protocol review and training.

On September 1, 2021, Dr. DiVasta assumed the position of Interim Chief of Adolescent and Young Adult Medicine in the Department of Pediatrics at Boston Children's Hospital.

How were the results disseminated to communities of interest?
Nothing to report at this time.

What do you plan to do during the next reporting period to accomplish the goals?
In the coming quarters, we will continue to focus on recruitment of new subjects to meet recruitment goals. We will hold weekly recruitment meetings as well as monthly team meetings to discuss challenges and create strategic recruitment solutions to address recruitment deficits as the pandemic continues. Recruitment updates will continue to be communicated monthly to our referring providers.

We have developed a COVID-19 contingency plan so the study can continue to enroll participants and conduct visits should the Delta variant and rising COVID-19 infections impact our ability to hold in-person visits. The written consent form contains all information necessary to inform participants of these potential changes.

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?
Nothing to report at this time.

What was the impact on other disciplines?
Nothing to report at this time.

What was the impact on technology transfer?
Nothing to report at this time.

What was the impact on society beyond science and technology?
Nothing to report at this time.

5. CHANGES/PROBLEMS:

In Year 2, 5 amendments to the study protocol have been submitted to and approved by our IRB. No significant changes to the primary study outcomes, interventions, risk/benefit ratio, study procedures, or sample size/patient population have occurred.

Amendment approved 10/1/2020

- Revised protocol and consent form to include the study's contingency plan for virtual visits in case of extenuating circumstances caused by COVID-19.
- Added a "Notification of Changes due to COVID" document to our IRB-approved documents to give to current participants in the event of protocol changes.
- Updated protocol to allow for a change in location and method of informed consent discussion. The informed consent discussion now takes place over a Zoom call preceding the baseline visit to minimize face-to-face contact and decrease baseline visit length. Documentation of consent via wet ink signature continues to occur at the time of the baseline visit.
- Updated the personnel details in the protocol to match the currently approved study staff.

Amendment approved 1/29/2021

- In order to have extra saved serum in the event of laboratory errors or other unanticipated events, we added an additional tube to the samples collected at each visit. All relevant personnel received training on this change, and study orders were updated to reflect changes in blood collection.

Amendment approved 2/17/2021

- The volume of blood collected for one test (ESR) was increased from 2mL to 3mL to reflect the volume requested by the laboratory for successful analysis. The total blood volume collected is still well under the 40mL limit stated in our protocol.
- We added a questionnaire to capture data from our study participants about the COVID-19 pandemic, including symptoms, testing, and vaccination status. The questionnaire was suggested by a DSMB member as to help differentiate symptoms of COVID-19 from possible medication-related symptoms. The questions were then developed in collaboration with Dr. Stacey Missmer, Director of the Boston Center for Endometriosis. The questionnaire is now being administered at each study visit.
- In an effort to reach our recruitment goal after falling behind due to the COVID-19 pandemic and research closures, our study team developed additional recruitment materials for outside organizations and social media. These materials included outreach letters to local clinics and women's health organizations, and recruitment information to post in relevant communities on websites such as Facebook. We have begun to send letters and informational materials to associated clinics and are actively searching for social media communities to recruit from in order to broaden our recruitment pool.
- The finalized Data and Safety Monitoring Board charter was added to IRB documentation and the DSMB members were updated.
- The National Clinical Trial number for our study was added to IRB documents.

Amendment approved 6/21/2021

- Updated study documents to reflect our recent study personnel changes (removal of Anna Kapral, adding Esther Kim). These documents include: Written Consent Form; Protocol; RA Outreach Letter for recruitment; Moderator message for recruitment
- Two changes were made to the consent form to clarify parts of the study.
    - Removing an extraneous sentence regarding norethindrone acetate that was kept in the consent form from the NOTE pilot study.
    - Updating the estimated time length of visits in the visit chart, based on how long visits are currently taking

Amendment approved 7/14/2021

- One sentence was modified in the consent form to increase clarity and accuracy.

Changes in approach and reasons for change

To address recruitment difficulties due to COVID-19 (hesitancy to come into the hospital, hesitancy to travel to Boston, inability to recruit patients due to limited in-person clinic visits), we have expanded our approach to recruitment. We are now working to recruit through social media and in local gynecology clinics. Nonetheless, our referring providers remain our greatest source of eligible participants. As some hospital restrictions lift, we hope to resume in-person recruitment from the Adolescent Gynecology Clinic at Boston Children's Hospital.

To create the safest study visit experience for our staff and participants, we initiated virtual informed consent calls to decrease face-to-face time at visits and the total length of participants' visit to the hospital. The research assistant conducts a consent discussion with the potential participant via a secure Zoom phone call; participants who choose to enroll review the form and

document their consent with a wet ink signature in person at the baseline visit. We also developed a robust contingency plan for virtual visits should restrictions related to COVID-19 arise.

Actual or anticipated problems or delays and actions or plans to resolve them
During Year 2, we fell short of our projected quarterly enrollment goal despite approaching 80 potential participants. We took action to address low enrollment by expanding our recruitment approach to include social media and local GYN clinics and initiating a monthly recruitment letter to our referring physicians to keep the study top-of-mind and encourage providers to continue referring. We held a virtual event for providers, nurses and office staff to educate about the aims of the NOTE study and remind clinic staff of inclusion/exclusion criteria and updated the Boston Center for Endometriosis website, where the NOTE-2 study is displayed, to increase site traffic and access to information about the study.

