Title of Research Study:	**IMPRES: IMProving Executive function Study**
Protocol Number:	826981
Principal Investigator:	C. Neill Epperson, M.D.
Address:	Penn Center for Women's Behavioral Wellness 3535 Market Street, 3rd Floor Philadelphia, PA 19104
Phone:	215-573-8886 Penn Center for Women's Behavioral Wellness Monday – Friday from 9 a.m. to 5p.m.
Study Contact (Regarding Participation):	James Loughead, Ph.D. Co-Principal Investigator 215-746-7279 Monday – Friday from 9 a.m. to 5 p.m
Emergency Contact (Regarding Medication):	Edwin Kim, M.D. Study Physician 602-842-3162 Monday – Friday from 9 a.m. to 5 p.m.

If you are experiencing a medical emergency after 5p.m., please contact 911 or go to the closest emergency room.

What is the purpose of this supplemental consent form?

You are being asked to participant in the IMPRoving Executive function Study (IMPRES) at the Penn Center for Women's Behavioral Wellness (PCWBW). This form provides details for an alternate version of the IMPRES study for participants unable to complete an MRI for one of the following reasons:

- You have metal in your body that would make it unsafe for you to undergo an MRI
- You have claustrophobia or anxiety pertaining specifically to the MRI
- You are left-handed
- Any other circumstance that would lead to an inability to complete the MRI, including travel restrictions

This document is updated to reflect the study procedures, risks and benefits, and compensation information excluding the MRI as a study procedure.

You are being asked to take part in a research study. This is not a form of treatment or therapy. It is not supposed to detect a disease or find something wrong. Your participation is voluntary which means you can choose whether or not to participate. If you decide not to participate there will be no loss of benefits to which you are otherwise entitled. Before you make a decision, you will need to know the purpose of the study, the possible risks and benefits of being in the study and what you will have to do if you decide to participate. The research team is going to talk with you about the study and give you this consent document to read. You do not have to make a decision now; you can take the consent document home and share it with friends, your family doctor, and family.

If you do not understand what you are reading, do not sign it. Please ask the researcher to explain anything you do not understand, including any language contained in this form. If you decide to participate, you will be asked to sign this form and a copy will be given to you. Keep this form, in it you will find contact information and answers to questions about the study. You may ask to have this form read to you.

What is the purpose of the study?

Following a medically induced menopause, many women report difficulty in remembering things, focusing and concentrating. The purpose of this study is to examine the effects of a stimulant medication called Vyvanse® on brain functioning. From this point on, we will refer to Vyvanse® as LDX (lisdexamfetamine). Stimulant medications are used to reduce interruptive behavior, fidgeting, and other hyperactive symptoms, as well as help a person finish tasks and improve his or her relationships for adults who have ADHD. Please note that the FDA has not approved the use of Vyvanse® for the treatment of memory and concentration difficulties related to medically induced menopause.

This study is examining how LDX affects executive functioning, such as attention, processing, organization, and memory in women who are experiencing executive functioning difficulties after having undergone a risk-reducing bilateral salpingo-oophorectomy (RRSO).

Why was I asked to participate in the study?

You have been invited to participate in this study because you have already completed our online or telephone prescreening interview and were deemed eligible to screen for study participation. In addition, you are a medically healthy woman between the ages of 35-58 years old who has

undergone a risk-reducing bilateral salpingo-oophorectomy (RRSO) within the previous 15 years. You must have been premenopausal before undergoing RRSO (meaning you were having regular periods).

In order to qualify for participation in this study, you must not suffer from a mental illness, including Attention Deficit Hyperactivity Disorder (ADHD), and you must not have a recent history of drug abuse. You must not have a history of seizures, uncontrolled hypertension or known renal impairment.

Where will the study take place?

- If needed, office visits for the physical exam and EKG will take place at the Penn Center for Women's Behavioral Wellness at 3535 Market St., 3rd Floor, Philadelphia.
- Remote visits can take place at any location that enables access tovideo chat, email, a scanner/fax machine, and a private area so that you and the study team can communicate in real-time while also protecting your confidentiality.

