Permission to Take Part in a Human Research Study

Endeavor to Stop Nausea/Vomiting Associated with Pregnancy (E-SNAP)

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Title of Research Study: ENDEAVOR TO STOP NAUSEA/VOMITING ASSOCIATED WITH PREGNANCY (E-SNAP)

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Key Information:
The first few pages of this document include a summary of this study to help you decide whether or not to participate. Detailed information is provided after the summary.

Why am I being asked to take part in this research study?

We are asking you to take part in this research study because you have severe nausea and vomiting of pregnancy (sNVP) that is not properly controlled by current standard treatments.

What should I know about a research study?

- Someone will explain this research study to you.
- Whether or not you take part is up to you.
- You can choose not to take part.
- You can agree to take part and later change your mind.
- Your decision will not be held against you.
- You can ask all the questions you want before you decide.

Why is this research being done?

Up to 80% of pregnant persons experience nausea and vomiting of pregnancy that reduces quality of life. Although nausea and vomiting often resolve by the second trimester of pregnancy, symptoms persist into the third trimester in 15-20% of pregnant individuals. Up to 3% of people develop hyperemesis gravidarum, a severe form of nausea and vomiting of pregnancy, that is the most common reason for hospitalization in early pregnancy. Current medications are helpful but not always fully effective, and several investigators and pregnant person's advocacy groups have identified the development of new treatments for sNVP as a priority.

The risks of sNVP to parents and infants include hospitalization, anemia, high blood pressure, blood clots, preterm birth and cesarean section. Newborns are at risk for low birthweight and being small for their age and for developmental delays in childhood. Anxiety and depression also are common in persons with sNVP due to extreme discomfort and the reduced quality of life that occur with sNVP symptoms.

A drug that is currently available and FDA approved for the treatment of depression, mirtazapine (Remeron®) also has strong antinauseant effects. It has several drug effects that block the sequence of biological events that trigger nausea and lead to vomiting. Mirtazapine is

prescribed for nausea in patients undergoing cancer chemotherapy and before surgery to prevent nausea and vomiting after surgery. Successful case reports of mirtazapine treatment of sNVP have been reported in 26 individuals. We are evaluating whether mirtazapine is acceptable to persons with sNVP, its tolerability when used to treat sNVP, the adequacy of the dose and its safety. Pregnant individuals who do not have an adequate response to medications that are commonly used to treat sNVP will be included.

Mirtazapine is not approved by the FDA for treatment of nausea and vomiting of pregnancy (NVP). In this clinical trial, mirtazapine is an investigational product.

How long will the research last and what will I need to do?

We expect that you will be in this research study until the end of your pregnancy and that this will include a minimum treatment period with mirtazapine for 3 weeks and a maximum of through the end of your pregnancy. After 3 weeks of study drug treatment, you will discuss with the study team whether you prefer to continue mirtazapine during the remainder of your pregnancy to control sNVP. Information about your pregnancy and newborn will be collected from your medical record. Therefore, we expect that data will be collected for the duration of your pregnancy.

You will be given mirtazapine and asked to come for 3 weekly visits during the initial 3-week treatment period. If you continue taking the drug after 3 weeks, you will have study visits every four weeks until you stop taking the drug or until you deliver your baby.

More detailed information about the study procedures can be found under the section: **What happens if I say "Yes, I want to be in this research"?**

Is there any way being in this study could be bad for me?

As is true for any medication used to treat severe nausea and vomiting in pregnancy, both maternal and fetal serious side effects are possible and must be balanced against the effects of sNVP.

More detailed information about the risks of this study can be found under **"Is there any way being in this study could be bad for me? (Detailed Risks)"**

Will being in this study help me in any way?

We cannot promise any benefits to you or others from your taking part in this research. However, the results of this study will be used to determine whether a randomized clinical trial to determine the effectiveness of mirtazapine to treat sNVP in a large group of pregnant persons who have not responded to standard medications is appropriate.

What happens if I do not want to be in this research?

Participation in research is completely voluntary. You decide whether to participate. If you choose to not participate, there will be no penalty to you or loss of benefit to which you are entitled. Your alternative to participating in this research study is to not participate and continue care with your obstetrical team.

