AWARD NUMBER: W81XWH-19-1-0219

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

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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

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON** USAMRMC
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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?

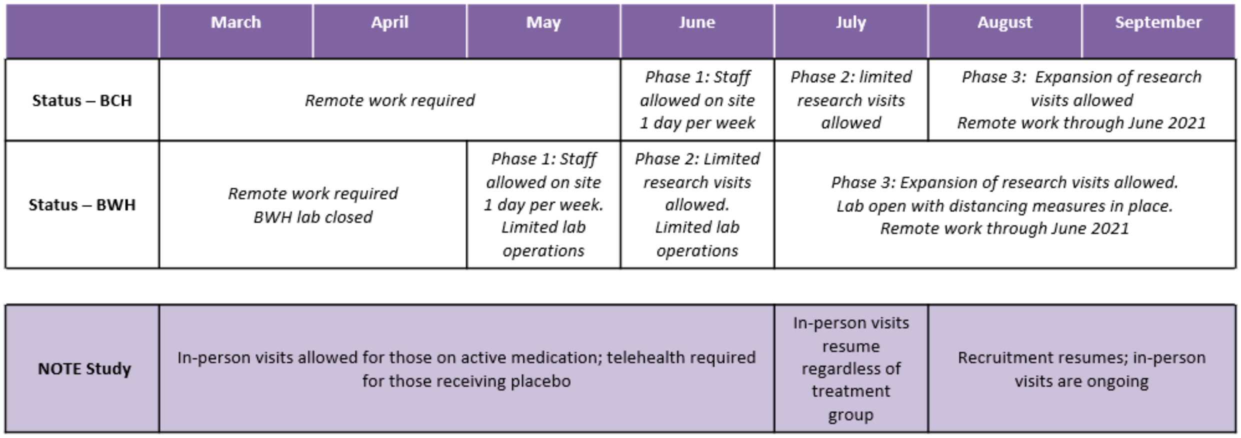
Major Task 1: Launch the randomized clinical trial (completed)
Institutional Review Board approval was obtained at both Boston Children's Hospital and Brigham and Women's Hospital. Brigham and Women's Hospital agreed to cede IRB review and approval to Boston Children's Hospital, allowing us to coordinate IRB communication through one site. The Investigational New Drug status was secured through the US FDA, and our IND Annual Report was submitted in 2020. The written consent form was finalized and remains up to date. All study amendments were submitted to the IRB. The Annual Continuing Review was approved by the IRB in Quarter 3.

The study research assistants have been trained in the conduct of the study visits within our Clinical and Translational Study Unit (now called the Experimental Therapeutics Unit). We had research assistant staff turnover as Laura Pavitt moved out of state; she was replaced by Ms. Emma Singleton. The research assistants led the building of our database, created data collection forms, and collaborated with nursing in the Experimental Therapeutics Unit to create order sets for study visits. They completed all required CITI coursework, and were trained in proper techniques for obtaining written informed consent. They were trained in how to administer the validated study measures, including the surveys, questionnaires, and central hypersensitization testing.

Study medications were obtained through collaboration with our Research Pharmacy, and randomization lists were generated. We worked with the Experimental Therapeutics Unit to develop the laboratory and nursing protocols for study visits and successfully launched study visits for participants.

The research database (both HIPAA and FDA-compliant) was built, tested by our biostatistician, and has been successfully utilized for data management of all participants to date.

<u>Major Task 2: Complete enrollment of the n=80 subjects (in progress)</u>
Subject recruitment, screening, and enrollment commenced in Quarter 2. Due to the COVID-19 pandemic, clinical research recruitment was shut down at Boston Children’s Hospital from March until August 2020 (Figure). During the times that clinical research has been open, n=74 patients were screened. Of those, 16 were lost to follow-up and did not respond to outreach from the research team; 13 were determined to be ineligible; 12 chose not to enroll, and 19 are in the process of screening and determining eligibility/interest. Eight participants have been enrolled. Of these, 5 completed the six-month study while 2 withdrew from study participation before completion. An additional 6 patients have been screened and are pending the scheduling of their baseline visit.



	March	April	May	June	July	August	September
Status – BCH	*Remote work required*			*Phase 1: Staff allowed on site 1 day per week*	*Phase 2: limited research visits allowed*	*Phase 3: Expansion of research visits allowed Remote work through June 2021*	
Status – BWH	*Remote work required BWH lab closed*		*Phase 1: Staff allowed on site 1 day per week. Limited lab operations*	*Phase 2: Limited research visits allowed. Limited lab operations*	*Phase 3: Expansion of research visits allowed. Lab open with distancing measures in place. Remote work through June 2021*		
NOTE Study	In-person visits allowed for those on active medication; telehealth required for those receiving placebo				In-person visits resume regardless of treatment group	Recruitment resumes; in-person visits are ongoing	

In our projected quarterly enrollment, we anticipated having n=13 subjects enrolled by the end of Quarter 4. We are currently behind on our projected enrollment due to the COVID-19 related research shutdown that occurred. However, we are optimistic about the interest that we’ve seen since the resumption of research activities and anticipate that we will move forward with enrollment goals over the upcoming year.