What will I be asked to do?

Screening

Remote Screening Appointment

The remote screening appointment requires that you have access to video chat, email, a scanner/fax machine, and a private area so that you and the study team can communicate in real-time while protecting your confidentiality. During the remote screening, you will be asked about your psychiatric history and to complete a number of ratings about your mood and emotions online. We will also collect a urine sample to complete a urine drug screen. The drug screen must be negative for all substances (marijuana and nicotine are permissible) or you will not be eligible to participate.

The remote screening visit also requires that you complete a brief medical evaluation and electrocardiogram (EKG) with your own doctor or at our clinic.

- Brief medical evaluation: Vital signs, including blood pressure and pulse, should be recorded. Women with a systolic blood pressure of >145 mm Hg or diastolic blood pressure >90 mm Hg at screening will not be enrolled and referred to their primary care doctors for further evaluation.
    - ***Optional***: If you have completed a hormone panel for estradiol recently and would like to share your results, please attach the results of your hormone panel to the physical exam form. Please note that providing hormone results is optional, so if you have not had a hormone panel completed recently then you do not need to complete one for this study.

- Electrocardiogram: An EKG is a recording of the electrical activity of the heart using electrodes that are attached to your skin on your chest. This procedure is non-invasive.

In total, the procedures that comprise the remote screening visit will take up to 3 hours. After this visit, we will review your medical and psychiatric history, and medical evaluation (if done by personal physician). If you are found to be eligible after reviewing these items, a member of the research team will contact you by telephone to schedule your next appointment. If you are not eligible for this study, we will contact you by phone to explain this to you.

Trial A

Visit 2: Remote Baseline Visit

If you fully meet criteria based on the admission-screening process you will be scheduled for the baseline visit. You will be asked to meet on video chat for 2.5-3 hours to complete ratings about their mood and emotions. You will also undergo a series of tasks assessing your memory and attention. You will be shipped all study materials including a scale (if needed), a blood pressure cuff, and the trial medication before the scheduled baseline visit.

Randomization to LDX or Placebo Treatment for Trials A and B

Before your baseline visit, you will receive your first bottle of study capsules for Trial A that you will begin using on a scheduled date. Your medication will be shipped to your home directly. Every participant will undergo testing pre and post a 6-week trial of LDX or placebo followed by an approximately 2-week break before crossing over to the next trial to repeat the process. A placebo is an inactive substance, or a "sugar pill." The placebo capsules will be filled with microcellulose.

The order in which the pills are administered will be randomly assigned. Random assignment is like flipping a coin for each study participant. The assignment will also be double blind, meaning you, the study doctor, and the research team will not know what your pill status is until your participation in the study is complete. The purpose of the placebo is to find out how memory and mental functioning are affected in the absence of study medication. Regardless of the order assigned to you, you will begin by taking the medication capsules at a daily dose of one capsule taken with each morning meal.

All women will start with one capsule per day (LDX = 20mg/d). The dose will be increased to two capsules after one week (LDX = 40mg/d). At the end of week 2 of medication use, the research staff will check-in with you by phone to assess any side effects. If you are experiencing more than mild side effects, you will be instructed to reduce your dosage back to one capsule per day. At your week 3 check-in, if the study drug is well tolerated, you will be asked to increase the dose to

three capsules a day (LDX = 60 mg/d) and will remain at this dose until the trial period has ended. During week 4, the research staff will reach out to you by phone to assess potential side effects. If you are experiencing more than mild side effects, you will be instructed to reduce your dosage back to two capsules per day.

Phone Check-in

At the end of week 2 of medication use, a member of the study team will check in with you by phone to speak about side effects. Participants who are having more than mild side effects will be instructed to reduce their dose back to one pill per day.

