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

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STUDY SUMMARY:

Investigational Agent(s) (Drugs or Devices)	Mirtazapine
IND / IDE / HDE #	N/A
Indicate Special Population(s)	☐ Children ☐ Children who are wards of the state ☐ Adults Unable to Consent ☐ Cognitively Impaired Adults ☐ Neonates of Uncertain Viability ☒ Pregnant Women ☐ Prisoners (or other detained/paroled individuals) ☐ Students/Employees
Sample Size	25
Funding Source	National Institute of Child Health and Human Development (NICHD)

Indicate the type of consent to be obtained	☒Written ☐Verbal/Waiver of Documentation of Informed Consent ☐Waiver of HIPAA Authorization ☐Waiver/Alteration of Consent Process
Site	☒ Lead Site (Single Site Research Study) ☐ Data Coordinating Center (DCC)
Research Related Radiation Exposure	☐Yes ☒ No
DSMB / DMC / IDMC	☒Yes ☐No

OBJECTIVES

Translational Research in Maternal and Pediatric Pharmacology and Therapeutics (PAR-20-299) supports research to "enhance the usage of existing drugs or drug repurposing for safer and more effective treatment for pregnant women" for "the early and conceptual stages of these projects. The primary objective of this proposal is to conduct an early Phase 2 clinical trial to determine the acceptability, dosing, tolerability and safety of mirtazapine for severe nausea and vomiting of pregnancy (sNVP) that is not adequately responsive to current standard treatments. This plan mirrors clinical practice since commonly prescribed antiemetic/ antinauseant drugs will be tested for efficacy before treating with mirtazapine.

Mirtazapine is a promising drug to repurpose for sNVP. It has potent anti-emetic properties and is available as an oral disintegrating formulation. It is used off-label to treat NV during cancer chemotherapy,[1] prevent post-surgical nausea and vomiting [2] and for gastroparesis.[3] It is marketed as the serotonin-norepinephrine reuptake inhibitor antidepressant Remeron®. Mirtazapine has multiple receptor effects beyond those involved in reducing depressive symptoms. In cancer and chemotherapy patients, it produces rapid resolution of nausea and vomiting by blocking physiologic inputs that coordinate emesis. It is hypothesized that repurposing mirtazapine for obstetric use overcomes the challenges of traditional pathways to develop new agents because its pharmacokinetics, safety and dosing have been established for general populations of patients[4] and exposure data are available because it is prescribed to pregnant persons with depression.

Up to 80% of pregnant persons experience NVP that impairs function and reduces quality of life.[5] Although NVP often resolves by mid-gestation[6], symptoms persist into the third trimester in 15--20% of pregnant persons[7]. A severe form, hyperemesis gravidarum (HG), affects 0.3-3% of pregnant persons[6,8] and is the most common reason for hospitalization in the first 20 weeks of pregnancy.[9] HG is characterized by intractable vomiting, dehydration, electrolyte abnormalities and weight loss that may require parenteral nutrition. HG is associated with preterm birth, small-for–gestational-age newborns,[10] and terminations of desired pregnancies in 14.4% of affected pregnant persons.[11]

Severe NVP (sNVP), defined as 5% weight loss or continuing beyond 20 weeks gestation, is associated with neurodevelopmental deficits and altered brain structure in offspring as documented by neuroimaging.[12] This definition is an entry criterion for the proposed project, which includes the most severely affected 15% of pregnant persons with NVP and HG.[12] The authors of two Cochrane Analyses and a systematic review reported that only low-quality evidence is available to direct treatment.[13-15] The NICHD report from the Task Force on Research Specific to Pregnant Women and Lactating Women[16] stated that the drug pipeline for conditions specific to pregnancy is "minimal at best" and listed hyperemesis as an area of need for treatment research.

Rapid reduction of sNVP with mirtazapine treatment has been reported in case series of pregnant persons[17,18] who have not responded to other medications. These cases include mothers who requested terminations of desired pregnancies due to inability to tolerate sNVP. Reproductive outcomes for mirtazapine do not indicate an elevated risk for birth defects, although the number studied is relatively small (≈500). Medications commonly used to treat sNVP are first-line drugs; however, a substantial number of pregnant persons do not respond adequately and novel therapeutics are urgently needed.

