Boston Children's Hospital

Date: Tuesday, June 11, 2019 11:54:17 AM Print Close

Title: Novel Treatments for Endometriosis (NOTE): Dopamine Receptor Agonist Therapy for Pain Relief in Women Suffering from Endometriosis Pilot Study

General Information

1 * **Protocol Title:** The NOTE Study: Novel Treatments for Endometriosis

Maximum of 230 characters may be entered.

2 **Full Title - If protocol title exceeds the 230 characters limited from field above, enter full title here. Otherwise, leave blank.**
Novel Treatments for Endometriosis (NOTE): Dopamine Receptor Agonist Therapy for Pain Relief in Women Suffering from Endometriosis Pilot Study

3 * **Provide a brief summary (in lay terms) of the research protocol.**
Endometriosis is a chronic illness which begins during adolescence and young adulthood. Current therapies for endometriosis are suboptimal, leaving many women trying to cope with chronic pain. Novel therapies are desperately needed to ameliorate the chronic course of this disease, and prevent ongoing suffering for these women. In this pilot study, we aim to estimate the efficacy and safety of a regimen of norethindrone acetate (a standard therapy) or cabergoline (a novel agent) for alleviating pain symptoms in young women with endometriosis. The results of this pilot study will be used to inform a future, larger randomized controlled trial.

4 * **Principal Investigator (PI):** Amy DiVasta

4.1 * **To serve as a PI you must qualify under one of the following eligibility requirements. (Residents, interns, fellows and postdoctoral candidates are not permitted to be PIs). Please select the appropriate category that applies to you.**
Physicians, Dentists and Psychologists credentialed through the hospital with the BCH medical staff registrar as an active medical staff member and having an appointment of Instructor or higher at Harvard Medical School.

If Other patient services professionals:

4.1.1 **Research is part of your scope of employment responsibility and not to meet a training or degree requirement. Please explain how this research falls within the scope of your responsibilities at the hospital.**

4.1.2 **You have training and experience and confirmed clinical research competencies. Please explain your training and experience in clinical research.**

4.1.3 **Are you employed at Children's as a nurse or do you have nursing credentials through Boston Children's Hospital?**
Please note if this is checked yes, in accordance with the policies of the Nursing Department your protocol will be sent to the Nursing department for both scientific review and departmental sign off.
○ Yes ○ No

5 * **Type Of Submission:**

- ● **New Research Activity**
- ○ **New Research Activity Limited to Secondary* Use of Biological Material and Data
- ○ Establishment of Human Biological Specimen Repository/ Data Registry (only) – repositories/registries are defined as a prospective collections of specimens or data that are processed, stored, distributed to multiple investigators for use in research.
- ○ Request for Exemption
- ○ Individual Patient Expanded Access
- ○ Humanitarian Use Device (HUD)

- ○ Reliance on Another IRB
- ○ Projects that lack immediate plans for involvement with human subjects, their data and/or their specimens (i.e.training grants)

*** Use this form only if:*
1) specimens/data are not identifiable or
2) specimens/data are identifiable but recorded by PI in de-identified format or meet the waiver of HIPPA authorization criteria listed below All other uses of secondary specimens/data must be submitted on a new research activity form.

** Secondary means the tissue or data will be or was collected for a primary or initial purpose other than the research (i.e data from medical records, tissue from pathology)*

Waiver of HIPPA authorization (all criteria must be met)
• The proposed use of this data/document/record/specimen presents no more than minimal risk to the privacy of individuals
•The research could not practicably be conducted without the waiver of HIPPA authorization
• The research could not practicably be conducted without access to and use of protected health information with identifiers
• Waiving HIPPA authorization will not adversely affect the subject's rights or welfare

This form may not be selected if the study involves interaction/intervention with subjects in order to obtain tissue/data specifically for this research.

6 * **Is this protocol related to child health (including perinatology, prenatal assessments, childhood antecedents of adult disease, and long-term follow up of pediatric disorders)?**

● **Yes** ○ No

7 * **Is this protocol related to cancer (primarily concerning malignancies, oncology patients, or involving use of malignant tumors)?**

○ Yes ● **No**

Note: If YES, your protocol will require review by the Dana Farber IRB instead.
For details, see: Catalyst and Dana Farber Cancer Center Reliance Agreements

8 * **Will this protocol utilize any of the services of the ETU (Experimental Therapeutics Unit)?**
Please select "No" for the following types of submission:
1. Request for Exemption
2. Projects that lack immediate plans for involvement with human subjects, their data and/or their specimens (i.e.training grants)

● **Yes** ○ No

These services include:

- *Use of space on the ETU or research space at Waltham*
- *Nursing assistance at above sites*
- *Off-site nursing and/or research coordinator services provided through ETU*
- *Specimen collection or processing, sample storage and preparation for shipping*
- *Assistance from nutritional Metabolic Phenotyping Core (preparation of research meals, analysis of food records, etc.)*
- *Use of specialist equipment located on the ETU (3DMD camera, DXA, pQCT, V-max, etc.)*

- First Name
- Last Name
- CHID# (if applicable)
- BCH Department (if applicable)
- Email Address

Research Team

If the person you need to add to your protocol cannot be found using the "Add" buttons below, please send an email to CHERP Support (cherp.support@childrens.harvard.edu) requesting that the person be added to the Research Staff. CHeRP Support will need the following information:

1 Research Staff - Children's Hospital Employees only:

	Last Name	First Name	Role	Editor	CC on Correspondence	Required Training Completed	CHeRP Training	Date Modified	Date Created
View	Gallagher	Jenny	Research Coordinator/Assistant	yes	yes	yes	yes	6/3/2015	6/3/2015
View	Hale	Andrea	Other Research Support	no	no	yes	yes	11/28/2017	11/28/2017
View	Laufer	Marc	Co-Investigator	no	no	yes	yes	6/3/2015	6/3/2015
View	Missmer	Stacey	Co-Investigator	no	no	yes	yes	6/3/2015	6/3/2015

2 *NOTE:* Accounts are no longer required for non-BCH researchers. These individuals remain under the jurisdiction of their home institution's IRB and should not be listed here. If you think there is a special circumstance, please contact your IRB Administrator.

Research Staff - Non Children's Hospital Employees only:

Last Name	First Name	Role	Email	Required Training Completed
There are no items to display				

3 PI: Amy DiVasta

Completed Training Courses:

Training Program	Continuing Education Description	Training Completed	Date Created
Continuing Education	EQuIP: IND/IDE Pre-review	10/25/2016	
Continuing Education	Collaborative IRB Training Initiative (CITI Continuing Education)	7/12/2016	7/12/2016
Continuing Education	Continuing Education/Department Meeting	3/10/2015	
Collaborative IRB Training Initiative (CITI Biomedical)		9/11/2012	9/11/2012
CHeRP Training		10/26/2010	
CHeRP Training		10/26/2010	
Continuing Education	Collaborative IRB Training Initiative (CITI Continuing Education)	9/2/2009	11/8/2010
Continuing Education	Continuing Education/Department Meeting	8/16/2006	11/8/2010
Collaborative IRB Training Initiative (CITI Biomedical)		2/4/2004	11/8/2010
Collaborative IRB Training Initiative (CITI Non-Interventional)		2/4/2004	11/8/2010

4 Reliance PIs - Employees who are listed on existing Reliance on BCH protocols.

	Last Name	First Name	Institution	Completed Training
View	Hornstein	Mark	Brigham & Woman's Hospital (BWH)	Training Received at Another Institution(1/29/2015) Continuing Education(7/27/2006) Training Received at Another Institution(7/6/2009) Training Received at Another Institution(9/30/2000) Training Received at Another Institution(9/30/2000) Training Received at Another Institution(4/9/2012) Reliance Agreement Training(1/29/2015)

5 Research Team Members - Employees who are listed on existing Reliance on BCH protocols:

	Last Name	First Name	Employee ID	Role	Reliance Institution
View	Fraer	Cameron	601480	Research Coordinator/Assistant	Brigham & Woman's Hospital (BWH) - FWA00000484
View	Hornstein	Mark	600364	Co-Investigator	Brigham & Woman's Hospital (BWH) - FWA00000484
View	Laufer	Marc	602498	Co-Investigator	Brigham & Woman's Hospital (BWH) - FWA00000484
View	Missmer	Stacey	82999	Co-Investigator	Brigham & Woman's Hospital (BWH) - FWA00000484

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Funding Sources

1 * Select funding category.

- (●) **Externally sponsored (federal, state, corporate, foundations)**
- ( ) Internally sponsored
- ( ) Externally and internally sponsored
- ( ) No sponsor
- ( ) Private Donor

1.1 If internally sponsored - select as appropriate:

- [ ] Department/ Division or Children's foundation funds
- [ ] Internal Children's Grant Award

1.2 Enter any additional information if applicable:
Supported with funds from the Marriott Family Foundation

1.3 If the protocol does not have a sponsor, please detail how the study will be conducted without funding.

1.4 Please provide the name of the private donor.

Funding Sources - Details

1 * List of external sponsors for this protocol.

	Sponsor	Funding Category
View	J WILLARD AND ALICE S MARRIOTT FOUNDATIO - 1754	External Foundation
View	MARRIOTT DAUGHTERS FOUNDATION - 1822	External Foundation

Financial Disclosure

1 * Do you or any person affiliated with the protocol have or expect to have any investment or financial relationship (examples below) with any entity that is providing funds or other support in connection with the protocol?

( ) Yes (●) **No**

If YES:

1.1 Please select the relationships as appropriate.

- ☐ Consulting
- ☐ Payments for protocol/study design
- ☐ Protocol-related payments not included in the research agreement budget
- ☐ Stock or Options
- ☐ Honoraria
- ☐ Scientific Advisory Board Membership
- ☐ Royalties or license fees related to the protocol, or to any test article or device which will be employed in the conduct of the research under the protocol (including any royalties or license fees received through an academic institution, including Children's Hospital).
- ☐ Equipment or other laboratory support
- ☐ Other support for research unrelated to the protocol
- ☐ Support for educational or other academic or medical efforts
- ☐ Other Grants
- ☐ Other

2 * **Do you or any person affiliated with the protocol have or expect to have any proprietary interest related to the protocol, or related to any test article or device that will be employed in the protocol? Include proprietary interests that you have assigned to any entity, including any institution you have been affiliated with.**

○ Yes ● **No**

If YES:

2.1 Please select the proprietary interest as appropriate.

- ☐ Patent-licensed, in whole or part, to an entity providing funds for the research
- ☐ Patent-licensed, in whole or part, to another entity
- ☐ Other

3 * **Do you or any person affiliated with the protocol have or expect to have any advisory role, appointment, or employment with any entity that is providing funds or other support for the research to be conducted under the protocol?**

○ Yes ● **No**

If YES:

3.1 Please select as appropriate.

- ☐ Scientific Advisory Board Membership
- ☐ Other Advisory Role
- ☐ Officer
- ☐ Director
- ☐ Employment
- ☐ Other

4 * **Do you or any person affiliated with the protocol have or expect to have any financial interest, financial relationship, or position or advisory role with any other entity that may be affected by the research to be conducted under the protocol (e.g. competitor, customer, collaborator or commercial sponsor affiliate)? Include any entity that may be benefited or harmed, directly or indirectly.**

○ Yes ● **No**

5 * **Do you or any person affiliated with the protocol have or know of any arrangement or**

understanding, tentative or final, relating to any future financial interest, financial relationship, future grant, position, or advisory role either related to the protocol, or dependent on the outcome of the research under the protocol?