Visit 3: End of Week 3 Follow-Up

Halfway through the 6-week trial (end of week 3), you will be scheduled for a remote, follow-up visit with the CRC via video chat to assess medication compliance and to monitor for side effects. You will complete various mood and symptoms ratings. This visit will last approximately 60 minutes and will also include measures of blood pressure, pulse, and weight.

Phone Check-in

During week 4, the CRC will check in with you by phone to assess for side effects. Participants who are having more than mild side effects will be instructed to reduce their dose back to 2 pills per day for the remainder of the trial.

Visit 4: End of Trial A Office Visit

You will be scheduled for a remote visit at the end of your first 6-week trial. You will be asked to complete ratings about your mood and emotions and undergo a series of cognitive tasks. Once completed, that means your participation in Trial A has ended and you will now begin your washout period. In total, Visit 4 takes approximately 2.5-3 hours. After this visit, you will start a two week washout period where you will not take any study medication. Additionally, you will ship back your Trial A prescription bottle and any unused medication. Upon completion of the washout period, you will receive your second bottle of medication for Trial B that you will not begin using until after your Trial B Baseline Visit.

****Approximate 2-week washout period****

Trial B

With the exception of the first baseline scan and cognitive testing, participants will undergo the exact same procedure for Trial B (Visits 5, 6, and 7) as they did for Trial A (Visits 2, 3, and 4). For Trial B you will be randomized to the opposite study drug/placebo group. For example, if you were randomized to the active study drug (LDX) for Trial A, you would be then be randomized to

the placebo capsules for Trial B. Keep in mind that because the study is double-blind, you will not be told when you receive active and when you receive placebo.

How long will I be in the study? How many other people will be in the study?

This entire study will include 100 people and will take place over 5 years. However, your participation will last approximately 4-5 months. We will ask that you complete a total of 7 visits with us remotely, including your initial screening visit, which is happening today.

What are the risks?
With the elimination of the MRI the related MRI risks are no longer relevant. The following risks still apply:

1. Participating in a Placebo-Controlled Study of Vyvanse® (also called LDX or lisdexamfetamine): Regardless of trial order, you may find that your symptoms do not change or even get worse during the study. Furthermore, LDX is classified as a stimulant medication that is likely to come up positive for amphetamines on a urine drug screen.

2. Side Effects of LDX: LDX is approved by the U.S. FDA for the treatment of ADHD in children, adolescents, and adults. This medication is also used to treat a condition called Narcolepsy, which is best described as Recurring Sleep Episodes During the Day. This medication does not treat physical symptoms of menopause such as hot flashes, night sweats, and vaginal dryness.

The reported adverse reactions to LDX treatment include: constipation, decreased appetite, diarrhea, dizziness, dry mouth, headache, increased sweating, mild irritability, nervousness, or restlessness, difficulty concentrating, or brain fog, nausea, trouble sleeping, unpleasant taste, upper stomach pain, vomiting and weight loss. The most common side effects reported by adults are decreased appetite, difficulty falling asleep, and dry mouth. LDX can also cause an increase in blood pressure and heart rate. Your blood pressure and heart rate will be monitored at each visit for any serious changes. While the likelihood that you will develop peripheral vasculopathy is very small, you will be monitored at each assessment for tingling and numbing sensations in your hands and feet. Sudden death has been reported in adults using stimulant medications within the normal dosing range. However, these deaths did not occur with LDX. LDX is classified as stimulant medication, as are other medications such as Adderall and Ritalin.

Although rare, stroke and heart attacks have been seen in adults taking stimulant medications like LDX within the normal dosing range. These risks are increased in adults who have a pre-existing cardiac condition such as serious heart arrhythmias, coronary heart disease and other serious heart

problems. Therefore, women with a known pre-existing heart condition will not be permitted to enroll for study participation.

Although rare, serotonin syndrome has been seen in adults taking medications like LDX within the normal dosing range. This risk is increased in adults who are also taking other serotonergic agents (e.g., SSRIs, SNRIs, triptans). Therefore, women taking serotonergic medications will be briefed on the symptoms related to serotonin syndrome and monitored for any side effects at every visit.