To better distinguish between symptoms of possible COVID-19 infection and adverse effects of the study medication, we introduced a COVID-19 symptom and vaccination status questionnaire. We believe this questionnaire will give context to symptoms and help to determine etiology of adverse symptoms, whether from study medication, COVID-19 infection or vaccination against COVID-19. The questionnaire is administered at all study visits.

As the COVID-19 Delta variant continues to spread, we remain wary of possible disruption to data collection on account of virtual visits due to participant illness or changes to institutional policy. Our robust COVID-19 contingency plan will streamline any virtual visits that may be necessary in the coming year.

Changes that had a significant impact on expenditures
Because of decreased study visit volume and associated costs (such as lab assays), expenses associated with in-person visits were decreased. These expenses will likely be shifted to the upcoming quarters as we catch up to our enrollment goal. Overall, long term expenditures are anticipated to be unchanged.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents
None to report.

Significant changes in use or care of human subjects
None to report.

Significant changes in use or care of vertebrate animals
Not applicable.

Significant changes in use of biohazards and/or select agents
Not applicable.

6. PRODUCTS:

- **Publications, conference papers, and presentations**

None to report.

Journal publications.
None to report.

Books or other non-periodical, one-time publications.
None to report**.**

Other publications, conference papers and presentations.
None to report

- **Website(s) or other Internet site(s)**
  Information about the study is posted on our Center's website:
  https://bostoncenterendometriosis.org/research/

- **Technologies or techniques**
  None to report.

- **Inventions, patent applications, and/or licenses**
  None to report.

- **Other Products**
  None to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name: Amy DiVasta, MD, MMSc
Project Role: Principal Investigator at Boston Children's Hospital
Researcher Identifier:
Nearest person month worked: 3.6
Contribution to Project: Dr. DiVasta continues to approve all materials and forms associated with the trial. She has been present at all ETU study visits, conducted subject physical exams, and reviewed all clinical relevant laboratory results. She prepared the blinded DSMB reports. She has assured regular communication with all study co-investigators and collaborators, as well as the clinical trial staff, and has led regular team meetings. She has handled all correspondence with the FDA, and reviewed all interactions and communications with the IRB, including protocol amendments and the annual continuing review.

Name: Mark Hornstein, MD
Project Role: Principal Investigator at Brigham and Women's Hospital
Research Identifier:
Nearest person month worked: 0.36

Contribution to Project: Dr. Hornstein is responsible for the organization of recruitment procedures in the Center for Infertility and Reproductive Services at Brigham and Women's Hospital.

Name: Marc Laufer, MD
Project Role: Co-Investigator at Boston Children's Hospital and Brigham and Women's Hospital
Research Identifier:
Nearest person month worked: 0.36
Contribution to Project: Dr. Laufer continues to assist with the identification and recruitment of eligible subjects in the Gynecology Clinic at Boston Children's Hospital and the Center for Infertility and Reproductive Services at Brigham and Women's Hospital.

Name: Christine Sieberg, PhD
Project Role: Co-Investigator
Research Identifier:
Nearest person month worked: 1.2
Contribution to Project: Dr. Sieberg trained the Research Assistants in the administering of the Quantitative Sensory Testing (QST) and will provide expertise in the interpretation and administration of the pain measures used in the clinical trial, which she helped to create in order to capture the full experience of adolescent chronic pain. Dr. Sieberg is available to answer any questions or concerns regarding the QST testing interpretation or administration.

Name: Caterina Stamoulis, PhD
Project Role: Senior biostatistician
Research Identifier:
Nearest person month worked: 0.6
Contribution to Project: Dr. Stamoulis continues to assist in creating the reports for the DSMB meetings and oversees blinded and unblinded data for the study. She meets periodically with the study team to review the database.

Name: Anna Kapral, BA
Project Role: Research Assistant
Nearest person month worked: 4.5
Contribution to Project: Ms. Kapral conducted study visits in the ETU, including delivering questionnaires, conducting QST and assisting with PWV testing. She coordinated between the ETU staff, cardiology, and Dr. DiVasta to schedule participant visits, managed study folders, performed data entry, and screened/enrolled participants. She prepared study materials for the third study monitoring visit and the third DSMB meeting. Ms. Kapral left her position in May 2021 and was replaced by Ms. Esther Kim.

Name: Emma Singleton, BS
Project Role: Research Assistant
Nearest person month worked: 6
Contribution to Project: Ms. Singleton has conducted study visits in the ETU, including delivering questionnaires, conducting QST and assisting with PWV testing. She is

responsible for screening potential participants and managing recruitment webpages. She conducts the REDCap data double-checking procedure, manages study folders, performs data entry and enrolls patients. She has drafted amendments submitted to the IRB, assisted in preparing the annual report to the FDA, and prepared materials for the third DSMB meeting. She is now preparing study materials for the fourth monitor visit in October 2021. She is working with Dr. DiVasta and Ms. Sadler Gallagher to train the new Research Assistant, Esther Kim.