○ Yes ● **No**

6 * **The IRB prohibits special incentives in connection with clinical research, including, finder's fees, referral fees, recruitment bonuses, enrollment bonuses for reaching an accrual goal, or similar types of payments. Will you or anyone else in connection with the conduct of any research under the protocol receive money, gifts or anything of monetary value that is above and beyond the actual costs of enrollment, research conduct, and reporting of results, from the sponsor or any other entity?**

○ Yes ● **No**

7 * **Is there anything not disclosed above which you believe might constitute a conflict of interest or an appearance of a conflict of interest in connection with the protocol?**

○ Yes ● **No**

8 **If any of the questions above are checked "Yes", please provide the name of the individual for whom the disclosure is made and describe in further details the disclosure. This section must include a full description of the financial relationship, including but not limited to, a detailed description, as applicable, of any test article of device involved; the advisory role or appointment; the competitor, customer, collaborator; any arrangement related to the research; and so on. Please also include actual amounts of any consulting or other monies received and the time period for which it was received. This section will not be reviewed without a full disclosure.**

9 **Upload any other pertinent documentation.**

Name	Date Last Modified	Version	Owner

There are no items to display

Protocol Design

1 * **Is this a multi center study?**

● **Yes** ○ No

If YES:

1.1 **Is Children's Hospital, Boston the lead site or coordinating center?**

● **Yes** ○ No

If YES:

1.2 **Describe the plan to ensure communication among sites in terms of adverse events, unanticipated problems, protocol modifications, interim results, etc.**

While CHB is the coordinating center, this is truly a joint venture between CHB and BWH. Study staff will be employed at both institutions. Weekly Boston Center for Endometriosis meetings are held on an ongoing basis, so that study staff will be in constant contact regarding study progress and any adverse events and deviations from protocol.

A reliance agreement has proposed, and already completed, and we are asking BWH to cede review to CHB.

2 * **Is the person who will be primarily responsible for conducting the study at BCH different from the PI?**

○ Yes ● **No**

3 * **Has the PI, or if question #2 was YES has that person, previously served as a PI of a protocol involving interaction/intervention with human subjects at CHB?**

● **Yes** ○ No

Subject Information

1 Enrollment Numbers

1.1 * Specify the number of subjects enrolled at Boston Children's Hospital, or at sites relying on BCH IRB review, that are required to complete data analysis.
10 subjects

1.2 If a larger number of subjects must be enrolled to account for such things as screening failures and drop-outs, please indicate the total number of subjects to be recruited at BCH or at relying sites. If not applicable, please leave blank.
14 subjects

1.3 If this is a multi-center study, please specify the total number of subjects required to enrolled across all sites, including BCH and reliance sites, for data analysis.
10 subjects

1.4 If this is a multi-center study and a larger number of subjects must be enrolled across all sites to account for such things as screening failures, drop-outs, and lost to follow-up, please indicate the total number of subjects to be enrolled.
If not applicable, please leave blank.
14 subjects

2 Types of Subjects

2.1 *Gender

- [ ] Males
- [x] Females

2.2 *Age

- [ ] Neonates (up to 30 days)
- [ ] Infants (between 30 days and 2 years)
- [ ] Children (between 2-12 years)
- [x] Adolescents (between 13-17 years)
- [x] Adults, Ages 18-35
- [x] Adults over 35

Specify entire age range.
15-40 years

2.3 Special Populations

- [ ] Mentally Incapacitated
- [ ] Employees/Staff (Note: Employees/staff under the direct supervision of the PI may not be recruited.)
- [ ] Normal/Healthy Controls
- [ ] Students

Specify from where.

- [ ] Pregnant Women/Fetuses
- [ ] Prisoners/Incarcerated Youth (this would include children under the care of the Department of Youth Services). Consider if your target population will be or at higher risk of incarceration. If this category is chosen, you will be prompted to answer additional questions to meet federal regulations.
- [ ] Wards of the State (consider if your target population may contain wards of the state or children at risk of becoming a ward of the state (this includes foster children or any child that is in state custody))
- [x] Minorities

If NOT checked:

Provide scientific justification for excluding minorities.

- [ ] Non-English Speaking Subjects

If checked:

What plans do you have to provide the subject/family with a written translation of the consent form and other study materials and to ensure that all study interaction will be in a language

understandable to the subject/family?

If NOT checked:

Please provide scientific justification for excluding non-English speaking subjects.

In addition to the fact that there is no known difference in endometriosis prevalence with regards to race and ethnicity, the additional burden of translation services on personnel and funding would make performing the study impossible. As noted above, the consent process will be in-person and there will be three in-person CTSU visits, all of which would require translator services. In addition to the consent form, there are multiple questionnaires that would all need to be translated into multiple languages. The requirement to include non-English speaking individuals would be unusually burdensome for a study of this magnitude.

☐ Other populations potentially subject to special considerations not identified above (i.e. socially, educationally, economically disadvantaged, elderly, terminally ill or adults with questionable decision making capabilities)

Specify population.

Specify what additional safeguards will be taken to protect the rights and welfare of these subjects.

☐ Adults With Decisional Impairment

*__Decisional Impairment__ is defined as: *persons who have impaired ability to make decisions as a result of intellectual or mental health challenges as well as individuals who have lost capacity to make decisions because of clinical situations such as unconsciousness.*

Please describe the type and range of decisional impairment of the adult subjects to be included in the research.

Provide a rationale for why it is necessary to include adults with decisional impairment as participants in research, including information regarding the potential benefit to the individuals in relationship to potential risks.

Describe the criteria and procedures or measurements for evaluating the decisional status of the prospective participant to determine whether they are capable of consenting on their own behalf. This would include the use of standardized measurements, consults with another qualified professional, etc...

Describe how persons authorized to obtain legally valid consent will be identified in the event any individual is judged incapable of consenting on their own behalf. Please review the IRB policy to the right of this question that describes the requirements for determining a legally authorized representative for the subject. Briefly, these are court-appointed guardians, health care proxies, or durable power of attorney. Please note that family members are not automatically considered for this role and may only be permitted when there is documentation that neither of the previous exist.Please also explain how legal records regarding authority will be obtained, reviewed by the research team, and documented in the research record.

When possible if legally valid consent cannot be obtained from the subject, assent should be obtained. Please describe if you plan to obtain assent and provide criteria used to evaluate the assent or dissent of the adult with decisional impairment.

If applicable to your population, provide a description of how the participant will be protected if their capacity to consent is lost or fluctuates. What provisions have been made to protect the subjects's rights? This may include the use of an ombudsman, frequent cognitive status evaluations, etc...

Study Location

1. If your research is conducted in any of the following location(s) please check all that apply. If your research does not include any of these sites, please leave the questions blank.

☑ **Adolescent Medicine**

☐ Adolescent Surgery

☐ Cardiac ICU

☐ Cardiac Surgery

- [ ] Infant Toddler Surgical
- [ ] Infant/Toddler Medical
- [ ] Intermediate Care Program (ICP, 11 South)
- [ ] Medical/Surgical ICU (7 South)
- [ ] Medicine ICU (11 South)
- [ ] Neonatal ICU
- [ ] Neurology
- [ ] Oncology/Hematology
- [ ] Psychiatry
- [ ] School Age Medical
- [ ] School Age Surgical
- [ ] Sleep Study
- [ ] Solid Organ Transplant
- [ ] Stem Cell Transplant

Other CH Locations

- [ ] Cardiac Cath Lab
- [ ] Children's Hospital Primary Care Center (CHPCC)
- [x] **Clinical and Translational Study Unit (CTSU)**
- [ ] Emergency Department
- [ ] Martha Elliot Health Center (MEHC)
- [ ] MRI
- [ ] Nuclear Medicine/PET
- [ ] OR/PreOp/PACU
- [x] **Other Satellites (Lexington, Peabody, South Shore, etc.)**
- [ ] Radiology

Off Premises e.g. Schools, other Hospitals, Home

- [ ] Beth Israel Deaconess
- [x] **Brigham and Women's Hospital**
- [ ] Boston Medical Center
- [ ] Dana Farber Cancer Institute
- [ ] Harvard Medical School
- [ ] Harvard School of Public Health
- [ ] Subject's Homes
- [ ] Joslin Diabetes Center
- [ ] Mass Eye and Ear Infirmary
- [ ] Mass General Hospital
- [ ] MIT
- [x] **Other**
- [ ] Physician Office
- [ ] School

☐ Tufts – New England Medical Center

1.1 *If Other:*
Specify:
221 Longwood Ave, Boston, MA 02115

Recruitment and Remuneration

Recruitment

1 * **Describe plans for recruitment, including identification of potential participants, who is responsible for recruitment and how and when subjects will be recruited.**

Potentially eligible participants will be identified during visits to the Pediatric Gynecology program at BCH (including satellite sites) or the CIRS or MIGS programs at BWH. Patients will be identified by their clinical provider as potentially eligible.

If the patient is interested, the provider will contact the study team. An IRB-approved study brochure may be given to the patient, to allow her to contact the study team directly. A study coordinator or another member of the study team will meet with the patient to discuss options for involvement.

In some instances, providers may wish to give blanket approval for the study team to contact their patients, rather than referring individual patients. In these instances, the study team will contact patients through the mail or email with a recruitment letter (appendix L), and then follow up with the patient (by phone or email, if patient approved for research) one week later. This allows patients of very busy providers the opportunity to participate in the study. Patients are able to opt out of the follow up call/email by returning the opt out postcard (Appendix N) to the study team. Providers who give patient contact information to study staff will be only IRB-approved participants in the research.

We will also recruit by posting IRB-approved brochures in the waiting rooms of the clinics and other hospital areas and in local clinics. After a patient expresses interest in participating in the trial, a research assistant or another approved member of the study team will meet with the patient/family to discuss options for involvement and to sign the consent form. Prior to enrollment, patients will be asked what their highest endometriosis pain score has been within the last month. Only those patients with a score of 3/10 or greater will be eligible to enroll.

In addition, potentially eligible participants from the Boston Center for Endometriosis (BCE)' "Women's Health Study: from Adolescence to Adulthood" cohort (CHB IRB# IRB-P00004267) will be identified from the enrollment logs of the BCE. Patients meeting inclusion criteria will be identified by the study team (all of whom will jointly have IRB approved roles in the BCE Study and current proposed trial), and will be contacted by their previously selected preferred method of contact (either phone, email, text) in the manner outlined below. Patients may also be recruited from Craig's List, Facebook, and the BCH and Partners' research websites and employee intranet pages, and will all be screened for eligibility by the study team. Recruitment materials may also be made available at the Gynecology department's annual endometriosis patient day.

2 * **Will you need to search through BCH medical records or institutional databases such as i2b2 or BCH360 for the initial screening for potentially eligible subjects?**

○ Yes ● **No**

If YES:

2.1 **Will you be accessing records or contact information of patients not seen by your department, your service or your co-investigators?**

○ Yes ○ No

In general, recruitment of patients from services outside of the investigators' area is not to be done without involvement of the departments in which the patients were seen.

If YES:

2.1.1 **Please describe how you will coordinate with other departments or care providers during the recruitment process.**

3 **If applicable, how will prospective subjects' healthcare providers (e.g., physician, dentist, etc.) be involved in the recruitment and/or be notified of their individual patients' participation in the study?**

Subjects' healthcare providers may choose to give potentially eligible patients a study brochure, or refer them to a study team member for further discussion regarding study participation. Participation or non-participation in the study will not alter clinical care for patients in any way.

Prospective subjects' gynecologic and primary care healthcare providers will be notified of their individual patients' participation in the study by means of an email as well as a written letter, if agreed to by the participant.

4 * **Describe measures that will be implemented to avoid participant coercion or undue influence.**

All prospective participants will meet with a member of the study team trained in proper recruitment and consenting of study participants. All prospective participants will be made aware that study involvement is completely voluntary. Choosing to participate or not participate will not affect patients' care. The consent forms will explicitly state that participation is voluntary and the decision to participate or not participate will not affect a patient's clinical care.