Detailed Information:
The rest of this document includes detailed information about this study (in addition to the information listed above).

Whom can I talk to?

If you have questions, concerns, or complaints, or think the research has hurt you, talk to the research team at

Katherine L. Wisner, M.D., M.S., Principal Investigator,
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Phone: 312-695-8441
Email: katherine.wisner@northwestern.edu

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This research has been reviewed and approved by an Institutional Review Board (IRB). You may talk to them at (312) 503-9338 or irb@northwestern.edu if:

- Your questions, concerns, or complaints are not being answered by the research team.
- You cannot reach the research team.
- You want to talk to someone besides the research team.
- You have questions about your rights as a research participant.
- You want to get information or provide input about this research.

How many people will be studied?

We expect about 25 pregnant persons will be in this research study.

What happens if I say "Yes, I want to be in this research"?

Locations: The initial visit will take place at the Asher Center for the Study and Treatment of Depressive Disorders (676 North St. Clair Street, Suite 1000), or in Prentice Women's Hospital's outpatient or inpatient units. The principal investigator and research staff may also evaluate you when you present to the obstetrical Triage at Prentice Women's Hospital with sNVP.

The blood samples will be collected at the Diagnostic Testing Center (DTC) (Northwestern Memorial Hospital, 2nd Floor of the Arkes Pavilion, 676 N St Clair), in the Asher Center laboratory, or in Prentice Women's Hospital.

Initial Visit (approximately 2 hours)

- This visit occurs once. The purpose of this visit is to determine whether you qualify to continue in the study. If at this initial visit you do not qualify, we will provide an explanation as to why you are unable to participate.
- Obtain information about you, such as age, race, marital status, and medical conditions, and the medications you have used to treat sNVP and other conditions
- Answer questions about alcohol and cigarette use

- Answer questions about your nausea and vomiting symptoms, frequency and severity
- Investigators will review the results of your bloodwork and ECG before you are enrolled in the study.
- Your blood pressure, weight, and height will be recorded.
- If you are eligible and you consent, you will be given mirtazapine and a dose schedule. You will begin taking a dose of 15 mg of mirtazapine in the evening as a dissolvable tablet by mouth.

Mirtazapine Treatment – 3 weeks

- After 1 week of treatment - Blood samples will be collected to check your thyroid function (5 mL), test genes that control how quickly your liver breaks down mirtazapine and other medications, and may be associated with increased risk for sNVP (5 mL). Your blood concentration of mirtazapine (5 mL) will also be obtained (total of 15 mL, or about Tablespoon). If you are tolerating mirtazapine but continue to have nausea and vomiting, you will receive a dose of 30 mg of mirtazapine. If the mirtazapine was tolerable and effective, you will continue this dose.
- After 2 weeks of treatment - A blood sample will be collected to determine the concentration of mirtazapine (5 mL, or about 1 teaspoon). If you are tolerating mirtazapine but continue to have symptoms of nausea and vomiting, you will receive a dose of 45 mg of mirtazapine. If the mirtazapine was tolerable and effective, you will continue this dose.
- After 3 weeks of treatment - A blood sample will be collected to determine the concentration of mirtazapine (5 mL, approximately 1 teaspoon). If the mirtazapine was tolerable and effective, you can continue to take the medication, or you can decide to taper and stop it (see Optional Continuation of Treatment below).

Your blood will be drawn at exactly the same time of day for the following reasons:

- As your body metabolizes and gets rid of the mirtazapine throughout the course of the day, the concentration of mirtazapine in your body does not stay the same, it decreases.
- We want to compare the concentrations at the different doses throughout the course of this study. The concentration of mirtazapine in your body changes across the course of the day, so we need to collect the samples at the same time to be able to compare them.