Mirtazapine is a compelling candidate to expand therapeutic options for sNVP. This exploratory/developmental phase 2 project is designed to determine whether a Phase 3 randomized controlled trial (RCT) is warranted by establishing the acceptability, tolerability, dosing and safety of mirtazapine for sNVP. Mirtazapine is not approved by the FDA for treatment of nausea and vomiting of pregnancy (NVP); therefore, in this clinical trial, mirtazapine is an investigational product.

We will conduct a 3-week open trial of 25 pregnant persons who have not responded to at least two antiemetic drugs. We hypothesize that mirtazapine will exhibit satisfactory acceptability, tolerability and safety in pregnant persons with sNVP. After the initial trial, a continuation period or a mirtazapine tapering regimen with monitoring will be offered. The aims of the trial are:

1. Determine the acceptability of mirtazapine for sNVP that does not respond to two standard drugs.
2. Define the tolerability and safety of an escalating 3-week mirtazapine dose regimen.
3. Assess the duration of treatment required following the initial 3-week trial and the adequacy of a tapering regimen for persons who discontinue mirtazapine.
4. Determine pregnancy and neonatal outcomes for all enrolled persons. We will collect data on delivery outcomes only with the peripartum events scale
5. Explore the relationship of study drug dose and plasma concentration with side effects and pharmacogenetics by obtaining weekly plasma.

This application was driven by the commitment of our multidisciplinary team to improve pharmacotherapy for sNVP as reviewed in our paper on this topic.[18] We will obtain critical data to determine whether a Phase 3 RCT is warranted and to inform its design. The subsequent RCT will have the power to compare mirtazapine to placebo and adjust for the effects of co-prescribed drugs before and during the trial. This study also will inform the covariate selection and sample size estimation for the definitive RCT.

BACKGROUND

Although mild nausea and vomiting in pregnancy has not been linked to poor maternal and neonatal outcomes, sNVP is associated with preeclampsia, thrombosis, preterm birth, cesarean section and small- for-gestational-age neonates. Adding to these established risks are recent data from the NIH-funded, 21-site ABCD Study, a long-term study of fetal exposures, brain development and child health in the USA. The rate of offspring exposure to severe sNVP (defined as maternal weight loss and/or continuation beyond 6 months gestation) was 13.98%, which is consistent with the incidence rate of 10–15% in the general population of pregnant persons. The ABCD investigators reported that sNVP-exposed offspring had decreased brain cortical volume which mediated the relationship between sNVP and developmental deficits in language, learning, and motor skills. These structural neurological changes and developmental problems persisted through 9–11 years of age. Authors of another recent retrospective cohort study (N=469,789 mother-child pairs) reported that offspring exposed to sNVP had a 3-fold increase in risk for Autism Spectrum Disorder. These findings highlight the significance and potential short- and long-term benefits of treatment for sNVP.

Despite the frequency and complications of sNVP, only low-quality evidence is available to direct treatment. This exploratory/developmental Clinical Trial Planning Grant is a Phase 2 study that will provide data on the acceptability, dose regimen, tolerability and safety of mirtazapine (Remeron®) for the treatment of sNVP that has not responded to at least two standard medications. We will determine whether a larger randomized controlled trial to evaluate

mirtazapine's efficacy for sNVP is warranted. An FDA application for an IND has been submitted and a DSMB has been constituted.

Mirtazapine is prescribed for nausea and vomiting during cancer chemotherapy and pre-operatively to prevent post-surgical nausea and vomiting. During pregnancy, rapid reduction of nausea and vomiting following mirtazapine treatment has been reported in case series of persons who have not responded to other medications. Mirtazapine impacts the serotonin receptor (similar to the anti-emetic drug ondansetron) as well as three additional receptors involved in the physiologic cascade that results in nausea and emesis. Reproductive outcome data for mirtazapine do not indicate an increased risk for birth defects, although the number of persons studied is relatively small (≈500). Additionally, pharmacogenetic factors that affect mirtazapine plasma concentrations and thereby affect its tolerability and safety will be considered in the proposed project.