5 * **Does the recruitment strategy involve contacting individuals multiple times in an effort to secure their enrollment into the study?**

● **Yes** ○ No

If YES:

5.1 Please describe how frequently and in what manner individuals will be contacted.

Potentially eligible participants from the BCE "Women's Health Study: from Adolescence to Adulthood" Study cohort will be identified from the enrollment logs of the BCE. Patients meeting inclusion criteria will be identified by the study team (all of whom will jointly have IRB approved roles in the BCE Study and the crurent proposed trial). Patients will be first contacted using the preferred method of contact (email, phone, text message) as indicated by the participant during enrollment in the BCE study. If no preference is indicated, the default method of contact will be email. If at any time a phone number, email, or mailing address is determined to be incorrect or invalid, the research assistant will use an alternative method to contact the participant. If a phone call is the participants preferred method of contact and they do not answer the phone call a pre-scripted voicemail will be left. If participants do not respond to the first contact within two weeks, a second attempt will be made. If no response occurs within two more weeks, a third attempt will be made A total of 3 contacts – including voicemail, email, or text message will be made. If a subject is not reached after 3 contacts, no further attempts to contact will be made. If a patient is interested, a study coordinator or another member of the study team will meet with the patient to discuss options for involvement.

6 Upload all recruitment materials, including letters, brochures, posters, phone interview scripts, newspaper ads, etc.

Name	Date Last Modified	Version	Owner
Appendix H.Voicemail script for recruiting	11/17/2015 4:23 PM	0.02	Amy DiVasta
Appendix I.Phone Enrollment Script	1/24/2017 4:04 PM	0.03	Amy DiVasta
Appendix J.NOTE Email Enrollment Script	11/17/2015 4:23 PM	0.02	Amy DiVasta
Appendix K.recruitmentflyer	12/20/2016 12:52 PM	0.06	Amy DiVasta
Appendix L.recruitmentletter	11/17/2015 4:24 PM	0.02	Amy DiVasta
Appendix M.recruitmentsmallcard	1/24/2017 4:06 PM	0.03	Amy DiVasta
Appendix N.optout card	11/17/2015 4:24 PM	0.02	Amy DiVasta
Appendix P.Text message script for recruiting	11/17/2015 4:24 PM	0.03	Amy DiVasta
Appendix Q: Craig's List ad	12/20/2016 12:54 PM	0.05	Jenny Gallagher
Appendix R: WHS facebook post	12/20/2016 12:55 PM	0.04	Jenny Gallagher
Appendix S: BCE website post	12/20/2016 12:56 PM	0.04	Jenny Gallagher
Appendix T: Trifold recruitment brochure	6/1/2017 3:15 PM	0.02	Jenny Gallagher

7 Please describe how each document uploaded in question #6 will be used.

Appendices K, M and T are printed recruitment materials used to advertise the study to patients. Appendix L: provider recruitment letter and Appendix N: opt-out recruitment postcard will be sent to patients whose providers approved contact outside of a clinic visit.

Appendix Q will be posted in the Community Volunteers section of Craig's List Boston not more than once per week, as well as on the BCH and Partners intranets and research pages. Appendix R will be posted on the Women's Health Study: From Adolescence to Adulthood facebook page as well as the Center for Young Women's Health website/social media with approved study images. The post directs interested patients to an external website rather than soliciting any interaction on the facebook page. Appendix S will be posted on the Research section of the Boston Center for Endometriosis website and may also be included on the Center for Young Women's Health site.

Remuneration

8 * **Will subjects/families receive a form of payment, compensation or reimbursement?**

● **Yes** ○ No

Please answer the following information regading ClinicalTrials.gov registration.

9 * **Into which of the following category(s) does this protocol fall (check all that apply):**

- [x] **(a) A controlled clinical investigation other than phase 1 of a drug subject to FDA regulation (requires registration). *CONTROLLED* is defined as a design to permit comparison of a test intervention with a control to provide a quantitative assessment of the drug/ effect. This can include concurrent control groups as well as non concurrent controls including historical controls or subjects as their own controls (requires registration by FDA regulations)**
- [ ] **(b)** Protocol prospectively compares a device-based intervention subject to FDA regulation against a control in human subjects (requires registration). An ***INTERVENTION*** broadly includes various techniques using the device such as, among other things device regimens and procedures, and use of prophylactic, diagnostic or therapeutic agents. This applies to studies other than a small clinical trial to determine feasibility of a device, or a clinical trial to test prototypes devices where the primary outcome measure relates to feasibility and not health outcome. **(Requires registration by FDA regulations)**
- [ ] **(c)** A device trial that is a pediatric post-market surveillance trial (requires registration by FDA regulation)
- [ ] **(d)** Protocol prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes." Health-related interventions include any intervention used to modify a biomedical or health-related outcome (for example, drugs, surgical procedures, devices, behavioral treatments, dietary interventions, and process-of-care changes). Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. **(ICMJE requires registration)**
- [ ] **(e)** Protocol does not meet any of the criteria above (a-d) but research will be registered on clinicaltrials.gov (voluntary registration, statement optional)
- [ ] **(f)** Protocol does not meet any of the criteria above (a-d) and research will not be registered on clinicaltrials.gov

If (a), (b), (c), or (d) is checked, either FDA regulations or International Committee of Medical journal Editors (ICMJE) Guidelines *http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html* ***require that this trial be registered on a clinical trial registry. FDA requires registration on ClinicalTrials.gov site. ICMJE requires registration on one of a broader list of registries, including clinicaltrials.gov.***
For further information about required registrations you may go to:

• *http://clinicaltrials.gov/ct2/manage-recs* ***(FDA regulations)***
• *http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html* ***(ICMJE)***

Note if (a), (b) or (c) is checked, FDA regulations require that the consent form contains the following statement:

"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 results. You can search this web site at anytime."***

If (d) or (e) is checked you may voluntarily choose to include the statement above. Please make the appropriate updates to the consent form accordingly.

9.1 Who will be responsible for registering the trial?

- [ ] Sponsor (if other than BCH PI/Sponsor-Investigator)
- [x] **BCH PI or Sponsor-Investigator**
- [ ] Investigator at another site
- [ ] Other

If Other:

9.1.1 Please specify who.

9.2 If you have selected CHB PI or Sponsor-Investigator do you have a Clinical Trial registration NCT number for this study at this time?

● **Yes** ○ No

If YES:

9.2.1 Please insert "NCT" number for this trial
ClinicalTrials.gov Identifier: NCT02542410

NOTE: A valid NCT number must be included before the IRB releases final approval for this protocol. If the NCT number is not included in the original submission you will need to register the trial and submit an amendment to include the NCT registration number before final approval is released.

Final approval for the protocol will not be issued until a valid NCT number is listed in the CHeRP smart form

Remuneration Details

Enter information about all forms of payment that will be used in this study and answer the corresponding questions.
Please note, any payment or gift should not be so large as to unduly influence the parent/child to participate.

1. ☑ **Reimbursement: payment for research-related expenses incurred. E.g. transportation, parking, meals, childcare.**

1.1 What form (check, cash) and total amount will be provided?
A parking voucher for hospital parking garage or MBTA single-ride Charlie card

1.2 Who will receive the reimbursement (subject, parent or both)?
Subject

1.3 When and how will the reimbursement be distributed?
For participants making a research-specific visit to CHB or BWH, a parking voucher or MBTA single-ride Charlie cards will be provided at the time of the appointment to the participant.

1.4 How was this form and amount determined?
This was determined based on past studies at CHB.

2 ☐ **Compensation: payment for time and inconvenience from participation. E.g. compensation for time-off work.**

2.1 What form (check, cash) and total amount will be provided?

2.2 Who will receive the compensation (subject, parent or both)?

2.3 When and how will the compensation be distributed?

2.4 How was this form and amount determined?

3 ☑ **Tokens of Appreciation: small payments or gifts for participation. E.g. toys, gift certificates, small payment.**

3.1 What form (gift, payment) and total amount will be provided?
$225 in Amazon or Target gift cards

3.2 Who will receive the token of appreciation (subject, parent or both)?
Study subject

3.3 When and how will the token of appreciation be distributed?
Subjects will receive the tokens of appreciation upon the completion of the study, or upon termination of study participation.

Subjects will be given one $75 gift card for each study visit completed.

3.4 How was this form and amount determined?
Amount were based on previous studies involving subjects recruited from the Adolescent Clinic at CHB or from the CIRS Clinic at BWH. These gift cards will show subjects our appreciation for the time taken to complete the questionnaires, provide blood samples, attend study visits, and adhere to a daily medication regimen.

4 ☐ **Incentives: payments/gifts to encourage subject enrollment or continued participation. E.g. completion bonus.**

4.1 What form of incentive and total amount will be provided?

4.2 Who will receive the incentive (subject, parent or both)?

4.3 When and how will the incentive be distributed?

4.4 How was this form and amount determined?

Research Data, Documents, Subject Reports & Consent/Assent Forms: Storage

1 ***Where will research data, documents and subject reports be sent and stored? Check all that apply.**

☑ Children's Hospital Medical Record

☐ Departmental Medical Record

Separate Research Record

- [x]
- [ ] Subject/family will receive results
- [x] Sponsor, Collaborator and/or Coordinating Center
  Specify:
  BWH
- [ ] Medical Record at another institution, hospital, physician's office, etc.
  Specify:
- [ ] Research Registry
  Will data include patient identifiers (name, medical record, SS #)?
  ○ Yes ○ No
- [ ] Other
  Specify:

2 ***Where will the signed informed consent and assent be stored? Check all that apply.**

- [x] Children's Hospital Medical Record
- [ ] Departmental Medical Record
- [x] Separate Research Record
- [x] Sponsor, Collaborator and/or Coordinating Center
- [ ] Medical Record at another institution, hospital, physician's office, etc.
- [ ] Research Registry
- [ ] Not Applicable

3 * **Explain the rationale for including or not including research data and the informed consent/assent forms in the CHB medical records.**

Given that this is an interventional trial, knowledge of the medications that a subject may be randomized to may be helpful to members of the subjects' healthcare team. As such, the consent form will be available to be viewed in the medical record.

For subjects who are not patients at BCH, operative reports will be collected to ensure they meet inclusion criteria. These reports will be scanned into the newly created BCH medical record as source documentation.

Please note: the confidentiality section of the consent form must specify whether research data and/or the informed consent/assent form(s) will or will not be included in the Children's Hospital or Departmental medical records. A sample statement is included on the Informed Consent Template.

Medical Expenses for Research Related Adverse Events

1 ***How will the cost of reasonably foreseeable medical care in the event of a research related adverse event be covered?**

- [ ] Corporate sponsor agreement
- [x] Likely to be covered by insurance
- [ ] Philanthropic or other grant
- [ ] Foundation or Departmental Funds
- [ ] Interdepartmental arrangements
- [ ] Other
  Explain:
- [ ] Not applicable

Privacy and Confidentiality

Privacy

1 * **'Privacy' refers to a person's desire to control access of others to themselves. Describe the steps that will be taken to protect and assure the privacy of the subject.**
Detail specific actions the Research Team will take to ensure that privacy is protected through each phase of the study (e.g. access to medical records for recruitment, mailings to subjects, phone calls with subjects, research visits).

Patients with endometriosis will be approached about the study in the gynecology clinic where they receive clinical care. In most cases, the treating physician will discuss participation in the study with the patient in a private office or treatment room, and will ask if they are willing to speak with the study coordinator. The physician will provide each patient with a study brochure for her review. Interested patients will meet with the study coordinator in a private setting to discuss involvement in the study. Patients will be made aware the study is voluntary and participation will not affect clinical care. For all participants, the consent process will take place in a private setting. Participants will be encouraged to ask questions and to illustrate full understanding of the study procedure and risks/benefits.