Name: **Esther Kim, BS**
Project Role: Research Assistant
Nearest person month worked: 1.5
Contribution to Project: Ms. Esther Kim joined the study team in June 2021. She has been trained in consenting participants and conducting study visits in the ETU, including delivering questionnaires and assisting in PWV testing. She manages study folders, performs data entry and enrolls patients. She is now preparing study materials for the fourth monitor visit in October 2021.

Name: Jenny Sadler Gallagher, MPH
Project Role: Research Coordinator
Nearest person month worked: 1.6
Contribution to Project: Ms. Sadler Gallagher oversees the study budget and financial management of the study. She has provided oversight of the research assistants, and has reviewed materials for the study monitoring visit, DSMB meeting and IRB, FDA, and DoD submissions. She is developing new recruitment strategies to increase enrollment and assisting in social-media based recruitment.

Name: Hannah Palfrey, BS
Project Role: Research Assistant, Cardiology
Nearest person month worked: 0.12
Contribution to Project: Ms. Palfrey conducts Pulse Wave Velocity testing. She has been trained in standard protocol for measurements of Pulse Wave Velocity and conducted these assessments for all study participants. She assisted in training Ms. Singleton and Ms. Kim on the PWV protocol.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Dr. DiVasta: No changes

Dr. Laufer: No changes

Dr. Hornstein: No changes

Dr. Sieberg was awarded a grant from the Cathedral Fund that began in December 2020 as below.

PI: Sieberg	12/01/2020-11/30/2021	1.0 Cal Mos

THE CATHEDRAL FUND
Psychophysical and Neural Mechanisms Contributing to Chronic Post-Surgical Pain in Adolescents and Adults: A Pilot Study
The goals of this pilot study are to utilize neuroimaging to explore pain inhibitory mechanisms and age-related differences in the development of chronic post-surgical pain.
No overlap.

Dr. Stamoulis was awarded a grant from the National Heart, Lung, and Blood Institute that began in July 2021 as below.

R21HL156186 (PI: Stamoulis) 07/01/2021-06/30/2023 2.4 Cal Mos
National Heart, Lung and Blood Institute (NHLBI)
Robust Characterization of Brain-Heart Coupling Across Development and Modulations by Disordered Sleep
Using novel signal processing and machine learning tools and Big Physiological Data from existing clinical studies and the Childhood Adenotonsillectomy Trial (CHAT), this project aims to first develop a blueprint of electrodynamic cardiovascular-neural coupling during wakefulness and sleep and robustly characterize its developmental trajectory. This blueprint of the two systems' electrodynamic interaction will then be used to elucidate the adverse impact of disordered sleep (as a result of Obstructive Sleep Apnea), in children age 5-10 years.
No overlap.

What other organizations were involved as partners?

Organization Name: Brigham and Women's Hospital, Department of Obstetrics and Gynecology
Location of Organization: Boston, MA
Partner's contribution to the project: Brigham and Women's Hospital is another participating site in the current trial. Co-Investigators there are involved in the study protocol development and identification/recruitment of eligible study subjects. Co-Investigators participate in preparation for ongoing project meetings, and will ultimately participate in data analysis and dissemination. Brigham and Women's Hospital research computing team provided support for the REDCap database.

Organization Name: Boston Center for Endometriosis
Location of Organization: Boston, MA
Partner's contribution to the project: Urine and blood samples are recorded and stored utilizing facilities of the Boston Center for Endometriosis, located within Brigham and Women's Hospital.

8. SPECIAL REPORTING REQUIREMENTS
Not applicable.

9. APPENDICES:
Appendix: Written informed consent form, current version

Boston Children's Hospital

RESEARCH CONSENT FORM

This section only to be edited by IRB office.

Use Plate or Print:

MRN#:

DOB:

Subject's Name:

Gender:

Protocol Title: Novel, non-hormonal therapy for treatment of chronic pain due to endometriosis

Principal Investigator: Amy DiVasta, MD, MMSc

This consent form gives you important information about a research study. A research study helps scientists and doctors learn new information to improve medical practice and patient care.

Please read this consent form carefully and take your time making a decision. The first section gives you an overview of the key information you should know about the research study. More detailed information about these topics may be found in the pages that follow.

The form may contain words that you do not understand. Please ask questions about anything you do not understand. We encourage you to talk to others (for example, your friends, family, or other doctors) before you decide to participate in this research study.

Please check one of the following:

_____ You are an adult participant in this study.

_____ You are the parent or guardian granting permission for a child in this study.

If the participant is a child the use of "you" refers to "your child"

Summary of Important Information

We are asking you to participate in this research study. Participation in this research study is voluntary. You may choose not to take part in this research study or may choose to leave the research study at any time. Your decision will not impact the clinical care you receive at Boston Children's Hospital.

In this research study we want to learn more about a potential new therapy for pain associated with endometriosis. We want to determine if a non-hormonal medication, cabergoline, will help patients with endometriosis.

Cabergoline is a medication that is approved by the Food and Drug Administration (FDA) for treatment of other medical conditions. In this study, the use of cabergoline is investigational. This means the drug is not approved by the FDA for the treatment of endometriosis. Cabergoline is a "dopamine receptor agonist." Cabergoline binds to and stimulates specific chemical receptors on our cells that respond to dopamine, a chemical your body uses to help cells communicate with each other. Studies of these types of drugs show that cabergoline may help to prevent endometriosis lesions from growing.