Optional Continuation of Treatment

At the end of the 3-week trial, after consultation with the study team, you will be asked whether you prefer to continue taking mirtazapine to control sNVP. If you choose to continue treatment, mirtazapine will be prescribed at the dose you were taking at the end of the 3-week trial. Mirtazapine will be provided in pill form for this part of the study. The length of treatment will be decided by you and the study physician based upon your response and comfort with stopping the drug. For pregnant persons who continue to be treated with mirtazapine until delivery, monthly blood samples will be obtained at the same time of day as in the initial 3-week trial. If you take mirtazapine until you deliver your baby, maternal and cord blood will be taken to measure plasma mirtazapine concentration. No blood will be taken from your baby.

Participants who choose to stop treatment after 3 weeks will gradually decrease the dose to reduce the risk of sNVP recurrence and symptoms related to discontinuation of the study drug. The dose will be reduced in reverse of the way the dose was increased in the 3-week trial. For example, if you are taking 45 mg at the end of week 3, you will begin a weekly decrease in dose

from 45 to 30 to 15 to 7.5 mg to 0 mg. If you relapse or have discontinuation symptoms, the previous effective dose will be given. You may attempt to taper again later with the same approach.

What are my responsibilities if I take part in this research?

If you take part in this research, you will be responsible for:

- Answering questions regarding age, race, marital status, medical conditions, alcohol and cigarette use, your nausea and vomiting symptoms, frequency and severity
- Filling out questionnaires and a medication record at each assessment
- Completing 3 questions from the PUQE questionnaire about your nausea and vomiting symptoms online every day during the 3-week trial. The research coordinator will send you this questionnaire to your email address every day.
- Taking the mirtazapine every evening during this research study
- Coming in for weekly visits to collect blood samples, answer questionnaires, and measure weight and blood pressure

We expect that you will be taking mirtazapine for 3 weeks, and you may choose to continue the medication. For all participants, information on pregnancy and infant outcomes will be collected from the medical chart for delivery. Therefore, we expect that you will be in this research study for the duration of your pregnancy.

What happens if I say "Yes", but I change my mind later?

You can leave the research study at any time and it will not be held against you.

If you decide to leave the study, contact the investigator so that she is aware you no longer want to be contacted for follow-up. If you stop being in the study, your collected data will not be removed from the study database.

Choosing not to be in this study or to stop being in this study will not result in any punishment to you or loss of benefits to which you are entitled. Specifically, if you choose not to be in this study, it will not negatively affect your right to any present or future medical treatment.

If you take back your consent to use any blood or tissue taken for the study, the Principal Investigator will make sure that these samples are destroyed or will make sure that all information that could identify you is removed from these samples.

Detailed Risks: Is there any way being in this study could be bad for me?

Your participation in this study includes the following risks, some of which may be serious and/or life threatening to you and/or your baby:

Side Effects of Mirtazapine: The following side effects have been reported for mirtazapine:

- Severe skin reaction [may include rash, fever, swollen glands, and other organ effects such as liver, kidney, lung and heart]
- Suicidal thoughts and behaviors (1.9% of patients)
- Reduction in white blood cells counts [symptoms include fever, sore throat, flu-like symptoms, chills, mouth or nose sores, and infections] (0.07% of patients)
- Serotonin syndrome [agitation, confusion, fast heartbeat, dizziness, flushing, tremor, stiff muscles, muscle twitching, seizures, hallucinations, coma, blood pressure changes, sweating, high body temperature, loss of coordination, or nausea, vomiting, diarrhea]

- Trouble with vision [eye pain, changes in your vision, swelling or redness in or around the eye]
- Changes in heart rhythm [such as in increase in rate by 3 beats per minute, or palpitations] (an ECG will be administered prior to starting mirtazapine)
- Increased appetite and weight gain (17% of patients)
- Fatigue (54% of patients)
- Mania or hypomania [greatly increased energy, racing thoughts, unusually grand ideas, talking more or faster than usual, severe trouble sleeping, reckless behavior, or excessive happiness or irritability] (0.2% of patients)
- Seizures (0.03% of patients)
- Elevated blood cholesterol and triglycerides which may lead to hardening of the arteries with long-term use, which is not expected during the period of pregnancy (15% of patients)
- Lowering of sodium in the blood [may include headache, memory changes, weakness and unsteadiness, difficulty concentrating, and confusion]
- Liver enzyme increases which may represent liver damage (2% of patients)
- Discontinuation Syndrome (dizziness, nausea, headache, tingling sensation in the skin) if the medication is stopped abruptly (a gradual reduction in the dosage, rather than an abrupt stop, is recommended to limit dizziness, agitation, fatigue, or other symptoms)

Blood Draws: The risks are pain and/or discomfort with needle insertion, bruising and risk of infection at the site of the blood draw and fainting.