Other potential subjects may approach the study team in response to flyers posted in clinic, or given to them by their medical provider at the time of a clinic visit. Phone calls with potential subjects to screen for eligibility for participation will also be conducted in a private setting.

During research visits, participants will complete study questionnaires in a private room setting.

Participants will determine their preferred means of communication (phone call, email, text), and if there are any means of communication that they never wish to employ. When phone calls are made, the study will be referred to in general terms that will not disclose the exact nature of study participation. Information which may identify the purpose of the study or the disease status of the participant will not be recorded on voicemail or answering machine.

Examples of issues:
- Potential subjects may not want to be approached for research purposes by someone they do not know.
- Potential subjects may not want others to know they have a disease or were previously treated for a condition; therefore, you may want to avoid sending a recruitment letter in the mail that may be opened by others.
- Subjects may not want to be seen in areas that may stigmatize them (i.e. pregnancy counseling center).

Confidentiality

2 * **Investigators are required to obtain only the minimum data necessary to achieve the research goals.**
Please justify why the data you are obtaining is the minimum necessary.

For subjects, the date of diagnostic surgery, stage of endometriosis at diagnosis, and other comorbid health conditions will be obtained from the medical record or by self-report from the patient. All participants will complete questionnaires regarding their overall health, pain status, functional status, medical history, gynecological history, and mental health. These data are all necessary to assure the patient's eligibility for participation, to quantify our outcome measures, and to account for confounding or mediating factors that may impact the effects of our interventions. Identifying information from all data sources will be removed at collection. All data samples will be identified by a randomly generated study ID number unique to each participant.

3 * **Describe where data will be kept, how it will be secured and who will have access to the data. If links to identifiers are used, please describe the coding mechanism, whether the code is derived from subject information, and how and where the mechanisms for re-identification will be protected and maintained.**

Each participant will be assigned a unique study ID number which will be used to label and track all of her study data. Study ID numbers will be randomly generated at the time of study enrollment. The date of collection will also be placed on each sample and survey. To protect confidentiality, no names will be used on samples to link samples to a specific person.

A key to the code linking samples to the participant will be kept in a secure MS Access database management system. This database system will be accessible by password only by the database manager and approved study staff who have been trained in HIPAA guidelines and requirements. The password will be provided on an as-needed basis.

The INFORM database will house the study data. This database will include information from participants' questionnaires, as well as clinically relevant information (date of diagnosis, stage of disease, current treatment regimen) for subjects. Again, this database will only be accessible to approved members of the study team. Information in the database will be identified using the same study ID numbers placed on participants' blood samples and surveys.

4 * **Provide a plan to protect the identifiers from improper use and disclosure.**

When participants enroll in the study, their name, date of birth, and CHB/BWH medical record number will be recorded alongside their newly assigned study ID number in the Access database. This will be accessible only to certain approved members of the study team. No one else will have access to the key or other identifying patient information.

5 * **Provide a plan for destroying the identifiers at the earliest opportunity consistent with the conduct of the research or provide a health or research justification for retaining the identifiers. For protocols that may be subject to future continuing and secondary data analysis, the IRB highly recommends providing justification for not destroying identifiers permanently.**

When samples are collected from participants, samples will immediately be deidentified from the patient and will be identified by the participant's study ID number and not with name or DOB. The visit date will be placed on the sample to prevent errors in

specimen processing or handling, since participants will be coming for more than one visit. Similarly, surveys will only be marked with the participant's study ID number.

The information gathered in this pilot study will serve as important preliminary data for researchers studying endometriosis, and will go on to inform future larger randomized trials. Because this research gains strength and depth as the number of patients increases, there is no immediate plan to destroy the master list which will tie data/samples to patient identifying information.

6 * **Will a certificate of confidentiality be obtained for this research?**

○ Yes ● **No**

If YES:

6.1 Please upload certificate, if available.

Name	Date Last Modified	Version	Owner
There are no items to display			

6.2 ☐ **Check here if certificate is pending and will be submitted via an amendment at a later date.**

Protected Health Information and HIPAA Authorization Information

Protected Health Information (PHI) is information acquired by Children's Hospital, including demographic information, that could reasonably identify an individual **AND**:

- Relate to the past, present, or future physical or mental health, condition or treatment of an individual; **OR**
- Describe the past, present, or future payment for the provision of healthcare to an individual.

There are some limited situations when research protocols will not use or create protected health information. For example, educational research conducted in a school setting.

1 ***The following information is considered identifiable PHI under the Privacy Rules regulations. Indicate which of the following will be obtained.**

- ☑ **Patient/Subject Name or the names of relatives, employers, or household members**
- ☑ **Medical record numbers (or specimen #)**
- ☑ **Address street location**
- ☑ **Address town or city ***
- ☑ **Address state***
- ☑ **Address zip code***
- ☑ **Elements of Dates (except year) related to an individual. For example date of birth, admission or discharge dates, date of death, dates of procedures***
- ☑ **Telephone number**
- ☐ Fax Number
- ☑ **Electronic mail (email) address**
- ☐ Social security number
- ☐ Health plan beneficiary numbers
- ☐ Account numbers
- ☐ Certificate/license numbers
- ☐ Vehicle identification numbers and serial numbers including license plates
- ☐ Medical device identifiers and serial numbers
- ☐ Web URLs
- ☐ Internet protocol (IP) address

- [ ] Biometric identifiers (finger and voice prints)
- [ ] Full face photographic images
- [ ] Any unique identifying number, characteristic or code
- [ ] NONE OF THE ABOVE: this protocol will not use any identifiable PHI

** These items may be included and considered a "limited data set". Use of data under the provisions of a "limited data set" require the signing of a data use agreement by the recipient (this includes researchers).*

Protected Health Information and HIPAA Authorization Information - Continued

1 **Please check all of the categories that indicate where a research subject's PHI may be disclosed. For this purpose, "disclosure" means release, transfer, provision of access, or otherwise divulging protected health information outside the entity initially acquiring the information as specified in the protocol; most often that will be Children's Hospital Boston.**

- [x] Internal at Children's Hospital
- [ ] Data Safety Monitoring Committee
- [ ] Food and Drug Administration (FDA)
- [ ] Other health care providers of subject
- [ ] Third Party Payers - if third parties are billed for procedures performed during research
- [ ] Sponsor of Trial
- [ ] Contract Research Organization (CRO): organizations contracted to perform portions of the study (i.e., screening, data collection)
  Specify the name/organization.
- [x] Collaborator
  Specify who and the location.
  Brigham and Women's Hospital
- [x] Cooperative Group/Network
  Specify the name of the network/group.
  Boston Center for Endometriosis
- [ ] Other
  Specify who and the location.

Data and Safety Monitoring

All protocols that present greater than minimal risk require a data and safety monitoring plan(DSMP). Investigators may also choose to submit a plan for any protocol.

1 * **Please check one of the three categories.**

- (●) **This protocol is greater than minimal risk and therefore requires a DSMP (responses to all questions below are required).**
- ( ) This research is minimal risk but we have included a DSMP (respond to the questions below that apply to your DSMP).
- ( ) This protocol is minimal risk and we are not including a DSMP (do not respond to the questions below).

2 **Which individual or group will be responsible for monitoring the data and safety for this study?**

- [x] Principal Investigator/Research Team
- [x] Independent Monitor(s)
- [x] Internal Committee at the Hospital

- ☐ Data and Safety Monitoring Board (DSMB) or Data Safety Committee (DSC) Independent of PI and Sponsor
- ☐ Data and Safety Monitoring Board (DSMB) or Data Safety Committee (DSC) Not Independent of PI and Sponsor
- ☐ Other

Specify:

3 Provide a description of the individuals who will be responsible for data safety monitoring, including the following details:
(1) association with the research or study sponsor;
(2) nature of expertise and;
(3) whether they are independent of the commercial sponsor.
If those monitoring the study are not independent of the sponsor, please describe how any potential conflicts of interest or biases will be avoided.

1. The following co-investigators will be responsible for data safety monitoring: Drs. Amy DiVasta, Mark Hornstein, and Stacey Missmer. In addition, Dr. Raymond Anchan will serve as an independent monitor.
2. Drs. DiVasta and Hornstein have successfully conducted multiple clinical trials involving recruitment of research subjects from CHB and BWH. Dr. Missmer is an experienced epidemiologist with expertise in the field of endometriosis, and will be essential in thoughtful analysis of the data and any adverse events. Dr Anchan is an experienced obstetrician/gynecologist and researcher at BWH.
3. We have no commercial sponsor, so no conflict of interest or bias will occur.
4. Oversight will also occur from the BCH CTSU Monitoring Group.

Note: If this information is in the protocol, please specify where (by the section number) the relevant information can be located.

4 What data will be reviewed?

- ☑ **Adverse events/Unanticipated problem**
- ☐ Aggregate data
- ☑ **Enrollment numbers**
- ☑ **Individual subject data/case report forms**
- ☑ **Protocol violations/deviations**
- ☑ **Subject withdrawals/terminations**
- ☐ Other

Specify:

5 How often will data and safety monitoring be performed? Please specify if this is a specific number of times, at defined time points, after a certain number of subjects have been recruited or as needed (i.e. every 6 months, every SAE, every 5 subjects, etc.). If this information is in protocol, please specify where relevant information is located.

As every 3rd subject is enrolled, or as needed/immediately for any serious adverse event.

6 Describe the responsibilities that have been given to the data and safety monitoring function. This should include a discussion of whether the data and safety monitoring plan includes a charter, whether stopping rules will be developed, and if any interim analysis will be performed (if so, on what basis). If this information is in protocol, please specify where relevant information is located.

Risks of this study are low, but greater than minimal risk, due to the fact that the medications to be used have minimal potential side effects and will be given in traditionally accepted/clinically utilized doses

Given that this is a small pilot study with somewhat subjective outcomes, aggregate unblinded data will not be reviewed by the DSMB for fear of introducing bias. Potential side effects of the medications will be reviewed at each study visit by the research coordinator, and laboratory data obtained, looking for any significant safety issues. Any concerns regarding side effects of the medication, or any laboratory values outside of the expected range, will be brought to the attention of the PI by the research coordinator immediately.

7 If this protocol is for a multicenter trial what mechanisms are in place to either receive or distribute results of the data and safety monitoring function in a prompt manner.

The protocol will be conducted at BWH and CHB. The same investigator group is overseeing and running the trial at both institutions, so dissemination of data and results will be seemless. The monitoring group will have access to all data, regardless of at which institution the subject is seen.

8 If a DSM charter exists, please upload it.

DiVasta Monitoring Plan.Signed.03.31.17.pdf	3/31/2017 11:58 AM	0.02	Amy DiVasta
MONITORING SOP.Signed.03.31.17.pdf	3/31/2017 11:58 AM	0.02	Amy DiVasta

Risks and Benefits

Risks

1 * **Provide a description of the foreseeable risks to subjects. Consider all types of risks, including physical, psychological, social/reputation, legal, financial, privacy and breach of a promise of confidentiality.**

The potential risks and discomforts include a bruise at the site of venipuncture (for subjects electing to provide a blood sample); infection resulting from venipuncture is also a risk, albeit very rare. Subjects may also experience discomfort when asked sensitive questions about their lifestyle as part of the questionnaire.

Another potential risk to participation would be a breach of confidentiality. In order to minimize this risk, all samples are stored with a code number unique to each participant. Samples will not be labeled with any type of identifying information such as name or medical record number. All health information is also de-identified, and labeled only with the code number. All data are kept in a secured server, in files that are password protected. Only authorized personnel within the Boston Center for Endometriosis will have access to identifying information. If samples are shared with researchers, they will be identified only by the unique code number and possibly by non-identifying information such as age, race, or ethnicity. Samples will not be sold for profit. If results of tests performed on the specimens are ever published in the medical literature, no identifying information will be included. The results of the tests performed for research purposes will not be placed in the medical record. A copy of the consent form will not be placed in the medical record. In this manner it will be unlikely that others within the hospital, an insurance company or employer would ever learn of such results.