3. Reproductive Risks: Vyvanse® (LDX) is not recommended for use during pregnancy. Because of the effects of LDX, there could be serious harm to unborn children or children who are breastfeeding. These effects could also harm the mother. It is also possible that harmful side effects that are not yet known could happen to both the mother and unborn or breastfeeding child. Due to the nature of the study, women who have had a hysterectomy or oophorectomy are not at risk for pregnancy.

4. Urine Test: Your urine will be tested to make sure that you are not using illegal drugs. There is no risk in providing a urine sample. The results of this test will be confidential.

5. General Risks and Inconveniences: Any medication may have unforeseen side effects. You should know that the prediction of drug effects in any individual cannot be done with certainty and unexpected potentially harmful effects sometimes occur with any type of drug. A doctor is available 24 hours a day, 7 days a week. In the case of emergency, the identity of any medication can also be obtained by calling the psychiatrist on call at (215) 573-8886 during working hours. Beyond normal work day hours, you may call 911 or go to your closest emergency room. The staff at hospital can contact the study principal investigator, Dr. Epperson or a physician covering for her. In addition, you may use this informed consent form as a point of reference to let the hospital staff know what you are currently participating in.

6. Completing Visits Remotely: It is important to note that the study team will make every effort to keep remote communication with you strictly confidential (i.e., ensuring phone calls and video sessions are happening on a secured network, in an empty office in our clinic.) Therefore, we ask you to ensure that our communication with you is limited to a private area so as to protect your privacy and confidentiality.

How will I benefit from the study?

Participation in this study will not benefit you directly; however, you may experience an improvement in perceived cognitive functioning during the course of the study. Participation in this study may help researchers understand more about the effects of LDX on the brain.

What if new information becomes available about the study?

During the course of this study, we may find more information that could be important to you. This includes information that, once learned, might cause you to change your mind about being in the study. We will notify you as soon as possible if such information becomes available.

What other choices do I have?

Your alternative to being in the study is to not be in the study. If you choose not to be in the study, nothing will change if you are receiving services from doctors at Penn.

What happens if I do not choose to join the research study?

You are free to decide whether or not to participate in this study and are free to withdraw from this study at any time during its course. A decision not to participate in the study, or to withdraw, will not adversely affect your relationship with the University of Pennsylvania. We ask that you let our staff know whether or not you wish to stay in the study. You may do so by contacting our staff member by telephone.

There is no penalty if you choose not to join the research study. You do not lose any benefits or advantages that are now coming to you, or would come to you in the future. Your therapist, social worker, nurse, doctor, or the study personnel will not be upset with your decision. If you are currently receiving services and you choose not to volunteer in the research study, your services will continue.

If you decide not to participate in this study but would still like to seek treatment for memory and concentration difficulties, we recommend that you speak with your primary care physician.

When is the study over? Can I leave the study before it ends?

This study is expected to end after all participants have completed all visits and all the information has been collected. The study may be stopped without your consent for the following reasons:

- The PI feels it is best for your safety and/or health – you will be informed of the reason why.
- You have not followed the study instructions.

- You no longer are eligible for study participation for any reason based on study criteria.
- The PI or the Office of Regulatory Affairs of the University of Pennsylvania can stop the study anytime.

You have the right to drop out of the research study at anytime during your participation. There is no penalty or loss of benefits to which you are otherwise entitled if you decide to do so. Withdrawal will not interfere with your future care.

If you decide to withdrawal from the research study before you have completed it, we ask that you contact the staff member who signed the consent form. Their telephone number is printed next to their name on the last page of this document. . Or you may call Dr. Epperson at the telephone number on page 1. You do not have to explain your reason for withdrawing from the study if you do not feel comfortable doing so, however, if you are unable to reach anyone at our clinic, please leave a brief message stating your decision to withdraw from the study. You are also welcome to write a letter to Dr. Epperson, letting her know of your decision to withdraw from the study. Her address is on page 1, of this form. No other action on your part, besides letting the staff know of your decision, is required if you decide to withdraw from the study.