Mirtazapine is a compelling candidate repurpose to expand therapeutic options for this disabling disorder. A total of 26 cases in of mirtazapine for sNVP have been published.[17,18] These people did not respond to first-line drugs for sNVP (doxylamine/pyridoxine, ondansetron, metoclopramide, dimenhydrinate and promethazine). The mirtazapine dose ranged from 15-45 mg/day, with a modal dose of 30 mg/day. Response was rapid, with reduction of nausea on the first day of treatment.[28] In a recently published series of seven cases,[29] the mean gestational age at initiation was 11.6 weeks (range 7–14). The mean treatment duration was 9.1 weeks (range 4–24). Mirtazapine's antiemetic properties derive from multiple effects on the cascade of events that culminate in emesis[30 31] which do not depend on its antidepressant effects. Mirtazapine adds therapeutic value by improving sleep and appetite. These actions of mirtazapine do not depend upon the presence of an underlying psychiatric disorder; however, people with unremitting sNVP often have depressive and anxiety symptoms secondary to stress and functional impairment.

Mirtazapine provides nausea control with once-daily dosing[32] and is available as an orally disintegrating tablet. Ondansetron, prochlorperazine and metoclopramide require multiple daily doses. In patients with cancer, mirtazapine (15-30 mg) rapidly improved nausea, appetite, insomnia and overall function.[33] Mirtazapine also is effective in preventing post-anesthesia NV. People scheduled for gynecological surgery were randomly assigned to mirtazapine 30 mg plus dexamethasone vs. dexamethasone alone. The rate of post-operative NV was 20% vs. 50%, respectively ($P< 0.01$).[2] In a meta-analysis, mirtazapine significantly reduced post-operative NV vs. placebo (risk ratio=0.44; 95% CI 0.32--0.62).[34] For the first time, mirtazapine was identified as an option for sNVP by obstetricians in a review published in 2020.[35]

Mirtazapine is well-absorbed with or without food and peak plasma concentrations are reached in 1 to 2 hours. Hepatic cytochrome P450 (CYP) 2D6 and 1A2 enzymes contribute to the formation of the 8-hydroxy metabolite, which has 10% of the parent drug's activity. CYP3A4 is responsible for subsequent metabolism. Mirtazapine is a weak inhibitor of CYP450 enzymes and is unlikely to result in significant drug interactions.[30]

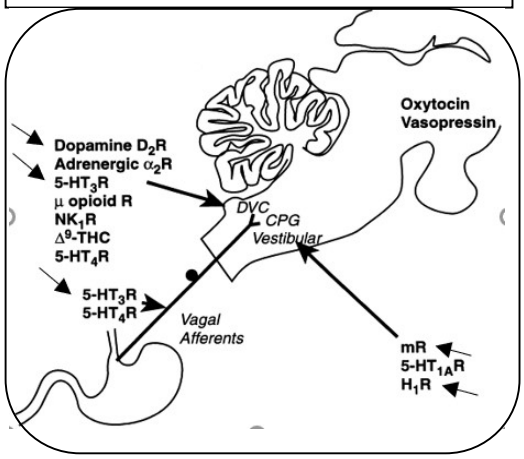
Variability in pharmacokinetics is associated with variation in genes encoding drug-metabolizing enzymes involved in drug elimination or biotransformation. Mirtazapine is primarily metabolized by CYP2D6, which has important genetic polymorphisms[36,37] that influence drug clearance and plasma concentrations. The activity of CYP2D6 varies across pregnancy by genotype. CYP2D6 substrate drug levels decline in rapid and extensive metabolizers and increase in intermediate and poor metabolizers.[38] Genotypes that determine the activities of CYP2D6, and minor pathways 3A4/5 and 1A2, will be explored for associations with mirtazapine plasma

concentrations. Genotypes that increase risk for HG will also be determined. In a genome-wide association study for binary (HG) and ordinal (severity of nausea and vomiting) phenotypes of pregnancy complications, two loci, chr19p13.11 and chr4q12, were genome-wide significant ($p < 5 \times 10-8$) and replicated in an independent cohort.[39] The genes implicated at these two loci are GDF15 and IGFBP7 respectively, both known to be involved in placentation, appetite, and cachexia.

These analyses will be exploratory due to the limited sample size achievable in an R21 study.