During the clinical research shutdown, study visits were allowed for participants actively in the trial who were randomized to active medication only. Telehealth visits were required for those receiving placebo. As such, the blind was broken for n=4 study subjects to determine whether an in-person visit or telehealth visit was recommended. In-person visits regardless of treatment assignment resumed. July 2020. Although this temporary practice unblinded the investigator team to treatment assignment, the participants remained blinded to medication assignment (cabergoline versus placebo) to preserve the integrity of the outcome measures.

The Data and Safety Monitoring Board members were finalized, and a DSMB charter was developed. The DSMB conducted its first meeting in spring 2020; the second meeting is scheduled for fall 2020. No safety concerns were identified by the DSMB.

The independent study monitor has conducted oversight of the clinical trial launch; the next monitor visit is scheduled for October 2020. No significant concerns were identified by the study monitor.

Major Task 3: Obtain data required to successfully complete Specific Aim 2 (in progress)
Study outcome measures have been collected at all in-person completed visits to date. We have had no major issues with laboratory analyses or processing of specimens. During the temporary research shut-down, when telehealth visits were required, we were unable to obtain blood samples on study subjects, as those samples need to be collected in person. In addition, from March until August 2020, we were unable to perform the Pulse Wave Velocity testing. To date, that testing has been performed by our collaborators in cardiology. During the current pandemic, the hospital limited significantly the number of on-site non-essential personnel allowed at one time. As a result, we were temporarily unable to measure this secondary outcome. To prevent this issue in the future, the cabergoline study RAs will be trained in the administration of the Pulse Wave Velocity testing in September 2020. Despite staffing and visit restrictions, all visits were conducted within the study timeframe designated in our protocol.

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 to date. During the temporary research shut-down, when telehealth visits were required, we were unable to obtain Quantitative Sensory Testing measures on one participant as they need to be performed in person.

Major Task 5: Complete study and analyze the data from the trial (in progress)
The data are being prospectively entered into our REDCap database, which is both HIPAA and FDA compliant. A systematic data double-checking protocol is now underway and is approved by the PI. 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. The DSMB requested safety measures to be analyzed in an unblinded fashion before DSMB meetings. Our statistician performed these analyses, which were shared only with the DSMB and not with the investigators.

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 creation of the REDCap database. Also, they were trained in the standardized protocols for performing the Quantitative Sensory Testing by Dr. Sieberg.

Dr. DiVasta was supposed to attend the Society for Adolescent Health and Medicine conference, the North American Society for Pediatric and Adolescent Gynecology conference, and the Pediatric Academic Society meeting in the spring of 2020. Sadly, each of these conferences was canceled due to the COVID-19 outbreak. The NASPAG conference abstract presentations were held virtually at a later date, but the rest of the conference was not.

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?
We have resumed subject recruitment to full capacity and hope to meet or exceed our enrollment goal in the coming quarters. We have developed a COVID-19 contingency plan so the study can continue to enroll participants and conduct visits even if a second wave of cases and statewide or hospital-wide research shutdown occurs. The written consent form has been slightly modified to inform participants of these potential changes in the event of another hospital research shutdown.

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:

1) As we disclosed in our last quarterly report, we had to change study procedures in response to Boston Children’s Hospital’s policy on research operations during the COVID-19 pandemic. Several study visits were conducted virtually (rather than in person) per BCH IRB requirements, and virtual visits may continue in the future. To be proactive in case of another research shutdown, we have developed—and our IRB has approved--- a contingency plan for changing study visits to virtual visits, including the delivery of study medications to the participants’ homes, allowing for participants to have safety laboratory samples obtained at a local facility, the adoption of written informed consent procedures via remote means, and informing participants of possible study changes at the time of consent. Some of our study outcome measures that can only be conducted in person (Pulse Wave Velocity testing, Quantitative Sensory Testing, blood, and urine assays) were not obtained on some participants during the research shutdown. To better prevent any testing disruptions due to staffing restrictions, our staff will be trained on Pulse Wave Velocity testing by members of the Cardiology team. We have submitted these changes to the IRB as a pending amendment.