Risks of the medications to be given in this study are low when eligibility criteria are met, as described below:

Norethindrone acetate is a synthetic hormone, which will be given to subjects at physiological doses. Thus, we do not anticipate adverse events associated with use of the medication. In the numerous studies of adult women with endometriosis to whom norethindrone acetate was given, no significant adverse events were reported. Side effects could include: weight changes, edema, acne, headache, or change in mood. We will assess for these side effects with repeated physical examinations and the self-administered assessments, the SF-36, Beck Depression Inventory, the pain measures, and the MRS.

The safety of cabergoline has been evaluated in approximately 1,200 patients with Parkinson's disease in controlled and uncontrolled studies at dosages of up to 11.5 mg/day which greatly exceeds the maximum recommended dosage of cabergoline for hyperprolactinemic disorders, and the dosage used in the proposed pilot study. When used in similar populations of reproductive aged women for other indications, at doses identical to those proposed in the current study, cabergoline side effects include: GI distress (constipation, pain), dizziness, headache, tingling, or swelling of the extremities. In addition to the adverse events that occurred in the patients with hyperprolactinemic disorders, the most common adverse events in patients with Parkinson's disease (and treated with doses of ~3 mg/day) were dyskinesia, hallucinations, confusion, and peripheral edema. Heart failure, pleural effusion, pulmonary fibrosis, and gastric or duodenal ulcer occurred rarely. Postmarketing cases of cardiac valvulopathy have been reported in patients receiving cabergoline. These cases have generally occurred during administration of high doses of cabergoline (>2mg/day) for the treatment of Parkinson's disease.
No significantly increased risk of clinically relevant cardiac valve disorders was found in subjects treated with long-term cabergoline therapy at the doses used in endocrine practice. Current expert recommendations state that patients prescribed cabergoline should be screened by a clinical cardiovascular examination and that echocardiogram should be reserved for those patients with an audible murmur, those treated for more than 5 years at a dose of more than 3 mg per week, or those who maintain cabergoline treatment after the age of 50 years.

Erythrocyte sedimentation rate (ESR) has been found to be abnormally increased in association with pleural effusion/fibrosis. We will utilize a measurement of ESR at each study visit to screen for the very unlikely development of a fibrotic disorder associated with low-dose cabergoline use. If we find that the ESR increases to abnormal levels, a clinical evaluation would be indicated, including a chest x-ray. Serum creatinine measurements can also be used to help in the diagnosis of fibrotic disorder, and will be checked at each visit.

The effects of the study drugs on the reproductive system (sperm, eggs) or to the developing fetus are not well understood. Norethindrone acetate is labeled by the drug manufacturer as "contraindicated during pregnancy". Of note, norethindrone (another first generation progestin) 0.35 mg PO daily is FDA approved and marketed as an effective method of birth control. In our study, patients randomized to

norethindrone acetate will receive 5 mg po daily. Cabergoline has no known effect on pregnancy, based upon animal reproductive studies, and is approved for use during pregnancy "if needed". For these reasons, a pregnancy test will be performed at each visit. Women who become pregnant during the study would be terminated from further study participation. For this reason, participants taking the drug should not become pregnant. To be a part of the research, participants will be advised that they must not have sexual intercourse or must use reliable, effective birth control during participation.

During research visits, participants may be asked questions that lead to feelings of discomfort, emotional upset, or frustration. Participants will be advised that they may not be able to answer all the questions and do not need to answer any questions that they do not wish to answer. If the participant were to become distressed, the Principal Investigator will be notified by the Research Coordinator. We will offer to have the participant speak to a mental health professional regarding her feelings. The Beck Depression Inventory-II will be scored by the Research Coordinator during the study visit, while the participant is still present. It is possible that the study team could identify concerns for depression from the answers to the questionnaires. If the participant has a score ≥ 20 (indicating moderate or severe depression) or responds anything other than 0 to Item 9 (I don't have any thoughts of killing myself), the Research Coordinator will alert the Principal Investigator immediately. The study team will notify the participant regarding our findings from the Depression Inventory, and encourage the participant to allow us to share the information with her parent (if she is age<18 years) or her healthcare provider. Additionally, mental health resources will be made available to the participant. Participants are informed within the consent form that "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 parent (if you are age<18), your therapist(s) if applicable, or other individuals. If you are

2 * **What is the likelihood and seriousness of such risks?**

The likelihood of such risks is low, and no serious risks are anticipated.

3 * **Describe provisions for minimizing risks to participants.**

Subjects are monitored closely throughout the course of participation by both the study team, and with their clinical care gynecology provider.

At the baseline study visit, we will measure blood samples for total cholesterol, HDL cholesterol, and triglyceride levels. This lipid profile will allow us to monitor for any individual changes in serum lipids from baseline, and for differences between treatment groups. In some studies of adult women, mildly deleterious effects on circulating lipid profiles have been seen in patients receiving treatment with norethindrone acetate (decreased HDL). Lipid profiles will be repeated at follow-up visits scheduled for 3 and 6 months after initiation of therapy. Blood samples will also be taken for liver function tests (AST, ALT) at each visit to allow us to monitor for any liver inflammation associated with the drug therapy. HbA1c will be taken at baseline and at 6 months to monitor for impairments in glucose metabolism. We will utilize a measurement of ESR and serum creatinine at each study visit to screen for the very unlikely development of a fibrotic disorder associated with low-dose cabergoline use. A physical examination will be performed at each visit to assess for acne, and cardiac auscultation will be done to assess for the presence of a cardiac murmur. The presence or absence of hormonal symptoms (mood changes, breast tenderness, acne, and changes in menstrual bleeding patterns) will be queried at each visit. The hormonal milieu will be assessed using serum measurements of estradiol and prolactin at baseline and each subsequent study visit. These laboratory studies will allow us to monitor cabergoline activity, and to determine compliance with cabergoline treatment in Group 2. If any cardiac murmur is identified during study participation, an echocardiogram will be performed.

Subjects will be discontinued from further study participation if any of the conditions that are listed as exclusion criteria for participation develop during the six months of active participation in the study. Because of the potential risk of adverse side effects, patients in the treatment trial will be monitored closely during the 6-month study period with laboratory assessments and physical examinations every three months.
Study participants will be able to contact one of the study physicians at any time if questions or concerns arise. No confidential information from this study or other data within a patient's medical record may be furnished to anyone unaffiliated with Children's Hospital without written consent, except as required by law or regulatory agencies (e.g., FDA).

All participants will be advised to abstain from sexual intercourse, or to use reliable birth control to prevent pregnancy. A pregnancy test will be performed at each of the 3 study visits.

Potential Benefits

4 * **Are there potential direct benefits to the research participants?**

● **Yes** ○ No

If YES:

4.1 Describe the potential direct benefits to the research participants.

The medications used will be provided to the patient at no cost, and will potentially ameliorate

ongoing endometriosis-associated pain. Participants will be given information about their results to share with their primary care provider, including monitoring of lipid panels, liver function, and hormonal status.

5 * **Describe how the research may result in knowledge expected to benefit society.**

With the information gathered from the proposed study, we hope to develop evidence-based guidelines for the utilization of norethindrone acetate and/or cabergoline for treatment of endometriosis. This study has the potential to benefit a large number of patients who suffer from endometriosis.

Pediatric Risk/Benefit Determination

All protocols that include children/adolescents must be classified into a risk/benefit category.

Does your study involve more than one risk/benefit category for different groups? If so, answer questions 1, 1.1, 1.2 and 1.3 to describe the least favorable risk/benefit scenario, and use the questions 2, 2.1, 2.2, 2.3, 2.4 to explain the risk/benefit assessment for the other groups of subjects in your study.

"Minimal risk" means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

1 * **Check the category below that best represents the degree of risk and benefit which children in this study will be exposed to. If your study involves more than one group of subjects (eg. .experimental and placebo groups) consider whether the research presents a different risk/benefit assessment for each group. If this is the case select the least favorable risk/benefit ratio that might apply to any of the subjects.**
For example, a study may present greater than minimal risk with potential for direct benefit for an experimental group, but no potential for direct benefit for a placebo group. In this case you should select "Greater than Minimal Risk; No Potential for Direct Benefit" in this section and use section 2 below to describe the risks and benefits for the group for which there a potential for benefit.

- ○ No more than Minimal Risk; Potential for Direct Benefit
- ○ No more than Minimal Risk; No Potential for Direct Benefit
- ● **Greater than Minimal Risk; Potential for Direct Benefit**
- ○ Greater than Minimal Risk; No Potential for Direct Benefit, but likely to yield generalizable knowledge about the subject's condition

1.1 If Greater than Minimal Risk; Potential for Direct Benefit

1.1.1 How is the risk justified by the benefit?

The medications used will be provided to the patient at no cost, and will potentially ameliorate ongoing endometriosis-associated pain. Participants will be given information about their results to share with their primary care provider, including monitoring of lipid panels, liver function, and hormonal status. Both medications are commonly used in the reproductive-aged group of females that we are recruiting for the current study.

1.1.2 How is the benefit to risk assessment at least as favorable as presented by alternative approaches?

No patient is denied treatment, or receives only placebo therapy. We are recruiting patients who remain in pain from their endometriosis with the hope of identifying a novel therapy to ameliorate symptoms. The two medications are frequently used within this age group.

1.2 If Greater than Minimal Risk; No Potential for Direct Benefit

1.2.1 How is the risk of the protocol a minor increase over minimal risk?

1.2.2 How do the procedures present experiences to the subjects that are reasonably commensurate with those inherent in the subjects' actual or expected situations?

1.2.3 How is knowledge to be gained of vital importance for the understanding or amelioration of the condition?

1.2.4 Can the consent of both parents be obtained if reasonably available?

1.3 To which group of subjects does this risk/benefit assessment apply?

All subjects 15-40 years of age who will be recruited for study participation.

2 * **Does your protocol have more than one risk/benefit group?**

○ Yes ● **No**

If YES:

2.1 Check the category below that best represents the degree of risk and benefit which children in this study will be exposed to.

- ○ No more than Minimal Risk; Potential for Direct Benefit
- ○ No more than Minimal Risk; No Potential for Direct Benefit
- ○ Greater than Minimal Risk; Potential for Direct Benefit
- ○ Greater than Minimal Risk; No Potential for Direct Benefit, but likely to yield generalizable knowledge about the subject's condition

2.2 If Greater than Minimal Risk; Potential for Direct Benefit

2.2.1 How is the risk justified by the benefit?

2.2.2 How is the benefit to risk assessment at least as favorable as presented by alternative approaches?

2.3 If Greater than Minimal Risk; No Potential for Direct Benefit

2.3.1 How is the risk of the protocol a minor increase over minimal risk?

2.3.2 How do the procedures present experiences to the subjects that are reasonably commensurate with those inherent in the subjects' actual or expected situations?

2.3.3 How is knowledge to be gained of vital importance for the understanding or amelioration of the condition?

2.3.4 Can the consent of both parents be obtained if reasonably available?

2.4 To which group of subjects does this risk/benefit assessment apply?

Non-Genetic Incidental Findings and Dissemination of Research Results

Non-Genetic Incidental Findings

This section addresses incidental findings that are not genetic. Genetic incidental findings and return of genetic results are addressed in the "Genetic Research Results" section.