It is important to consider reasons why you would or would not want to participate in this research.

You do not have to be in this research study to be treated for endometriosis. Your healthcare provider has discussed with you what your clinical treatment options are and which clinical treatment(s) might be right for you considering your medical history. These clinical treatment options include continuing your current medical treatment, which may include oral contraceptive pills, norethindrone acetate, or an intrauterine device (IUD), without adding study medication. Each of the clinical treatment options has known rates of being effective, known risks, as well as possible drawbacks.

The study treatment has not yet been proven to be safe and/or effective for the treatment of endometriosis. The study treatment may work better, the same, or worse and may have less, more, and/or other risks compared to the clinical care options. It is important to consider the trade-offs of the clinical care options as well as this research study before you decide whether you take part or not take part in this research study.

If you decide to join this research study, the following things will happen: you will receive either the study drug (cabergoline) or a placebo pill (sugar pill) to take twice a week for 6 months. We will ask you to complete questionnaires, keep a symptom diary every day, have an ultrasound of the blood vessels, complete sensory testing, and provide urine and blood samples to give us information about how these treatments are working and about any potential side effects.

You will be "randomized" into one of two study groups. Randomization means that you are put into a group by chance. It is like flipping a coin. You have a 50% chance of being placed in either group. Neither you nor the research investigator can choose what group you will be in. Neither you nor the research investigator will know which drug you get until the study is over. But, if there is an emergency, the research investigator will be able to get this information.

The most important potential risks to know about are the potential side effects of cabergoline, which could include: upset stomach/nausea, constipation, dizziness, headache, tingling, or swelling of the hands or feet.

The most important potential benefits to know about are: study drugs may help with your endometriosis pain, but they may not. You will receive the results of some research tests (cholesterol levels, liver function tests, hormonal status) to share with your primary care provider.

It will take you about *6 months* to complete this study. During this time, we will ask you to make *3* study visits.

The research funds will cover costs associated with the study. Study medications will be paid for by the study. You will receive up to $225 for the completion of the study. Some of your travel related costs may be covered by the study, such as parking garage fees, up to $10.

How are individuals selected for this research study?

You are being asked to participate in this research study because you have endometriosis and are experiencing pain. All participants are females between the ages of 15-40 years.

Patients who have cardiac valve disorders (including murmurs), high blood pressure, blood clots, active liver disease, breast cancer, fibrotic disorders, stroke or heart attack, or are taking other medications that affect dopamine (such as phenothiazines, butyrophenones, thioxanthenes, or metoclopramide) are not eligible to participate. Patients who are currently breastfeeding, who have had a baby in the last 6 months, who are pregnant, or who plan to become pregnant in the next six months are not eligible to participate.

Why is this research study being conducted?

In this research study, we want to learn more about treatments for endometriosis that may help to control pain. We want to determine if a non-hormonal medication, cabergoline, will help patients with endometriosis in a different way than hormonal treatments help.

Cabergoline is a medication that is approved by the Food and Drug Administration (FDA) for treatment of an endocrine condition called hyperprolactinemia that also affects young women. In this study, the use of cabergoline is investigational. This means the drug is not approved by the FDA for the purpose we are studying, the treatment of endometriosis. Cabergoline is a "dopamine receptor agonist." Cabergoline binds to and stimulates specific chemical receptors on our cells that respond to dopamine, a chemical your body uses to help cells communicate with each other. Studies of these types of drugs show that cabergoline may help to prevent endometriosis lesions from growing.

Who is conducting this research study, and where is it being conducted?

The research study is being conducted at Boston Children's Hospital under the direction of Dr. Amy DiVasta, Co-Scientific Director for the Boston Center for Endometriosis, and physician in the Division of Adolescent Medicine. The study is also affiliated with Brigham and Women's Hospital under the direction of Dr. Mark Hornstein. Dr. Christine Sieberg and Dr. Marc Laufer are co-investigators.

A grant from the United States Department of Defense is providing funding for this study.

How many people will participate in this research study?

Approximately 80 people will participate in this six-month study at Boston Children's Hospital and Brigham and Women's Hospital.

What do I have to do if I am in this research study?

This is a six month study that involves 3 visits to the Clinical and Translational Study Unit (CTSU) on the 6th floor of the main building at Boston Children's Hospital, plus 2 phone calls with the study team.

If you agree to participate in the study:

- Because no one knows if cabergoline is helpful for endometriosis, you will be "randomized" into one of the 2 study groups. *One group will receive drug and one group will receive placebo*. Randomization means that you are put into a group by chance. It is like flipping a coin. You will have a 1 in 2 chance of being placed in either group. Neither you nor the research investigator can choose what group you will be in.

- Since the expectations of patients and doctors can influence the results of a study, neither you nor the research investigator will know which drug you get until the study is over. But, if there is an emergency, the research investigator will be able to get this information.

- You will be asked to take one capsule by mouth twice per week for six months. These capsules will contain either the study drug or a placebo. The study drugs will be provided to you during your research visits in the CTSU. You are responsible for remembering to take the capsules. We will give you a medication diary to help you remember to take your capsules. A study team member and a research nurse will teach you about these medications at your first visit.