2) The written consent form has been modified very slightly as per recommendations from the FDA following our annual report submission. Specifically, the FDA asked us to 1) add thioxanthenes to the list of exclusionary drugs with dopamine agonist activity; 2) edit our description of the Pulse Wave Velocity to more accurately describe the non-invasive procedure, and to replace the word "catheter" with "probe" to reflect the fact that this procedure is non-invasive; 3) revise the statement regarding whether cabergoline is FDA-approved for the treatment of endometriosis to read: “This means the drug is not approved by the FDA for the treatment of endometriosis.”; 4) edit the statement regarding the mechanism of action of cabergoline to be more accurate, but also to leave the statement understandable to the patients and families; 5) update the side effects of cabergoline; 6) to replace the word “parent” with ‘parent/guardian” in the section that addresses suicidal ideation). No changes to study outcomes, intervention, risk/benefit ratio, or study procedures were made.

3) Since HRPO approval was received, 3 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 3/17/2020

   - Increasing blood volume collected for one previously-approved lab assay. One laboratory study included in the protocol (ESR) requires 2 mL of plasma. The initial study protocol involved the collection of exactly 2 mL of plasma. However, we had 2 samples return “not resulted” due to "insufficient quantity". As such, we amended the protocol to increase the volume collected from 2 mL to 3 mL for this specific test. The addition of this 1 mL of blood sample still keeps the blood volume collected well within the upper limit of 40 mL.
   - Changing daily symptom diary from online to paper. Our initial protocol stated that the daily symptom diary would be in the form of a REDCap survey. However, in working with the REDCap team and talking with patients, we decided to change this measure to a paper diary. Our version of REDCap is not able to automatically send out a daily survey, which would require our study team to manually send it daily (prone to error). Additionally, our subjects provided feedback that paper surveys would be their preferred method.

   Amendment 8/24/20 (submitted in response to recommendations from the FDA following submission of our annual IND report)

   - Added thioxanthenes to the list of exclusionary drugs with dopamine agonist activity
   - Edited our description of the Pulse Wave Velocity to more accurately describe the non-invasive procedure, and to align the protocol with the language in the informed consent document. The word "catheter" was replaced with "probe" to reflect the fact that this procedure is non-invasive.
   - Specified/clarified that pill counts were occurring at both the 3 month and 6 month visits
   - Modified the statistical analysis plan to specify that we will control for changes in pain medication use in the efficacy analysis

Changes in approach and reasons for change

Apart from the interruptions to normal research activities as outlined above, we have made no additional changes to our original approach. We have tried to be proactive in anticipating another research shutdown, and developed strategies to allow for the project to successfully continue even if that should occur in the future. Switching from a REDCap symptom diary to a paper survey diary was based upon the limitations of the REDCap product utilized by our institution. The changes to the written consent form and the most recent amendment were made at the request of the FDA following our annual report submission.

Actual or anticipated problems or delays and actions or plans to resolve them

As discussed above, we saw some disruption to our data collection for currently enrolled participants due to the COVID-19 pandemic. We anticipate that there may be a second wave of COVID-19 cases and restrictions, and have therefore developed a contingency plan that is approved by our IRB. This plan allows us to continue in-person visits with safety measures in place, or virtual visits if required by Boston Children's Hospital's IRB.

Changes that had a significant impact on expenditures

Because of decreased study visit volume, expenditure on lab assays, and 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 has been responsible for the launch of the randomized clinical trial, obtained the IRB approvals, and approved all materials and forms associated with the trial. She has been present at all CTSU study visits. She prepared the first DSMB report. 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.

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 oversaw the BWH IRB approval, and has been 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 has assisted 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: Caterina Stamoulis, PhD
Project Role: Senior biostatistician
Research Identifier:
Nearest person month worked: 0.6
Contribution to Project: Dr. Stamoulis is reviewing and approving the REDCap database for the clinical trial, and assisted in creating the report for the first DSMB meeting.

Name: Anna Kapral, BS/BA
Project Role: Research Assistant
Nearest person month worked: 6
Contribution to Project: The full-time research assistant position (12 calendar months) has been divided among two research assistants (Ms. Kapral and Ms. Singleton), to ensure adequate coverage for the clinical trial recruitment and visit needs regardless of illness, vacation, etc. on the part of the research assistant staff. Ms. Kapral assisted with the launch of the randomized clinical trial, including collaborating with the CTSU for study visit implementation. She has completed training on the validated outcome measures used in this study by working closely with members of Dr. Christine Sieberg’s Pediatric Pain Lab for Quantitative Sensory Testing training, and members of Dr. Sarah DeFerranti’s team for Pulse Wave Velocity testing procedures. She created all case report forms for the study and helped create the REDCap database. She has conducted the majority of the study visits in the CTSU. She has drafted all amendments submitted to the IRB. She prepared all study materials for the first study monitoring visit and the first DSMB meeting.