1 * **Is there a possibility of clinically significant non-genetic incidental findings being discovered during the research study? These may include the unexpected discovery of abnormal results following an MRI of a healthy control, or indications of subject depression following review of quality of life assessments etc. This should also be explained in the consent form.**

● **Yes** ○ No

IF YES:

1.1 Please describe any potential non-genetic incidental findings that may result from the study.

Mental Health surveys that will be administered during the pilot study include the Beck Depression Inventory-II. This is an updated version of a validated measure which has been widely used in studies of adolescents, and is validated for use in persons aged 13-80 y. It is possible that subject depression may be uncovered after review of these assessments.

It is also possible that a previously unidentified cardiac murmur will be identified during the study.

1.2 Outline the plan for addressing non-genetic incidental findings (e.g., contacting the participant's primary care provider, referral, etc.).

This scale will be scored and screened at the time of the subjects' study visits. Any subject who reports a moderate level of depressive symptoms or higher (defined as a Beck Depression Index-II score ≥20) or who circles a response other than "0" to question 9 (which addresses suicidal ideation) will be referred to a mental health provider or their medical provider at the time of the study visit according to standard clinical practice.

If a cardiac murmur is identified, the patient will be notified. We will also notify the patient's medical provider with permission.

Dissemination of Non-Genetic Results

Research subjects express the desire to receive information about study progress as well as aggregate or individual results. In addition, subjects appreciate being acknowledged for their participation. As part of our ongoing efforts to recognize the efforts and partnership with research subjects, investigators are asked to take whatever steps possible to acknowledge subjects for their participation and, when appropriate, to provide individual and aggregate results. Although it is not always possible to provide results within a defined period of time (sometimes for years), it may be possible to provide research subjects with periodic updates or, in certain circumstances, to inform subjects about the progress of the research in lieu of actual results. Please complete the following questions as they apply to your research. All investigators are expected to acknowledge subjects' participation and, when appropriate, to provide results. We ask that investigators take steps beyond only providing results if a subject/family requests it.

2 * **Will this research produce individual results for research participants?**

● **Yes** ○ No

If YES:

2.1 Will this research produce individual genetic results to research participants?

○ Yes ○ No

IF YES: Please complete the Section on Genetic Research Results Return.

2.2 Will you be able to produce individual non-genetic results to research participants?

● **Yes** ○ No

If YES:

2.2.1 What types of results will you provide? How will you provide the results? When will you provide the result?

Subjects will have access to their clinically relevant laboratory results, such as lipid labs. These results will be provided to the patient within 1-2 weeks after each study visit.

2.2.2 Will you give participants an option (opt-in or opt-out) to receive these results?

If NO:

2.3 Please explain why you will not provide individual results to families.

Dissemination of Aggregate Results

3 * **Will you be able to provide aggregate results to participants?**

● **Yes** ○ No

If NO:

3.1 Please explain why you will not provide aggregate results.

If YES:

3.2 When will you provide aggregate results and how will they be provided?

Aggregate results will be available to participants after all participants have completed the trial, and analysis has been performed on the data.

3.2.1 What format will you use to provide aggregate results to families? (check all that apply)

Letter to all participants

Copies of peer focused publications, upon subject/family request

If Other:

3.2.1.1 Please describe.

4 **If it is not possible to provide either individual or aggregate results (e.g., biorepository protocols), what steps will you take to thank participants and advise them about the progress of the study? For example, some investigators will provide a thank you letter and develop newsletters or website that participants may learn about the progress of the research in general .**

Research Categories and Special Considerations

1 **Please select the appropriate research category for your research. A primary category must be selected. A secondary category should be selected only if applicable.**

* **Primary Research Categories:**

- (●) **Intervention/Trial Therapeutic (e.g. drugs, devices, comparison of therapeutic approaches, new procedures)**
- ( ) Intervention/Trial Non-Therapeutic (extra ECHO, MRI, physical exams for non-therapeutic purposes)
- ( ) Behavioral/Psychosocial Interventions/Trials
- ( ) Establishment of Specimen Repository
- ( ) Epidemiology/Observational Study – e.g. survey, case/control/data registries, cohort studies
- ( ) Quality Improvement
- ( ) Lab Specimen Studies – e.g. blood, urine, extra tissue during biopsy, genetic research
- ( ) Educational/Training – e.g. training of residents or other professional staff

Secondary Research Categories:

- ( ) Intervention/Trial Therapeutic (e.g. drugs, devices, comparison of therapeutic approaches, new procedures)
- ( ) Intervention/Trial Non-Therapeutic (extra ECHO, MRI, physical exams for non-therapeutic purposes)
- ( ) Behavioral/Psychosocial Interventions/Trials
- ( ) Establishment of Specimen Repository
- ( ) Epidemiology/Observational Study – e.g. survey, case/control/data registries, cohort studies
- ( ) Quality Improvement
- ( ) Lab Specimen Studies – e.g. blood, urine, extra tissue during biopsy, genetic research
- ( ) Educational/Training – e.g. training of residents or other professional staff

2 **Please check all of the following that apply to the proposed research.**

- [x] This protocol involves the use of a drug, biologic, nutritional supplement, herbal or homeopathic medicine, medical food, medical gas, inhalation therapy, topical cream, chemical or other compound that will be administered as the object of the protocol or because it is relevant to the aims of the research protocol.
- [ ] This protocol involves a device that will be used, administered, implanted, or applied to the subjects, as the object of the protocol or is relevant to the objectives of the protocol. This includes investigational devices classified as both significant risk and non-significant risk as well as FDA approved/marketed devices.
- [ ] This protocol involves the collection and use of material for genetic studies or creation of IPS lines as part of this current study and/or for potential genetic studies in the future.
- [x] This protocol involves the use of a placebo.
- [ ] This protocol includes an imaging exam or procedure to be done in Radiology or Nuclear Medicine for research purposes. Please contact Simon Warfield (Simon.Warfield@childrens.harvard.edu) and Samantha Taylor (Samantha.Taylor@childrens.harvard.edu) . Simon and Samantha will collect some additional information from you and coordinate the review of the information through Radiology to assure that the imaging protocol can be performed, the correct charges have been established and that Radiology will be able to accommodate the study in the imaging schedule. You will not be able to have imaging performed without this. It is imperative that you contact Simon or Samantha immediately.
- [ ] This protocol requires for research purposes 1) radiological assessments and procedures that involve radiation exposure (X-ray, CT, PET scans) or 2) nuclear medicine procedures (imaging or therapeutic). (Do not check this category if these procedures and assessments will be performed as part of clinical care).**
- [ ] This protocol requires for research purposes MRI scans (Do not check this category if these procedures and assessments will be performed as part of clinical care).**
- [ ] This protocol involves the establishment of a human biological specimen repository. Repositories are defined as prospective collections of specimens that are processed, stored and distributed to multiple investigators for use in research.
- [ ] This protocol involves the collection of a tissue removed for clinical purposes that would routinely go to pathology.
- [ ] This protocol acquires fetal biospecimens (this includes specimens taken from pregnant women or acquisition of fetal tissue obtained from terminations).
  If fetal tissue from terminations are proposed please be sure to include in your protocol document or smartform detailed information about where it is acquired from and how it will be used. In addition, submit copy of IRB approvals from sites where the tissue was actually obtained.
- [ ] This protocol includes an intervention with human subjects that involves either
  a) the derivation of stem cells from embryos or,
  b) the implantation of stem cells obtained from fetal tissue or embryos.

- [ ] This protocol includes research that is conducted at a non US location.
Please check this off if you are conducting international research but be aware that these questions do not apply to multi-site studies that are also multi-national.
- [x] This protocol involves collection of blood samples other than discarded specimens.
- [ ] This protocol involves the use of a device that emits laser radiation.
- [x] Please check this off if you are using QoL measures or other surveys, questionnaires, etc. which may yield incidental findings requiring intervention for depression, anxiety, suicidal/homicidal ideation, domestic violence, child maltreatment or other acute safety concerns. Also, check this if you have included a Social Worker among the Research Team.

*** This must be selected if the protocol involves imaging, regardless of where the imaging may occur.*

Nursing/Biosafety/Gene and Cellular Therapy

1 * Will this protocol require any of the following nursing services for any research related direct care requirements?

● **Yes** ○ No

If YES:

1.1 Check all that apply:

- [x] **Assessment of physical/mental status of subjects**
- [ ] Monitoring requirement non invasive
- [ ] Monitoring requirement invasive
- [ ] Additional intravenous requirements
- [x] **Collection of blood and specimens**
- [ ] Frequent timed lab draws
- [ ] Accompany patients to test areas
- [ ] Patient/family education, including self and home care
- [x] **Administration of investigational drugs and other substances**
- [ ] Use of new technology/equipment in study protocol
- [ ] Symptom management/intervention
- [ ] Constant supervision
- [ ] Requirements from other services that require nursing coordinator

1.2 Specify required services.

Blood draw, height/weight and vital signs, urine pregnancy test, distribution of study medications

2 * Does your study involve the administration of any of the following to a human research participant?

○ Yes ● **No**

If YES:

2.1 Please check all that apply.

- [ ] Genetically-modified cells or seek to genetically modify patient tissues in vivo using recombinant or synthetic nucleic acid molecules (natural-derived or synthesized DNA or RNA)
- [ ] A cellular or biologic product that involves complex manufacturing (e.g. cell culture or cell selection in a GLP/GMP facility, outside the operating room)
- [ ] Biological agents or material containing biological agents. Biological agents include bacteria, viruses, parasites, rickettsia, fungi, prions and toxins of biological origin regardless of pathogenicity to humans (e.g. fecal microbiota transplantations, oncolytic viruses)
- [ ] Xenotransplantation (cells, tissues or organs from a nonhuman animal source or have come into contact with nonhuman sources)

NOTE: Please note if the first or second option is checked, the protocol will be routed to a specialized institutional scientific review committee and will not be sent for your own departmental scientific reviewers.

If option *"Genetically-modified cells or seek to genetically modify patient tissues in vivo using*

***recombinant or synthetic nucleic acid molecules (natural-derived or synthesized DNA or RNA)"* was selected, please check off as applicable for this research and answer the associated questions:**

2.1.1 The protocol uses a new vector, genetic material, or delivery methodology that represents a first-in-human experience, thus presenting an unknown risk.

○ Yes ○ No

2.1.1.1 If Yes, please describe vector, genetic material, and delivery method and what may be known about any associated risks.

2.1.1.2 If No, please indicate the section or location in the protocol where the vector, genetic material or delivery methodologies risks are clearly described based on previous experience in human studies.

2.1.2 The protocol relies on preclinical safety data that were obtained using a new preclinical model system of unknown and unconfirmed value.

○ Yes ○ No

2.1.2.1 If Yes, please describe the new preclinical model system of unknown and unconfirmed value.

2.1.2.2 If No, please explain why this is not a preclinical model system of unknown and unconfirmed value.

2.1.3 The proposed vector, gene construct, or method of delivery is associated with possible toxicities that are not widely known and that may render it difficult for oversight bodies (IRB, IBC) to evaluate the protocol rigorously.

○ Yes ○ No

2.1.3.1 If Yes, please describe why the possible toxicities are not widely known and may render it difficult for oversight bodies (IRB, IBC) to evaluate the protocol rigorously.

2.1.3.2 If No, please justify that the possible toxicities are widely known and oversight bodies (IRB, IBC) will be able to evaluate the protocol rigorously.