- You should know that the placebo is a capsule that does not contain any medicine and we do not expect it will do anything for your health. We use a placebo so we do not know whether you are receiving the study drug.

- At each visit, your blood pressure and pulse will be taken twice, once lying down and once standing.

- You will be asked to provide a blood and urine sample at each visit. The total amount of blood taken at each visit will be no more than 40mL, or less than 3 tablespoons.

- Before you start this research, you will be tested for pregnancy with a urine pregnancy test. You will be tested for pregnancy at each follow-up visit as well.

- At the beginning of every visit, you will be asked to fill out questionnaires. These will ask questions about your symptoms/discomfort, mood, quality of life, and sexual satisfaction (if you have had sexual intercourse). These will take about 20 minutes to complete.

- At the first visit, you will be asked to fill out a Health History questionnaire. This survey will contain questions about your date of diagnosis, stage of endometriosis, and medication history. This will take about 20 minutes to complete.

- We will look in your medical record to see things like your past prescribed medications and date of past visits or surgeries.

- At each visit, you will have a physical examination performed by a study physician to examine your skin, heart, and lungs.

- At the first and last study visit, you will have a measurement of the thickness and stiffness of your blood vessels. The Pulse Wave Velocity (PWV) test uses a machine (called a SphygmoCor) to measure artery stiffness. You will lie quietly while study staff takes measurements from your neck to the top of your leg. Sticky patches, called electrodes, will be placed on your chest and an instrument that looks like a pen (an ultrasound probe) will measure the speed of your pulse. This test does not hurt and does not include any radiation exposure.

- At each visit, you will complete testing of your skin sensations. This testing will be done with you seated comfortably in a recliner chair or bed. The testing procedure will ask you to report the touch, type of sensation, and pressure sensations applied to the abdominal (stomach) region. The test also includes your feelings of pressure and touch over the upper arm.

    - Threshold sensation: A plastic tip attached to a measurement probe will be brought into contact with your skin. The plastic tip will be brought into contact with the skin until a sensation of pain is felt. This will determine the pain threshold. This test will be repeated on the abdomen. As soon as the sensation of pain is felt, the test is over.

- Wind-Up testing: The plastic tip will be applied to your arm every second for 10 seconds with the same pressure felt in the threshold sensation test. At the end of the 10 seconds trial, you will report your pain on a scale from 0-10. There will be a total of 3 trials with 10 seconds rest between each trial. This test will be repeated on the abdomen.

- Pressure sensation: A pressure algometer, a handheld instrument with a tip located on the end, will be applied to the nail of your middle finger. The pressure on the nail will be slowly increased until you experience discomfort. This test will be conducted 3 times. The test will be repeated on the abdomen.

- Between visits, we will ask you to keep a symptom diary to track whether you are having any pain, bleeding, and use of any medications for pain (such as ibuprofen). This symptom diary will be in the form of a paper diary which will be given to you at each visit.

- We will send your gynecology provider and/or your primary care doctor a letter informing him/her that you are participating in this study and may be receiving the study drug. We can also send them results from your laboratory studies that may help with your clinical care (like cholesterol levels). We will not release any information to your primary care doctor unless you sign a release form.

Study Visit Timeline	Visit 1: Baseline 2.5 to 3 hours	6 week phone call: 10 minutes	Visit 2: 3 Month 2 hours	18 week phone call: 10 minutes	Visit 3: 6 Month 2 to 2.5 hours
Consent	X				
Vital signs	X		X		X
Blood, urine, saliva samples	X		X		X
Health History	X				
Physical Examination	X		X		X

Questionnaires	**X**	**X**	**X**	**X**	**X**
Medication Diary			**X**		**X**
Pulse Wave Velocity	**X**				**X**
Sensory Testing	**X**		**X**		**X**

What are the risks of this research study? What could go wrong?

Some procedures or treatments used in this research may present risks that are not well-known or understood. Therefore, there may be unforeseeable risks associated with participating in this research. Side effects of cabergoline could include: upset stomach/nausea, constipation, dizziness, headache, tingling, or swelling of the hands or feet. These side effects are likely to be short term and should go away when you stop taking the medication. We will be monitoring for any of these side effects carefully by using blood tests and questionnaires. If you have concerns, you should call your medical provider.

Possible Side Effects	**Common** Happens to >21 people out of every 100	**Occasional** Happens to 5-20 people out of every 100	**Rare** Happens to <5 people out of every 100
Cabergoline	• Nausea • Headache	• Dizziness • Fatigue • Constipation • Weakness	• Hot flashes • Heartburn • Dry mouth • Breast tenderness • Diarrhea • Swelling of hands or feet • Postural hypotension (low blood pressure) • Depression • Nervousness • Abnormal vision

Risks associated with a blood draw may include minor discomfort, bruising, fainting, and infection. When possible, we will draw blood at the time of a clinically-indicated procedure to reduce the number of needle sticks.

There is minor risk of pain during the skin testing; however, the sensations experienced should not feel worse

than shaving or bristles touching the skin. Experiences of the different sensory tests vary between participants. Some participants with low pain thresholds may be particularly sensitive to the touch of the tip and pressure algometer. You/Your child will be allowed to stop at any time.