Name: Laura Pavitt, BA and Emma Singleton, BS/BA
Project Role: Research Assistant
Nearest person month worked: 6
Contribution to Project: Ms. Singleton joined our team shortly after the launch of the randomized clinical trial, replacing Ms. Pavitt who left due to relocation. She has completed training on the validated outcome measures used in this study by working closely with members of Dr. Christine Sieberg’s Pediatric Pain Lab for QST test training, and members of Dr. Sarah DeFerranti’s team for Pulse Wave Velocity testing procedures. She has prepared case report forms and is conducting the data double-check process. She has conducted several study visits in the CTSU. She is preparing all study materials for the second study monitoring visit and the second DSMB meeting.

Name: Jenny Sadler Gallagher, MPH
Project Role: Research Coordinator
Nearest person month worked: 4.8
Contribution to Project: Ms. Sadler Gallagher has assisted with the launch of the randomized clinical trial, including oversight of the REDCap database building. She has conducted CTSU study visits. She is overseeing the study budget and financial management of the study. She has trained all study staff in Part 11 compliance. She has provided oversight of the research assistants, including supervision of their CITI training, IRB administration, clinical procedures for subject recruitment and enrollment, and collaboration with nursing staff in the Experimental Therapeutics Unit.

Name: Thomas Giorgio, BA and Hannah Palfrey, BS
Project Role: Research Assistant, Cardiology
Nearest person month worked: 0.12
Contribution to Project: Ms. Palfrey took over the Pulse Wave Velocity testing after Mr. Giorgio left the cardiology team. She has been trained in standard protocol for measurement of Pulse Wave Velocity and conducted these assessments for all study participants.

Name: Christine Sieberg, PhD
Project Role: Co-Investigator
Nearest person month worked: 0.6
Contribution to Project: Dr. Sieberg trained the Research Assistants in the administering of the Quantitative Sensory Testing and continues to provide expertise in the interpretation and administration of the pain measures used in the clinical trial, which she has helped to create to capture the full experience of adolescent chronic pain. She helped to determine the validated measures for the pain outcomes used in the trial.

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 U.S. Department of Defense that began in August 2019, and an R21 award from NICHD, as below.

W81XWH1910560 (PI: Sieberg) 08/15/2019-08/14/2022 1.41 Cal Mos
U.S. DEPT OF DEFENSE $1,038,196
Defining the Role for Descending Pain Modulation and Reward-Aversion Processes towards the Development of Chronic Pain in Endometriosis
The goals are to define changes in brain structure and function as a correlate of subjective measures of pain and psychophysical functioning in adolescent, young adult, and adult women with surgically confirmed endometriosis vs. healthy controls; to correlate psychophysical measures and brain changes with levels of Offset Analgesia (OA) and to compare brain metrics of adolescents, young adults, and adult women with endometriosis with female patients ages 12-44 with migraines.
No overlap.

R21HD096358 (PI: Missmer) 04/01/2019-03/31/2021 0.6 Cal Mos (to begin Year 2)
NICHD $246,648
Harnessing biomarker and phenotypic diversity among adolescents and women with endometriosis to advance personalized medicine for diagnosis and pain remediation

Within the Women's Health Study: from Adolescence to Adulthood (A2A; a prospective cohort of >1200 adolescents and young women, oversampled for those with surgically-confirmed endometriosis, followed for >4 years), we will combine WERF EPHect compliant data from participant surveys, electronic medical records, and stored blood samples collected annually. These data will capture informative changes in pain experience, inflammatory and oxidative stress milieu, and central sensitization to advance our understanding of phenotypic diversity among adolescents and women with endometriosis – the foundation for successful personalized, precision medicine to shorten diagnostic delay and maximize successful pain remediation.
Role: Co-I
No overlap.

Dr. Stamoulis had a grant from the National Science Foundation end on 8/31/2020, and has received a new award since the last report.

R03NS119799 (PI: Stamoulis) 12/01/2020-11/30/2022 1.2 Cal Mos
National Institute for Neurological Disorders and Stroke (NINDS) $50,000
Stress-Induced Hormonal Fluctuations and their Relation to Seizure Dynamics in Children with Epilepsy
The goal of this project is to measure stress hormone rhythms in children with epilepsy and assess the relationship between changes in these rhythms and seizure occurrence.
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 that is both FDA and HIPAA compliant.

Organization Name: Boston Center for Endometriosis
Location of Organization: Boston, MA
Partner's contribution to the project: Urine and blood samples are processed 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:

The updated written consent form is attached.

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 to 2.5 hours**	**6 week phone call: 10 minutes**	**Visit 2: 3 Month 1 to 1.5 hours**	**18 week phone call: 10 minutes**	**Visit 3: 6 Month 1.5 to 2 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. 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 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. It is possible that this care would include norethindrone acetate, since this is a medication we use regularly in our clinic to treat pain related to endometriosis. 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.

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 **Anna Kapral**	Phone: **617-355-2212** Pager: **1108**	▪ 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