Physiology of Emesis. Vomiting is a complex neuromuscular cascade of events coordinated by the central and autonomic nervous systems.[40] Neurons that orchestrate emesis are located throughout the medulla and organized by a central pattern generator (CPG) that coordinates the sequence of events leading to emesis. The CPG receives input from the area postrema and abdominal vagal afferents. Anti-emetic drugs antagonize neurotransmitters (Figure 1[40]) that orchestrate the progression of nausea to vomiting. Commonly used anti-emetics antagonize the following receptors: muscarinic acetylcholine (mR), dopamine (D_2), serotonin (5-HT_3), histamine (H_1) and neurokinin (NK_1). Both ondansetron and mirtazapine are serotonin ($5HT_3$) receptor antagonists[40] which prevent vagal afferent signaling to the hindbrain; however, mirtazapine offers three additional sites of action to impede the emetic process (Figure 1[40]): 1) histamine (H_1R), which has input directly to the vomiting center; 2) muscarinic (mR) which also has input directly into the vomiting center; and 3) central presynaptic adrenergic α_2 (adrenergic α_2R), which activates emesis.

Figure 1. Neurotransmitters involved in emesis and sites of action: **α_2R**=adrenergic α2-receptor; CPG=central pattern generator; D_2R=dopamine 2-receptor; Δ^9-THC=Δ9-tetra-hydrocannabinol; DVC=dorsal vagal complex; **5-HT**=serotonin; **H**=histamine; NK=neurokinin; **mR**=muscarinic; mirtazapine's action indicated by arrows at receptor sites that are bolded below and arrows are receptor site.



STUDY ENDPOINTS:

The primary outcome is the change in PUQE (Pregnancy Unique Quality of Emesis)[43] score. Secondary outcomes include: (1) Self-administered Comorbidity Questionnaire, (2) NIH PROMIS Global Health scale, (3) Patient Health Questionnaire-9 (depression scale), (4) Generalized Anxiety Disorder-7 scale, (5) Asberg Side Effects. Plasma will be obtained for quantitation of mirtazapine concentrations at each assessment during mirtazapine treatment. DNA will be obtained to explore whether pregnant persons who are most (or least) likely to benefit from treatment can be identified through pharmacogenetics.

STUDY INTERVENTION(S) / INVESTIGATIONAL AGENT(S):

Mirtazapine has potent anti-emetic properties and is available as an oral disintegrating formulation. It is used off-label to treat nausea and vomiting during cancer chemotherapy,[1] prevent post-surgical nausea and vomiting [2] and for gastroparesis.[3] It is marketed as the serotonin-norepinephrine reuptake inhibitor antidepressant Remeron®. Mirtazapine has multiple receptor effects beyond those involved in reducing depressive symptoms. It produces rapid resolution of nausea and vomiting by blocking physiologic inputs that coordinate emesis (Figure 1).

Mirtazapine is available as RemeronSolTab® (oral dissolvable) and tablet forms, which will be prescribed for the 3-week trial, and Remeron® tablets will be prescribed for the continuation phase. The acquisition and dispensing of the drugs will be under the organizational SOP for the Research Pharmacy at Northwestern Medicine.

An IND will be submitted along with the approved consent form following this review. The IND submission is included in the documents section of this application. The sponsor is the PI, Dr. Katherine L. Wisner.

PROCEDURES INVOLVED

Enrollment**.** The participant will provide demographic data (age, self-identified race and ethnicity), height and weight. All prescription, over-the-counter medications, alcohol and other drugs taken by the subject in the week prior to study entry and during labor and delivery will be recorded.

Blood pressure, heart rate, fetal heart rate, complete blood count, comprehensive metabolic screen (includes electrolytes and liver function studies) and urinalysis will be collected for assessment of sNVP. Any electrolyte abnormality will be corrected before the administration of mirtazapine. An ECG will be performed in all subjects at baseline, at the end of the initial three weeks, and monthly in subjects who continue mirtazapine beyond the three-week study. The ECG will be done to evaluate the emergence of QT prolongation, Torsades de Pointes, ventricular tachycardia, or other abnormal cardiac findings. Although maximum QTc interval, Tp-e interval and Tp-e/QT ratio are increased in the late pregnancy, they all remain within the normal ranges.[42]