Minor skin irritation is possible from the sticky patches placed on your skin for the vascular tests.
You may be asked questions that make you uncomfortable or cause you to remember situations that were upsetting to you. You may become frustrated if you are asked questions that you do not know how to answer. You may not be able to answer all the questions and you do not need to answer any questions that you do not wish to answer. If you become upset at any time, you can stop the questionnaires. We will also offer to have you speak to someone about how you are feeling. It is possible that the study team could identify concerns for depression when you answer the questionnaires. If we became concerned for depressed mood, we would notify you and encourage you to allow us to share the information with your healthcare provider. Additionally, mental health resources would be made available to you.

If, during your participation in this research, there is reason to believe that you are at risk for being suicidal or otherwise harming yourself or others, the research team is required by law and Hospital policy to act on this suspicion. This may include notifying your therapist(s) if applicable, or other individuals. If you are under age 18 years and there is reason to believe that you are at risk of being suicidal or otherwise harming yourself or others, we are required to notify your parent(s)/guardian(s) and would not be able to assure confidentiality. We would let you know that we plan to disclose this information because we felt it best for your safety or the safety of others.

The effects of the research drug on the reproductive system (eggs) or to the developing fetus are unknown. For this reason, participants taking the drug should not become pregnant. To be a part of the research, you must remain on your hormonal medications (birth control pills, progestin-only pills, IUD) for pregnancy prevention. Before you start this research, you will be tested for pregnancy. You will be tested for pregnancy at each follow-up visit as well. During the research, if you become pregnant, there is a chance that you are pregnant, or you intend to become pregnant, you should contact the research investigator immediately so that we may provide medical assistance and counseling. If you become pregnant during the research, we must withdraw you from the research.

Adolescent Assent for Pregnancy Testing:

Because participation in this research study could result in harm to a fetus, you cannot be pregnant while you are in the study. To be a part of the research, you must not have sex or you must use a barrier method of contraception, like condoms with spermicide every time. Before you start this research, you will be tested for pregnancy. One of the research nurses or doctors will meet privately with you to tell you your pregnancy test results. We will not tell your parent(s)/guardian(s) your results without your permission, except under certain circumstances (for example, if your life was at risk, or if the pregnancy was the result of suspected abuse). In these instances we may need to tell your parent(s)/guardian(s) or relevant authorities.

Even if we do not tell your parent(s)/guardian(s) about the positive results, they may guess that you are pregnant because we may need to tell them you cannot participate in the research. During the research, if you become pregnant, or if there is a chance that you are pregnant, you or your parent(s)/guardian(s) should contact the research personnel immediately so that we may provide assistance and counseling. If you become pregnant during the research, we must remove you from the research. Confidential pregnancy testing is available in the Boston Children's Hospital Adolescent/Young Adult Medicine Clinic who can be reached at 617-355-7181.

You have been informed about special concerns about pregnancy and unknown reproductive risks of the drug(s). You have informed the study personnel that you will abstain from sexual intercourse or use condoms with spermicide during the study.

Sign here (15-17 year olds): _____ Date:_____

What are the benefits of this research?

The study drugs may reduce your endometriosis pain and improve your quality of life, but they may not. The study medications will be provided at no cost. You will receive the results of some research tests (cholesterol levels, liver function tests, hormonal status) to share with your primary care provider. When we finish the research, we hope that we will know more about endometriosis and determine if this new therapy is effective. This may help other women with endometriosis in the future.

Will I receive my study results?

During this research we may learn information from the study results which could be important for your health or your treatment. This information will be made available to you and your health care provider. The information we may share is cholesterol levels, liver function tests, hormonal status; the results will be provided in letters mailed to your primary care provider.

Will my samples/information be used for research in the future?

Identifiable samples and/or identifiable private information collected from you during this study may be used for future research studies or shared with other researchers for future research. The identifiable samples and/or identifiable private information may be used for future research of endometriosis. If the research investigator distributes your samples and/or information to other researchers or institutions, your samples and/or information will be labeled with a research code without identifiers so that you cannot be identified. No additional consent will be requested for the future use of your samples or information.

If you have questions about storing samples or would like to request that samples be removed from storage, please let us know. It is not always possible to remove samples from storage or to retrieve samples from which identifiers have been removed and/or that have already been sent to other investigators.

Are there costs associated with this research? Will I receive any payments?

There are no costs associated with the study. We will pay for the study drugs and your visits in CTSU. We will also give you a parking voucher or up to $10 for each study visit for travel expenses.

You will receive a $75.00 Target or Amazon gift card for each research visit that you complete ($225.00 for the whole study). Gift cards are given out at your last study visit. If you leave the research study early, or if we have to take you out of the research study, you will be paid for the visits you have completed.

Although research funds will pay for some research-related items and services, we may bill your health insurer for routine items and services you would have received even if you did not take part in this 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 research staff.

We will offer you the care needed to treat any injury that directly results from taking part in this research. 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, tell the person in charge of the research as soon as possible. The researcher's name and phone number are listed in this consent form. If you go to the Emergency Room or to another hospital or doctor it is important that you tell them that you are in this research study. If possible, you should give them a copy of this consent form.

If I do not want to take part in this research, what are the other choices?

Participation in this research study is completely voluntary. You do not have to participate. If you choose not to participate, you will still receive standard clinical care at Boston Children's Hospital or the Brigham and Women's Hospital. The medication cabergoline is not currently approved for this use and is only available as part of this study.