Questionnaires: Some of the questions asked may be upsetting or you may feel uncomfortable answering them. If you do not wish to answer a question, you do not have to answer it.

This study involves the use of your identifiable, personal information and there is a chance that a loss of confidentiality could occur. The researchers have procedures in place to reduce the possibility of this happening. Your data will be stored with a secure, online data base called REDCap, and any hard copy paper files will be stored in a double locked room. Biological samples will not be labeled with your name or other identifying information. See the section below titled: "**What happens to the information collected for the research?".**

What do I need to know about reproductive health and/or sexual activity if I am in this study?

Pregnant and Lactating Persons

You are eligible for this study because you have sNVP after being treated with at least two antinauseant drugs. This study involves treatment with mirtazapine.

Because mirtazapine is FDA approved for the treatment of depression, information about dose is available, and the tolerability in persons with depression has been studied. However, the acceptability, tolerability, dosing range and best dose for pregnant persons with sNVP has not been established.

In the relatively small sample (about 500) of pregnant persons whose reproductive outcomes following mirtazapine exposure have been published, the rate of birth defects associated with taking mirtazapine is the same as in the general population of pregnant persons who have not taken mirtazapine (up to 5 out of every 100 pregnant persons; up to 5%). The average birth weight of babies whose mothers were exposed to mirtazapine was within normal limits. The rate

of preterm birth was higher for newborns exposed to mirtazapine (9 out of every 100 newborns; 9%) compared to almost 8 out of every 100 newborns (7.7%) not exposed to mirtazapine. In the majority of large-scale studies of individuals who have taken antidepressant medications similar to mirtazapine, neither birth defects nor developmental problems have been associated with the use of these drugs. When pregnant persons are treated with similar antidepressant drugs, their babies may need support for breathing at birth (about 13% of exposed newborns) compared to unexposed newborns (4.2%). Newborns are also twice as likely to be admitted to a neonatal intensive care unit admission. These problems are brief. The newborns went home with their mothers and there was no difference in the length of hospital stay in exposed compared to unexposed newborns. Signs of restlessness, rigidity and tremor may occur in newborns. These are usually brief and disappear gradually over the first two weeks after birth.

Hypertensive disorders in pregnancy, including preeclampsia (a pregnancy complication characterized by high blood pressure) and postpartum hemorrhage are not associated with mirtazapine exposure. Exposure to antidepressant drugs during fetal life is not associated with autism or attention deficit disorder in the child.

Drug treatment during pregnancy is associated with benefits and harms that must be balanced by the pregnant woman and her medical care professionals. All commonly used drugs for sNVP have benefits and harms that must be balanced against the risks associated with sNVP. In this study, mirtazapine is prescribed after two more commonly used medications have not been effective to determine if mirtazapine may be more or less acceptable and tolerable.

You do not need to change your sexual activity for this study.

Will it cost me anything to participate in this research study?

Taking part in this research study will not lead to any costs to you.

You and your insurance company will be charged for the health care services that you would ordinarily be responsible to pay. In some cases, insurance will not pay for services ordinarily covered because these services were performed in a research study. You should check with your insurance to see what services will be covered by your insurance and what you will be responsible to pay.

Will being in this study help me in any way?

We cannot promise any benefits to you or others from your taking part in this research. However, possible benefits include support from an experienced research team and improvement in sNVP symptoms.

What happens to the information collected for the research?

Efforts will be made to limit the use and disclosure of your personal information, including research study and medical records, to people who have a need to review this information. We cannot promise complete secrecy. Organizations that may inspect and copy your information include the IRB and other representatives of this institution. If we learn about current or ongoing child [or elder] abuse or neglect, we may be required or permitted by law or policy to report this information to authorities.