How will confidentiality be maintained and my privacy be protected?

All of your history and medical records are confidential. Any identifiable information that is obtained in connection with this study will remain confidential and will be disclosed only with your permission. Any documents you sign, where you can be identified by name, will be filed using an assigned code and kept in a locked drawer in a locked room in the clinic's office. The research team will make every effort to keep all the information you tell us during the study strictly confidential, as required by law. The Institutional Review Board (IRB) at the University of Pennsylvania is responsible for reviewing research studies to ensure they include an adequate plan for protecting the rights and welfare of research volunteers like you. The IRB has access to study information. In the case of published reports from this study, no individual subjects will be identifiable.
A description of this clinical trial will be available on http://www.clinicaltrials.gov, as required by U.S. Law. This web site will not include information that can identify you. At most, the web site will include a summary of the study results. You can search this web site at any time.

What happens if I am injured from being in the study?

We will offer you the care needed to treat injuries directly resulting from taking part in this research. We may bill your insurance company or other third parties, if appropriate, for the costs of the care you get for the injury, but you may also be responsible for some of them.

There are no plans for the University of Pennsylvania to pay you or give you other compensation for the injury. You do not give up your legal rights by signing this form.

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

Will I have to pay for anything?

You will not have to pay for any of the tests or drugs directly associated with participating in this study.

Will I be compensated for participating in the study?

For your time and travel to the PCWBW you will be compensated $500. The breakdown of payment by visit is as follows:

Screening

- Visit 1 – Screening: $50

Trial A

- Visit 2 – Baseline Scan: $100
- Visit 3 – End of week 3 follow-up: $50
- Visit 4 – End of Trial A Scan: $100

Trial B

- Visit 5 – Baseline Visit: $50
- Visit 6 – End of week 3 follow-up: $50
- Visit 7 – End of Trial B scan: $100

If you decide to withdraw from the study before the study is over, you will be compensated for the parts of the study that you have completed up until the point in which you decide to withdraw from the study.

Reimbursement will also be available if you completed study related procedures with your personal physician that were NOT covered by your insurance plan (i.e, medical evaluation, EKG, etc.).

Please note that if you receive more than $600.00 compensation in one year for participation in research studies at the University of Pennsylvania, you must report this is as income to the federal government for tax purposes.

What information about me may be collected, used or shared with others?

This study will utilize directly-identifiable protected health information (PHI). PHI, as defined by HIPAA, means individually identifiable health information about an individual that is transmitted or maintained by electronic media or in any other form or medium. PHI includes demographic information that is created or received by a health care provider, health plan, employer, or health clearinghouse. PHI relates to the past, present, or future physical or mental health or condition of an individual; the provisions of health care to an individual; or the past, present, or future payment for the provision of health care to an individual; and identifies the individual or can reasonably be used as a basis to identify an individual. We will be collecting the following PHI about you for this study:

- Name
- Postal address information
- All elements of dates such as birthdate, date of visit, date of sample collection (except year) for dates directly related to an individual and all ages over 89)
- Telephone and fax number
- Electronic mail addresses
- Social security numbers *(for study compensation)*
- Medical record numbers (*for ordering medication*)

In accordance to University of Pennsylvania's policy regarding how PHI is handled, managed, and disseminated, study personnel will utilize an institutionally secured and managed network drive.

Why is my information being used?

Your information is used by the research team to contact you during the study. Your information and results of tests and procedures are used to:

- Do the research
- Oversee the research
- To see if the research was done right

Who may use and share information about me?

The following individuals may use or share your information for this research study.

- The study lead investigator, Dr. C. Neill Epperson
- The study team who works directly for Dr. Epperson. This includes clinicians and research personnel.
- Other authorized personnel at the Penn School of Medicine such as the research pharmacist and laboratory at the Hospital of the University of Pennsylvania.