Are there other things I should know about?

If you choose to participate in this study, you will be assigned a unique study ID number. This is a random set of numbers and/or letters that does not contain any identifying information (birth date, medical record number, social security number). This number will be used to label all of your study questionnaires and samples. This helps to protect your confidentiality. All of your data will be stored in a locked filing cabinet in the research office. All computer files will be password protected. Your data will only be available to certain members of the study team who have been trained in conducting responsible and ethical research.

If we find out about new information from this research or other research that may affect your health, safety or willingness to stay in this research, we will let you know as soon as possible. For example, if we detect a previously unknown heart murmur, we will tell you as soon as possible and may ask your permission to share results with your medical provider.

Potential changes due to COVID-19 pandemic:

It is possible that the COVID-19 pandemic may disrupt usual research operations. If this disruptions occurs, we may need to adapt the research activities to ensure the safety of you as the participant. These changes may include converting the in-person study visits to virtual (telehealth) visits. If it is determined that your visit must be converted to a virtual visit, we will notify you via secure email. Virtual visits will be conducted as a password-protected Zoom meeting. The changes that occur in a virtual visit are:

- We will not perform a physical exam, measure vital signs, conduct sensory testing, or conduct Pulse Wave Velocity testing. Please note: we will continue to monitor your safety and wellbeing through patient report at all phone calls and virtual visits.
- Zoom study visits will be shorter than in-person visits. They will last roughly 30-45 minutes.
- Study medication will be sent directly to your home via FedEx. You will return extra medication to the Hospital via USPS in a prepaid envelope.
- We will mail you a pregnancy test and ask that you perform it at home.
- We may ask you to have laboratory studies (blood test) obtained at a clinic, laboratory, or hospital close to your home in order to monitor for safety. We would provide you with the laboratory order form, and pay for all laboratory studies.
- Study questionnaires and the Daily Symptom Diary will be mailed to your home via USPS. You will return these to the study team via USPS in a prepaid envelope.

If necessary, visits may be done remotely until the restrictions are lifted. The visit schedule will not change. A study Research Assistant will contact you via secure email with a Zoom virtual visit link and password.

To protect your privacy, do not share the Zoom link (including the password) with anyone, make certain you are in a private space (for example, be in a room with no one else if possible), login from a secure Wi-Fi network (e.g. password protected), and turn your camera on.

If you have any further questions about virtual visits, medication delivery or other study logistics related to COVID-19, please contact the Research Assistants at **617-355-2212** or bce@childrens.harvard.edu**.**

Why would I be taken off the study early?

The research investigator may take you out of this study at any time. This would happen if:

- The research is stopped.
- You are not able to attend the research visits required.
- You become pregnant.
- You develop an adverse effect of a study medication.

- You fail to follow the research requirements.
- You need a treatment or medication that may not be taken while on the research or the research investigator feels it is in your best interest to be taken out of this research.

If this happens, the research investigator will tell you.

Other information that may help you:

Boston Children's Hospital is interested in hearing your comments, answering your questions, and responding to any concerns regarding clinical research. If you have questions or concerns, you may email IRB@childrens.harvard.edu or call (617) 355-7052 between 8:30 and 5:00, Monday through Friday.

Who may see, use or share your health information?

A copy of this consent form will be placed in your medical record. If you do not have a medical record at Boston Children's Hospital, one will be created for you.

Information collected during this research will become part of your medical record, if the information is related to the care you receive at Boston Children's Hospital. Medical records are considered permanent records; therefore, information cannot be deleted from the record. Medical records are available to health care professionals at Boston Children's Hospital and may be reviewed by Hospital staff when carrying out their responsibilities; however, they are required to maintain confidentiality in accordance with applicable laws and Hospital policies. Information contained in your medical record may not be given to anyone unaffiliated with Boston Children's Hospital in a way that could identify you without written consent, except as required or permitted by law.

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. The study sponsor (the Dept. of Defense) or the FDA may also see your health information.

Contact for Future Studies: Your participation in any research is completely voluntary and you should feel no pressure to participate if you are contacted about another research study. **Please check and initial one** of the options below regarding future contact about other research done by us or other researchers we are working with (collaborators).

_____ ☐ Yes, I may be contacted about participating in other research projects studying endometriosis or related conditions. I give permission for my contact information (name and mailing address and/or phone number) to be given to other researchers working with the study investigator at Boston Children's Hospital.

_____ ☐ No, I do not want to be contacted about other research projects. **Do not** give my contact information to the staff of any other research studies.

What should you know about HIPAA and confidentiality?

Your health information is protected by a law called the Health Information Portability and Accountability act (HIPAA). In general, anyone who is involved in this research, including those funding and regulating the study, may see the data, including information about you. For example, the following people might see information about you:

- Research staff at Boston Children's Hospital involved in this study;
- Medical staff at Boston Children's Hospital directly involved in your care that is related to the research or arises from it;
- Other researchers and centers that are a part of this study, including people who oversee research at that hospital;
- People at Boston Children's Hospital who oversee, advise, and evaluate research and care. This includes the ethics board and quality improvement program;
- People from agencies and organizations that provide accreditation and oversight of research;
- People that oversee the study information, such as data safety monitoring boards, clinical research organizations, data coordinating centers, and others;
- Sponsors or others who fund the research, including the government or private sponsors.
- Companies that manufacture drugs or devices used in this research;
- Federal and state agencies that oversee or review research information, such as the Food and Drug Administration, the Department of Health and Human Services, the National Institutes of Health, and public health and safety authorities;
- People or groups that are hired to provide services related to this research or research at Boston Children's Hospital, including services providers, such as laboratories and others;
- And/or your health insurer, for portions of the research and related care that are considered billable.