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. This means that the researchers cannot release or use information, documents, or samples that may identify you in any action or suit unless you say it is okay. They also cannot provide them

as evidence unless you have agreed. This protection includes federal, state, or local civil, criminal, administrative, legislative, or other proceedings. An example would be a court subpoena.

There are some important things that you need to know. The Certificate does not stop reporting that federal, state or local laws require. Some examples are laws that require reporting of child or elder abuse, some communicable diseases, and threats to harm yourself or others. The Certificate cannot be used to stop a sponsoring United States federal or state government agency from checking records or evaluating programs. The Certificate does not stop disclosures required by the federal Food and Drug Administration (FDA). The Certificate also does not prevent your information from being used for other research if allowed by federal regulations.

Researchers may release information about you when you say it is okay. For example, you may give them permission to release information to insurers, medical providers or any other persons not connected with the research. The Certificate of Confidentiality does not stop you from willingly releasing information about your involvement in this research. It also does not prevent you from having access to your own information.

The sponsor, monitors, auditors, the IRB, the Northwestern University Office for Research Integrity, the US Office of Research Integrity (ORI), the US Office for the Protection of Human Research Protections (OHRP), and the US Food and Drug Administration (FDA) may be granted direct access to your medical records to conduct and oversee the research. By signing this document, you are authorizing this access. We may publish the results of this research. However, we will keep your name and other identifying information confidential.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Data Sharing

De-identified data from this study may be shared with the research community at large to advance science and health. We will remove or code any personal information that could identify you before files are shared with other researchers to ensure that, by current scientific standards and known methods, no one will be able to identify you from the information we share. Despite these measures, we cannot guarantee anonymity of your personal data.

Can I be removed from the research without my OK?

The person in charge of the research study or the sponsor can remove you from the research study without your approval. Possible reasons for removal include: 1) refusal to follow medication protocol, and/or 2) refusal to answer study questionnaires.

We will tell you about any new information that may affect your health, welfare, or choice to stay in the research.

What else do I need to know?

If you become ill or are injured as a result of this study (medications, devices or procedures), you should seek medical treatment through your doctor or treatment center of choice. You should promptly tell the study doctor about any illness or injury.

The hospital [university, researchers] will not pay for medical care required because of a bad outcome resulting from your participation in this research study. This does not keep you from seeking to be paid back for care required because of a bad outcome.

If you agree to take part in this research study, we will pay you $35 for each assessment completed with a maximum of 10 sessions ($350), your time and effort.

The Accounting Services at Northwestern University will be given your name, address, and Social Security Number in order to issue the checks for your study participation. Study payments are considered taxable income and reportable to the IRS. A Form 1099 will be sent to you if your total payments are $600 or more in a calendar year.

HIPAA Authorization

We are committed to respect your privacy and to keep your personal information confidential. When choosing to take part in this study, you are giving us the permission to use your personal health information that includes health information in your medical records and information that can identify you. For example, personal health information may include your name, address, phone number or social security number. Your health information we may collect and use for this research includes:

- Results of physical examinations
- Medical history
- Laboratory and other testing (such as EKG, ultrasound studies)
- Health information indicating or relating to sNVP as well questionnaires
- Records about any medication or medical conditions
- Substance abuse information: use of cigarettes, alcohol, and illicit drugs, including but not limited to, marijuana, cocaine, heroin, methamphetamines, ecstasy, and misuse of prescription drugs
- Mental Health information: diagnoses of mental health, treatment course, trajectory of mental health symptoms, psychiatric hospitalizations
- Genetic health information: analysis of DNA for genetic traits related to the metabolism of medications

You have the right to inspect and copy the mental health and developmental disabilities records that will be collected as part of this study.

During this study, you may be coming to a Northwestern Memorial HealthCare/Northwestern Medicine entity for research appointments or to get clinical services, such as lab tests, needed for the study. When that happens, you will be scheduled for these services through the NMHC computer system. When a clinical exam or lab is done by NMHC or one of its employees for the purpose of this research study, that information will be kept in both NMHC's clinical records and in the study records.