Electronic Medical Records and Research Results

What is an Electronic Medical Record?

An Electronic Medical Record (EMR) is an electronic version of the record of your care within a health system. An EMR is simply a computerized version of a paper medical record.

If you are receiving care of have received care within the University of Pennsylvania Health System (UPHS) (outpatient or inpatient) and are participating in a University of Pennsylvania research study, results of research – related procedures (i.e. laboratory tests, imaging studies and clinical procedures) may be placed in your existing EMR maintained by UPHS.

If you have never received care within UPHS and are participating in a University of Pennsylvania research study that uses UPHS services, an EMR will be created for you for the purpose of maintaining any results of procedures performed as part of this research study. The creation of this EMR is required for your participation in this study. In order to create your EMR, the study team will need to obtain basic information about you that would be similar to the information you would provide the first time you visit a hospital or medical facility (i.e., your name, the name of your primary care doctor, the type of insurance you have). Results of research procedures performed as part of your participation in this study (i.e., laboratory tests, imaging studies and clinical procedures) may be placed in this EMR.

Once placed in your EMR, these results are accessible to appropriate UPHS workforce members that are not part of the research team. Information within your EMR may also be shared with others who are determined by UPHS to be appropriate to have access to your EMR (e.g., health insurance company, disabled provider, etc.)

Who outside the School of Medicine, might receive my information?

- The Office of Human Research

Once your personal health information is disclosed to others outside the School of Medicine, it may no longer be covered by federal privacy protection regulations.

The Principal Investigator or study staff will inform you if there are any additions to the list above during your active participation in the trial. Any additions will be subject to University of Pennsylvania procedures developed to protect your privacy.

How long may the School of Medicine use or disclose my personal information?

Your authorization for use of your personal health information for this specific study does not expire.

Your information may be held in a research database. However, the School of Medicine may not re-use or re-disclose information collected in this study for a purpose other than this study unless:

- You have given written authorization
- The University of Pennsylvania's Institutional Review Board grants permission
- As permitted by law

Can I change my mind about giving permission for use of my information?

Yes, you may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the investigator for the study. If you withdraw your permission, you will not be able to stay in this study.

What if I decide not to give permission to use and give my health information?

Then you will not be able to be in this research study.

You will be given a copy of this form describing your confidentiality and privacy rights for this study. By signing this document, you are permitting the School of Medicine to use and disclose personal health information collected about you for research purposes as described above.

Who can I call with questions, complaints, or if I'm concerned about my rights as a research subject?

If you have any questions, concerns or complaints regarding your participation in this research study or if you have any questions about your rights as a research subject, you should speak with the Principal Investigator listed on page one of this form. If a member of the research team cannot be reached or you want to talk to someone other than those working on the study, you may contact the Office of Regulatory Affairs with any questions, concerns or complaints at the University of Pennsylvania by calling (215) 898-2614.

Who is the primary sponsor of this research?

This research study is supported by the National Cancer Institute (NCI) at the National Institutes of Health (NIH). In addition, the person leading this research study receives extra money from Shire Pharmaceuticals for work that is not a part of this study. Shire Pharmaceuticals is the primary owner of the trademark for the study medication, Vyvanse®. Her activities with these company may include consulting, advisory boards, giving speeches or writing reports. If you would like more information, please ask the researchers or the study coordinator.

Authorization:
When you sign this form, you are agreeing to take part in this research study. This means that you have read the consent form, your questions have been answered, and you have decided to volunteer. Your signature also means that you are permitting the University of Pennsylvania Health System and the School of Medicine to use your personal health information collected about you for research purposes within our institution. You are also allowing the University of Pennsylvania Health System and the School of Medicine to disclose that personal health information to outside organizations or people involved with the operations of this study.

A copy of this form will be given to you.

Name of Subject:_____

Subject's Signature_____Date:_____

Name of Person
Obtaining Consent:_____Date:_____

Signature of Person Obtaining Consent:_____

Telephone Number of Person Obtaining Consent:_____