If some law or court requires us to share the information, we would have to follow that law or final ruling.

Some people or groups who get your health information might not have to follow the same privacy rules. Once your information is shared outside of Boston Children's Hospital, we cannot promise that it will remain private. If you decide to share private information with anyone not involved in the study, the federal law designed to protect privacy may no longer apply to this information. Other laws may or may not protect sharing of private health information. If you have a question about this, you may contact the Boston Children's Hospital Privacy Officer at (857) 218-4680, which is set up to help you understand privacy and confidentiality.

Because research is ongoing, we cannot give you an exact time when we will destroy this information. Researchers continue to use data for many years, so it is not possible to know when they will be done.

We will also create a code for the research information we collect about you so identifying information will not remain with the data and will be kept separately. The results of this research may be published in a medical book or journal or be used for teaching purposes. However, your name or identifying information will not be used without your specific permission.

Your privacy rights

If you want to participate in this research study, you must sign this form. If you do not sign this form, it will not affect your care at Boston Children's Hospital now or in the future and there will be no penalty or loss of benefits. You can withdraw from the study and end your permission for Boston Children's Hospital to use or share the protected information that was collected as part of the research; however you cannot get back information that was already shared with others. Once you remove your permission, no more private health information will be collected. If you wish to withdraw your health information, please contact the research team.

You may have the right to find out if information collected for this study was shared with others for research, treatment or payment. You may not be allowed to review the information, including information recorded in your medical record, until after the study is completed. When the study is over, you will have the right to access the information again. To request the information, please contact the Hospital's Privacy Officer at (857) 218-4680.

Contact Information

I understand that I may use the following contact information to reach the appropriate person/office to address any questions or concerns I may have about this study. I know:

I can call…	At	If I have questions or concerns about
Investigator: **Dr. Amy DiVasta**	Phone: **617-355-7181** Pager: 617-355-7243 **[0630]**	▪ General questions about the research ▪ Research-related injuries or emergencies ▪ Any research-related concerns or complaints
Research Contact **Emma Singleton** **Esther Kim**	Phone: **617-355-2212** Pager: **1108** Email: bce@childrens.harvard.edu	▪ General questions about the study ▪ Research-related injuries or emergencies ▪ Any research-related concerns or complaints
Institutional Review Board	Phone: **617-355-7052**	▪ Rights of a research participant ▪ Use of protected health information. ▪ Compensation in event of research-related injury ▪ Any research-related concerns or complaints. ▪ If investigator/research contact cannot be reached. ▪ If I want to speak with someone other than the Investigator, Research Contact or research staff.

Documentation of Informed Consent and Authorization

- ☐ I have read this consent form and was given enough time to consider the decision to participate in this research.
- ☐ This research has been satisfactorily explained to me, including possible risks and benefits.
- ☐ All my questions were satisfactorily answered.
- ☐ I understand that participation in this research is voluntary and that I can withdraw at any time.
- ☐ I am signing this consent form prior to participation in any research activities.
- ☐ I give permission for participation in this research and for the use of associated protected health information as described above (HIPAA).

Parent/Legal Guardian Permission (if applicable)

If the child to be involved in this research is a foster child or a ward of the state please notify the researcher or their staff who is obtaining your consent.

■ _____ _____ _____

Date (MM/DD/YEAR) Signature of **Parent** or **Legal Guardian** Relationship to child

Child Assent

■_____ _____

Date (MM/DD/YEAR) Signature of **Child/Adolescent Participant**

Adult Participant (if applicable)

■ _____ _____

Date (MM/DD/YEAR) Signature of **Adult Participant**

Research Investigator /or Associate's Statement & Signature

- I have fully explained the research described above, including the possible risks and benefits, to all involved parties (participant /parents/legal guardian as applicable).
- I have answered and will answer all questions to the best of my ability.
- I will inform all involved parties of any changes (if applicable) to the research procedures or the risks and benefits during or after the course of the research.
- I have provided a copy of the consent form signed by the participant / parent / guardian and a copy of the hospital's privacy notification (if requested).

■ _____ _____

Date (MM/DD/YEAR) Signature of **Research Investigator or Associate**

Witness Statement & Signature

A witness must be present for the entire consent process in the following situations (please check the appropriate box)

☐ The individual cannot read and this consent document was read to the participant or legal representative, **or**

☐ The individual has certain communication impairments that limit the participant's ability to clearly express consent **or**

☐ Situations where the IRB requests a witness be present: please specify _____

I confirm that the information in this consent form was accurately explained to the participant, parent or legally authorized representative, the individual appeared to understand the information and had the opportunity to ask questions, and that informed consent was given freely.

☐ _____ _____

Date (MM/DD/YEAR) Signature of Witness