The following clinical providers may give the researchers information about you: all current and previous health care providers, including but not limited to the Shirley Ryan AbilityLab (SRALAB) and Northwestern Memorial HealthCare/Northwestern Medicine entities and its current and future affiliates.

Once we have the health information listed above, we may share some of this information with the following offices or entities outside of Northwestern University and its clinical partners (or affiliates): the Northwestern University Institutional Review Board Office and Office for Research Integrity; the US Office of Research Integrity; the US Office for Human Research Protections; the US Food and Drug Administration.

Any research information shared with outside entities will not contain your name, address, telephone or social security number or any other personal identifier unless disclosure of the identifier is necessary for review by such parties or is required by law or University policy [except that such information may be viewed by the Study sponsor and its partners or contractors at the Principal Investigator's office].

The following entities may receive your health information:

- Authorized members of the Northwestern University workforce, who may need to see your information, such as administrative staff members from the Office for Research, Office for Research Integrity and members of the Institutional Review Board.
- Clinical affiliates, including but not limited to the Shirley Ryan AbilityLab (SRALAB), Northwestern Memorial HealthCare, and the Ann & Robert H. Lurie Children's Hospital of Chicago (Lurie Children's). Your participation in this clinical trial may be tracked in an electronic database and may be seen by investigators running other trials that you are enrolled in and by your healthcare providers.
- Clinical affiliates, including but not limited to Northwestern Memorial HealthCare, for purposes including, but not limited to, the affiliate's provision of care to you and/or the affiliate's scheduling of appointments and/or billing activities.
- Other University research centers and University contractors who are also working on the study,
- Study monitors and auditors who make sure that the study is being done properly,
- Government agencies and public health authorities, such as the Food and Drug Administration (FDA) and the Department of Health and Human Services (DHHS).

Those persons who get your health information may not be required by Federal privacy laws (such as the Privacy Rule) to protect it. Some of those persons may be able to share your information with others without your separate permission.

Also, Federal law/42 CFR Part 2 prohibits unauthorized disclosure of these records.

The results of this study may also be used for teaching, publications, or for presentation at scientific meetings.

This consent expires on 03/31/2030. After this date, Northwestern University may not gather new information about you, use or disclose your personal health information collected in this study for any purpose other than the research study described in this consent unless Northwestern University obtains permission to do so from you. Illinois State Law permits use and disclosure of your mental health information only to the extent specified in this document.

Although you may revoke consent to participation in this research at any time and in any format, you must revoke authorization for use or disclosure of your health information in writing. To revoke your authorization, write to:

Dr. Katherine L. Wisner
Asher Center for the Study and Treatment of Depressive Disorders
676 N. St. Clair Street, Suite 1000
Chicago, IL 60611

You do not have to authorize the use or disclosure of your health information; however, you will not be allowed to take part in this research study. If you do not authorize the use or disclosure of your health information, it will not affect your treatment by health care providers, or the payment or enrollment in any health plans, or affect your eligibility for benefits.

A copy of this signed consent document, information about this study, and the results of any test or procedure done may be included in your medical records and may be seen by your insurance company.

Optional Elements:

The following research activities are optional, meaning that you do not have to agree to them in order to participate in the research study. Please indicate your willingness to participate in these optional activities by placing your initials next to each activity.

I agree	I disagree	
_____	_____	The researcher may contact me in the future to see whether I am interested in participating in other research studies by the Principal Investigator of this study.
_____	_____	The researcher may retain any leftover blood or tissue samples taken during the study. These samples may be used for other research not related to this study. These samples will be kept in non-identifiable form, meaning that there will be no information associated with the blood or samples that will allow anyone to identify that it is me. An example of use of these de-identified samples is placement in the National Institute of Child Health and Human Development Data and Specimen Hub to permit research use by other investigators.

Your signature documents your permission to take part in this research. You will be provided a copy of this signed document.

_____ _____

Signature of Participant Date

_____

Printed Name of Participant

_____ _____

Signature of Person Obtaining Consent Date

_____

Printed Name of Person Obtaining Consent

I attest that the identity of the individual giving consent has been verified.

_____ _____

Signature of Witness to Consent Process Date

_____

Printed Name of Person Witnessing Consent Process