Protocol and Appendices

* **All investigators must submit an experimental design and protocol with the CHeRP submission. If there is a protocol from a corporate sponsor or cooperative group available and it contains the following necessary elements you may attach that. For investigator initiated research a link to a protocol outline that may be completed and attached may be found at:**
CHeRP Protocol Outline

1 Upload Protocol - please be sure the protocol includes the following sections.

- Specific Aims/Objectives
- Background and Significance
- Preliminary Studies
- Design and Methods
  - Study Design
  - Patient Selection and Inclusion/Exclusion Criteria
  - Description of Study Treatments or Exposures/Predictors
  - Definition of Primary and Secondary Outcomes/Endpoints
  - Data Collection Methods, Assessments, Interventions and Schedule (what assessments performed, how often)
  - Study Timeline (as applicable)
- Adverse Event Criteria and Reporting Procedures
- Data Management Methods
- Quality Control Method
- Data Analysis Plan
- Statistical Power and Sample Considerations
- Study Organization
- References

Upload protocol

Name	Date Last Modified	Version	Owner
Cabergoline protocol	3/31/2017 11:28 AM	0.22	Amy DiVasta

2 Appendix Materials:

2.1 Survey, questionnaires, assessments

Name	Date Last Modified	Version	Owner
Appendix A.VAS.PNG	6/15/2015 12:37 PM	0.01	Amy DiVasta
Appendix B.Biberoglu and Behrman Score.docx	6/15/2015 12:38 PM	0.01	Amy DiVasta
Appendix C.BPI-SF_English-24h_Original_CURRENT.pdf	6/15/2015 12:38 PM	0.01	Amy DiVasta
Appendix D.Beck.doc	6/15/2015 12:38 PM	0.01	Amy DiVasta
Appendix E.PGIC_scale.pdf	6/15/2015 12:39 PM	0.01	Amy DiVasta
Appendix F.SF 12.pdf	12/9/2015 11:26 AM	0.02	Amy DiVasta
Appendix G.NSSSS.PNG	6/15/2015 12:39 PM	0.01	Amy DiVasta
Appendix T: Symptom checklist	3/31/2017 11:24 AM	0.02	Amy DiVasta
FDI	12/9/2015 11:27 AM	0.01	Jenny Gallagher

2.2 Flow charts, schemas

Name	Date Last Modified	Version	Owner

There are no items to display

2.3 Other

Name	Date Last Modified	Version	Owner
Med teach form	12/23/2015 10:16 AM	0.02	Jenny Gallagher
Provider letter	2/25/2016 3:06 PM	0.01	Jenny Gallagher
Test results letter	2/25/2016 3:11 PM	0.01	Jenny Gallagher

Method of Consent

1 * **Check all that apply:**

Please note that if a waiver of parental permission is requested, both "written informed consent/assent/authorization will be obtained from subjects" and "waiver of parental permission is requested" should be selected.

- [x] **Written informed consent/assent/authorization will be obtained from subjects.**
- [ ] Informed consent/assent/authorization will be obtained through a method other than a written document (i.e. verbal, survey completion).
- [ ] *Waiver of informed consent and authorization are requested. No consent/authorization will be obtained.
- [ ] *Waiver of parental permission is requested.
- [ ] Other method.

Please explain any other method of consent or issue you want the IRB to review regarding consent and assent.

** Please note that this option cannot be applied to FDA regulated research.*

Written Consent

1 * **Who will obtain informed consent/assent/authorization?**
A trained and IRB-approved member of the study team (PI or study coordinator) will obtain informed consent.

2 * **When and where will informed consent/assent/authorization be obtained?**
Consent will be obtained either at the time of recruitment or at the time of the initial study visit. Informed consent will be obtained in the Adolescent Clinic or Gynecology Clinic at CHB or BWH, in a private setting, or within the Research space of the CTSU.

3 * **Please indicate whether the children in this study are generally capable of providing assent. Take into account the ages, maturity and psychological state of the children involved.**

- (●) **All are capable.**
- ( ) Some are capable.
- ( ) None are capable.
- ( ) N/A - only adults will be enrolled

3.1 * **Explain your selection:**
Eligible subjects are at least 15 years of age and will be able to provide assent or consent as appropriate.

4 **If applicable, describe the process that will be used to obtain the child's assent.**
Pediatric patients will be involved in the consent discussion with the parent. The study team member will assess the adolescent's understanding of the study and will provide time for questions and consideration of the study.

5 * **How will you assure that the subject has adequate time to decide whether or not they want to participate?**
The consent form will be reviewed section by section with the potential participant. The study coordinator will allow and encourage questions to be asked at any point during the consent process. The study coordinator will give the potential subject time to ponder participation. An interested patient may choose to participate at a future clinical visit after thinking more about the matter privately.

6 * **How will you determine that the parent and/or child understand the elements required in the informed consent/assent/authorization process?**
In addition to providing sufficient time for the patient to thoroughly read the consent form, the person consenting will talk them through each portion of the consent. After each section is covered, the PI/RA will solicit questions before moving forward.

7 * **Could children reach the age of majority while still actively involved in the protocol?**
(●) **Yes** ( ) No

If YES, consent is required from the now adult, unless the committee grants a waiver of consent. Please answer one of the following two questions (7.1 or 7.2). You may also answer both if both apply.

7.1 **Please specify how you plan to obtain consent when a subject turns 18.**
If a subject turns 18 while actively enrolled in the six month trial, consent will be obtained at the next research visit, before any procedures take place.

7.2 If you are requesting a waiver of consent when the child turns 18, address each of the following regulatory requirements to obtain a waiver of informed consent. All criteria need to be met in order for a waiver to be granted.

7.2.1 **Explain why the research could not practicably be conducted without access to and use of the identifiable health information/data.**

7.2.2 **Explain why the research involves no more than minimal risk to subjects.**

7.2.3 **Explain why the research could not practicably be conducted without the waiver of informed consent and authorization.**

7.2.4 **Explain why the waiver of consent/authorization will not adversely affect the rights and welfare of the individuals.**

8 * **Will any of the children originally enrolled in the study reach the age of majority and not have the ability to provide consent when they turn 18 because of decisional impairment?**

○ Yes ● **No**

Please Note once a child reaches the age of 18 they must consent for themselves. For children with decisional impairment once they reach 18, a parent must apply for and be granted the legal ability to continue to serve as a legally authorized representative. Otherwise the IRB must approve for others to be able to provide surrogate consent.

If YES, please respond to the following questions:

8.1 Describe the criteria and /procedures or measurements for evaluating the decisional status of the now adult subject to determine whether they are capable of consenting on their own behalf. This would include the use of standardized measurements, consults with another qualified professional, etc.

8.2 Describe how you will determine who is authorized to provide legally valid consent for the now adult subject. This could include use of durable power of attorney for healthcare, a legally appointed guardian (this must be a court-appointed induvidual), or the use of surrogate consent as approved in IRB. Please include whether and how legal records regarding authority will be obtained and reviewed by the research team.

8.3 When possible if legally effective consent cannot be obtained from the now adult subject, assent should be obtained. Please describe if you plan to obtain assent and provide criteria used to evaluate the assent or dissent of the now adult sibject with decional impairment

9 * Regulations require that significant new findings developed during the course of the research, which may relate to the subject's willingness to continue participation, be provided to the subject. Describe how this requirement will be met.

If significant new findings develop, this information will be disseminated to all participants. The consent forms will also be amended to reflect any change in the risk/benefit ratio of the study.

10 * Upload all consent and assent forms. If there is more than one, list the titles or categories of each form submitted (e.g. experimental, control, sub-study).

	Name	Date Last Modified	Version	Owner
⟲ ⟷	Cabergoline consent	3/31/2017 11:29 AM	0.16	Amy DiVasta
⟲ ⟷	Cabergoline consent.03.31.17.docx	9/14/2017 9:35 AM	0.02	Theresa Williams

NOTE: Your consent must use the current required format.Click here to download the template

Drugs, Biologics or Other Products

Please provide information for the drug/product that will be used, administered, or applied to the subjects as the object of the study or that is relevant to the objectives of the protocol. If there is more than one drug/product, please be sure to enter each drug/product. More than one drug/product may be entered under each category.

1 The drug/biologic/product being administered is an investigational product (not approved by the FDA)

Generic Name	Type of Product	Manufacturer
There are no items to display		

2 The drug/biologic/product being administered is an FDA-approved agent but used outside of the FDA labeling in an unapproved dose, route of administration, population, disease, in concomitant medical use, etc.

	Generic Name	Type of Product	Manufacturer
View	cabergoline	Drug	Teva Pharmaceuticals

3 The drug/biologic/product being administered is FDA approved and being administered in accordance with approved labeling

	Generic Name	Type of Product	Manufacturer
View	norethindrone acetate	Drug	Amneal Pharmaceuticals

4 **The drugs/biologics/products being administered does not fit into any of the above categories.**

Generic Name	Type of Product	Manufacturer
There are no items to display		

5 **The product being administered is a dietary supplement, herbal medicine, or medical food.**

Product Name	Type Of Product
There are no items to display	

6 **Select the individuals that can prescribe the drugs listed in this protocol.**

Last Name	First Name	Employee ID
DiVasta	Amy	106866

Placebo

1 * **Briefly describe the placebo (drug, device, procedure, intervention, surgery, etc.) arm used in the study. Provide a justification for use of the placebo, including the length of subject participation in the placebo arm. Please justify why the study cannot be conducted without the use of the placebo. Your justification should address whether outcomes are subjective and how use of a placebo will address this issue, if applicable.**

No subjects in the proposed pilot study will be denied treatment. Subjects will be randomized to either receive norethindrone acetate (standard care) versus cabergoline (investigational drug).

However, since the two medications are administered on a different frequency, a placebo will be used to maintain blinding of drug assignment to both the investigators and the subject.

If a subject is randomized to norethindrone acetate, she will receive norethindrone acetate 5 mg tablet by mouth daily + one placebo pill by mouth twice weekly.

If a subject is randomized to cabergoline, she will receive one placebo pill by mouth daily + cabergoline 0.5 mg tablet by mouth twice weekly.

As a result, all subjects will take 1 pill daily and 1 pill twice weekly. This will allow both the patients and investigators to remain blinded to group assignment.

2 * **Describe any commonly used diagnostic/treatment approach(es) that will be withheld from subjects assigned to the placebo arm of this study. Will subjects be denied any type of treatment or diagnostics that would be considered a current standard of care?**

No subjects will receive only placebo. All subjects will receive active treatment. All subjects will receive either the intervention medication or the standard of care.

3 * **Summarize any risks to subjects in the placebo arm consequent to not receiving active treatment for their disease or condition.**

No subjects will receive only placebo. All subjects will receive active treatment.

4 * **Summarize the potential benefits from participation in this protocol for subjects in the placebo arm.**

No subjects will receive only placebo. All subjects will receive active treatment.

5 **If applicable, how will the condition or disease of subjects in the placebo arm of this study be monitored compared to the monitoring associated with standard care for this disease/condition?**

No subjects will receive only placebo. All subjects will receive active treatment.

6 **If applicable, what criteria will be used to determine that the participation of a subject, who may be receiving a placebo treatment, should be discontinued due to his/her worsening disease or condition?**

No subjects will receive only placebo. All subjects will receive active treatment.

Title: Novel Treatments for Endometriosis (NOTE): Dopamine Receptor Agonist Therapy for Pain Relief in Women Suffering from Endometriosis Pilot Study

Blood Collections

1 **Select the method(s) of blood collection.**

1.1 ☑ Venipuncture

1.1.1 ☑ At time of clinically indicated procedure

1.1.2 ☑ At time specifically for research

1.2 ☐ Heel/finger/ear sticks

1.3 ☐ From catheter or heparin lock

1.4 ☐ Other

If Other:

1.4.1 Please specify.

2 * **How many individual samples will collected (not number of sticks)?**
One sample will be collected per research study visit, for a total of 3 samples over 6 months.

Note: Multiple withdrawals of blood from an indwelling venous line are to be considered more than one collection.

3 * **What is the period of time the samples will be collected (please specify in weeks or if less than weeks in days)?**
Samples will be collected at baseline, 3 months, and 6 months.

4 * **Specify the total amount of blood collected in mls.**
maximum 40mLs

5 * **Will research subjects be less than 16.5 kg?**
○ Yes ● **No**

If YES:

5.1 Will the total amount of blood to be drawn from children less than 16.5 kg be more than 3mL/kg?
○ Yes ○ No

Title: Novel Treatments for Endometriosis (NOTE): Dopamine Receptor Agonist Therapy for Pain Relief in Women Suffering from Endometriosis Pilot Study

Additional Documents

1 Please upload any additional documents if it is necessary.

Name	Date Last Modified	Version	Owner

There are no items to display

PI's Statement

- **I assure the information I obtain as part of this research (including protected health information) will not be reused or disclosed to any other person or entity other than those listed on this form, except as required by law or for authorized oversight of the research project. If at any time I want to reuse this information for other purposes or disclose the information to other individuals or entity, I will seek approval by the Institutional Review Board (IRB).**
- **I assure the IRB that there are appropriate resources (funding, equipment, space, support services) to conduct this research safely and in accordance with all required human subject protection policies.**

* **The PI accepts responsibility for assuming adherence to DHHS, FDA, HIPAA and Children's Hospital's regulations and policies relative to the protection of the rights and welfare of patients/subjects participating in this study.**
● **Yes** ○ **No**

Detailed Sponsor Information

1 * **What is the sponsor's name?**
J WILLARD AND ALICE S MARRIOTT FOUNDATIO - 1754

1.1 If your sponsor is not in the list, please select "Other" from the list and specify your sponsor below.

Note: Use a '%' to conduct a wildcard search (e.g. a '%Pharm' search will return all options with 'pharma' at any place in the name).

2 * **Please select the appropriate category of funding.**

- ○ Federal
- ○ State
- ○ Corporate/Industry
- ● **External Foundation**

2.1 If the category of funding is "Federal", upload the grant(s) here. (Please include the scientific part. This is a requirement for federally supported research. You need not include biosketches or financial information here, just the description of the research.)

Name	Date Last Modified	Version	Owner

There are no items to display

3 * **What will the sponsor provide? Check all that apply:**
Research Funding - Committed

4 * **What is sponsor's contact name, if applicable?**
Anne Gunsteens

5 * **What is sponsor's contact phone number?**
301-380-3745

6 * **What is sponsor address?**
10400 Fernwood Rd, Dept 925, Bethesda, MD 20817

7 * **What is sponsor email address?**
anne.gunsteens@marriott.com

8 * **Is a Clinical Trial Agreement (CTA) required?**

- ○ Completed/Signed
- ○ Pending
- ● **Not Required**

ID: VIEW46F5DA7D2D400
Name: Detailed Sponsor Information

Detailed Sponsor Information

1 * **What is the sponsor's name?**
MARRIOTT DAUGHTERS FOUNDATION - 1822

1.1 If your sponsor is not in the list, please select "Other" from the list and specify your sponsor below.

Note: Use a '%' to conduct a wildcard search (e.g. a '%Pharm' search will return all options with 'pharma' at any place in the name).

2 * **Please select the appropriate category of funding.**

- ○ Federal
- ○ State
- ○ Corporate/Industry
- ● **External Foundation**

2.1 **If the category of funding is "Federal", upload the grant(s) here. (Please include the scientific part. This is a requirement for federally supported research. You need not include biosketches or financial information here, just the description of the research.)**

Name	Date Last Modified	Version	Owner

There are no items to display

3 * **What will the sponsor provide? Check all that apply:**
Research Funding - Committed

4 * **What is sponsor's contact name, if applicable?**
Nancie Suzuki

5 * **What is sponsor's contact phone number?**
301-380-1425

6 * **What is sponsor address?**
10400 Fernwood Rd, Dept 901, Bethesda, MD 20817

7 * **What is sponsor email address?**
nancie.suzuki@hosthotels.com

8 * **Is a Clinical Trial Agreement (CTA) required?**

- ○ Completed/Signed
- ○ Pending
- ● **Not Required**

ID: VIEW46F5DA7D2D400
Name: Detailed Sponsor Information

Use of an Approved Drug/Product for an Unapproved Indication

1 * **Select the type of product that will be administered that is relevant to the aims of the research protocol. If there is more than one product, enter information about one product at this time. You will be able to enter additional products at a later time.**

- ● **Drug**
- ○ Biologic
- ○ Combination
- ○ Other

If Combination:
Please describe. Include whether it is regulated as a drug/device/biologic. What is the mode of action?

If Other:
Please describe:

2 * **What is the generic name or descriptor of the product?**
cabergoline

3 **What, if any, is the commercial/trade name of the product?**
Dostinex

4 * **Who is the manufacturer of the product?**
Teva Pharmaceuticals

5 * **Who is the supplier of the product?**
Teva Pharmaceuticals

6 * **Briefly describe how the research use of the product departs from the FDA approved indication/labeling.**
Cabergoline will be used in the same population of patients as the FDA-approved labeling (reproductive-aged women), but for a different indication (for endometriosis rather than for hyperprolactinemia).

7 * **Describe the purpose of the evaluation (e.g. to support a new indication for the use of the drug, to support any other significant change in the labeling or advertising for the drug, etc.).**
To determine if cabergoline represents a potential safe and effective means of pain relief for women suffering from chronic pelvic pain related to endometriosis, and to generate preliminary data for a potential larger randomized clinical trial. We do not anticipate this pilot study will lead to any changes in labeling or indication.

8 * **Is this research being conducted under an IND?**
● **Yes** ○ No

If YES:

8.1 Who holds the IND?
○ A company, organization, NIH, consortium or university.
● **Children's Investigator**
○ Other

8.2 Specify the IND number if available (if it is not available, you need to submit an amendment to update this information when obtained).
132882

8.3 Specify the name of the IND holder.
Amy DiVasta

8.4 Upload a copy of FDA IND approval correspondence, if available.

Name	Date Last Modified	Version	Owner
FDA go ahead email 3-13-17.docx	3/17/2017 4:13 PM	0.01	Jenny Gallagher
FDA response to 0000.pdf	3/31/2017 11:34 AM	0.01	Amy DiVasta
FDA Response.01.09.17.docx	3/17/2017 4:13 PM	0.02	Jenny Gallagher
IND submission 0000.pdf	3/31/2017 11:34 AM	0.01	Amy DiVasta
IND submission 0001.pdf	3/31/2017 11:34 AM	0.01	Amy DiVasta

8.5 Is FDA IND approval pending?
○ Yes ● **No**

If NO:

8.6 Is this research being conducted under a formal IND exemption request to FDA?
○ Yes ○ No

If YES:

8.7 Upload a copy of the FDA letter granting the IND exemption.

Name	Date Last Modified	Version	Owner

There are no items to display

If NO:

8.8 Please confirm each statement or provide a justification for each criteria for IND exemption:

8.8.1 The drug product is lawfully marketed in the United States.
○ Yes ○ No

8.8.2 The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication and there is no intent to use it to support any other significant

change in the labeling of the drug.
○ Yes ○ No

8.8.3 In the case of a prescription drug, the investigation is not intended to support a significant change in the advertising for the drug.
○ Yes ○ No

8.8.4 The investigation does not involve a route of administration, dose, patient population, or other factor that significantly increases the risk (or decreases the acceptability of the risk) associated with the use of the drug product.
Please explain how the use outside of the approved labeling does not put participants at increased risk due to participation in the study:

8.8.5 The investigation is conducted in compliance with the requirements for review by an IRB and with the requirements for informed consent.
○ Yes ○ No

8.8.6 The investigation is conducted in compliance with the requirements of 21 CFR 312.7 (i.e. the investigation is not intended to promote or commercialize the drug product).
○ Yes ○ No

8.8.7 Please provide any additional information if necessary.

9 * **What is the dosage, route of administration or application, and frequency and total duration of use of the product?**
cabergoline 0.5 mg by mouth administered twice weekly for 6 months

10 * **What is the proposed mechanism of action of the product? Include any post-manufacturing modifications to the product expected to affect the proposed mechanism of action.**
Analysis of endometriotic lesions has demonstrated that a prerequisite for their formation and maintenance is the development of an adequate blood supply. The regulation of this ‘‘endometriotic vasculature’’ involves well-established pathways of angiogenesis, including vascular endothelial growth factor (VEGF) acting through the VEGF receptor 2 (VEGFR2).

Cabergoline is a long-acting dopamine receptor agonist with a high affinity for D2 receptors, a Drd2-A. In animal models, Drd2-A inhibit pathologic angiogenesis by inactivating VEGFR2 signaling while maintaining an acceptable safety profile and not interfering with the normal establishment and progression of pregnancy.

In a preliminary study that sought to evaluate the efficacy of Drd2-A in the treatment of peritoneal endometriosis in humans, researchers found that Drd2-A led to tissue degeneration, which was supported by down-regulation of VEGF/VEGFR2, three proangiogenic cytokines (CCL2, RUNX1, and AGGF1) and plasminogen activator inhibitor (PAI) 1,
a potent inhibitor of fibrinolysis in the L2 lesions

11 **List any contraindications or potential drug interactions.**
Potential Drug Interactions:
Ergot-alkaloids, macrolide antibiotics, other dopamine agonists (phenothiazines, butyrophenones, thioxanthenes, or metoclopramide)

Contraindications:
- uncontrolled hypertension,
- a history of pulmonary, pericardial and retroperitoneal fibrotic disorders
- a history of cardiac valvulopathy of any valve
• a known hypersensitivity to this drug or any ergot derivatives and to any ingredient in the formulation

12 **Are there any known antidotes? Please describe.**
In cases of overdose, symptoms of overdose would likely be those of over-stimulation of dopamine receptors. These might include nausea, vomiting, gastric complaints, hypotension, or thought/perception disturbances (hallucinations), nasal congestion and syncope.

General supportive measures should be undertaken to remove any unabsorbed drug and maintain blood pressure if necessary. In addition, the administration of dopamine antagonist drug may be advisable.

13 * **Will subjects, or their insurance providers, be charged for the investigational product?**
○ Yes ● **No**

14 **Please upload any additional documents, including the approved drug label or package insert.**

Name	Date Last Modified	Version	Owner
Dostinex prescribing information	6/3/2015 12:55 PM	0.01	Amy DiVasta
Dostinex prescribing information 2	6/3/2015 12:55 PM	0.01	Amy DiVasta

ID: VIEW470A4FA4F4400
Name: Use of an Approved Drug/Product for an Unapproved Indication

Drug/Product used under Approved Labeling

1 * **Select the type of product that will be administered that is relevant to the aims of the research protocol. If there is more than one product which is relevant to the aims of the protocol, enter information about one product at this time. You will be able to enter additional products at a later time.**

- (●) **Drug**
- ( ) Biologic
- ( ) Combination
- ( ) Other

If Combination:
Please describe. Include whether it is regulated as a drug/device/biologic. What is the mode of action?

If Other:
Please describe:

2 * **What is the generic name or descriptor of the product?**
norethindrone acetate

3 **If any, what is the commercial/trade name of the product?**
Aygestin

4 * **Who is the manufacturer of the product?**
Amneal Pharmaceuticals

5 * **Who is the supplier of the product?**
Amneal Pharmaceuticals

6 * **What is the dosage, route of administration or application, and frequency and total duration of use of the product?**
norethindrone acetate 5 mg by mouth daily for 6 months

7 * **Will subjects, or their insurance providers, be charged for the investigational product?**
( ) Yes (●) **No**

8 **Please upload any additional, pertinent documents.**

Name	Date Last Modified	Version	Owner
Aygestin prescribing information	6/3/2015 12:56 PM	0.01	Amy DiVasta

ID: VIEW470A5B5BA5400
Name: Drug/Product Used Under Approved Labeling