Figure 2. PUQE Scoring System

In the last 24 hours, for how long have you felt nauseated or sick to your stomach?	Not at all (1)	1 hour or less (2)	2-3 hours (3)	4-6 hours (4)	More than 6 hours (5)
In the last 24 hours have your vomited or thrown up?	7 or more times (5)	5-6 times (4)	3-4 times (3)	1-2 times (2)	I did not throw up (1)
In the last 24 hours how many times have you had retching or dry heaves without bringing anything up?	No time (1)	1-2 times (2)	3-4 times (3)	5-6 times (4)	7 or more times (5)
PUQE-24 Score: Mild < 6; Moderate = 7–12; Severe = 13–15					

sNVP Assessment. The Pregnancy Unique Quality of Emesis PUQE-24)(Figure 2)[43] was used in studies submitted for FDA approval of Diclegis® (doxylamine/ pyridoxine).[44] Subjects will record their PUQE score daily (for prior 24 hours) to track symptom change in a secure on-line REDCap system.

Participants. Subjects with clinically significant NVP will be recruited. An initial score of 10 or more (high moderate/severe NVP) on the PUQE[43] scale is required. We include the criterion from the study[12] that showed the association of sNVP with developmental deficits (with weight loss, defined as 5% loss from pre-pregnancy). Pregnant persons will be recruited from in- and out-patient practices and the Obstetrical Triage Service, where Co-I's Drs. Catherine Stika and Melissa Goslawski provide care, and from our academic obstetrical practices. Upon referral, a research coordinator will contact the participant's obstetrician, and meet with the participant to review eligibility criteria, the study procedures, and obtain written consent.

Trial Protocol Overview (Figure 3).

Figure 3: Data Collection and Measures: Acute Treatment

Intake	Week 1, Mirtazapine ODT dose = 15 mg							Week 2, Mirtazapine ODT dose = 30 mg							Week 3, Mirtazapine ODT dose = 45 mg						
Days	1	2	3	4	5	6	**7 Visit**	8	9	10	11	12	13	**14 Visit**	15	16	17	18	19	20	**21 Visit**
GA, CQ; ECG; Medical Review																					**ECG**
							DNA, Plasma							Plasma							Plasma
Wt, Ht, BP							Wt; BP							Wt; BP							Wt; BP
PUQE GH	→	→	→	→	→	→	PUQE GH	→	→	→	→	→	→	PUQE GH	→	→	→	→	→	→	PUQE GH
PHQ-9 GAD-7 C-SSRS							PHQ-9 GAD-7 C-SSRS							PHQ-9 GAD-7 C-SSRS							PHQ-9 GAD-7 C-SSRS
ASE SS		ASE SS					ASE SS		ASE SS					ASE SS		ASE SS					ASE SS
Med Log	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→

Arrows in gray areas show daily completion of the PUQE. ODT=orally disintegrating tablet of mirtazapine; GA=Gestational age; CQ= Comorbidity Questionnaire; ECG=electrocardiogram; Wt=weight; Ht=height; BP=blood pressure; PUQE=Pregnancy Unique Quality of Emesis; GH=PROMIS Global Health; PHQ-9=Patient Health Questionnaire; GAD-7=Generalized Anxiety Disorder; C-SSRS=Columbia-Suicide Severity Rating Scale; ASE=Asberg Side Effects Rating Scale; SS=Serotonin Syndrome Screen; Med Log=Medication Log of prescribed and over the counter medications in the week prior to assessment.

Acceptability. The participant's medical status and drug treatment for sNVP will be reviewed by the study obstetrician. As in clinical practice, other anti-emetic drugs may be continued if desired by the participant and recommended by the obstetrician. The subject's decision to accept or decline will be recorded and she will be asked to provide the reason(s) for her decision. Pregnant persons who enroll will be given mirtazapine to begin treatment that evening or at a time recommended by the obstetrician. Intervention for pregnant persons who decline to participate will be coordinated by their obstetrical care professional.

Mirtazapine Regimen. The dose of mirtazapine for depression (15-45 mg/day) may not be the same as for achieving its antiemetic effect because the targeted receptors differ. We will begin with 15 mg, which is the lowest dose of the oral disintegrating tablet available. A telephone or telehealth follow-up for side effects will be conducted on day 2. Dose increases will occur weekly during the visits as depicted in Figure 3 unless the patient has prohibitive side effects or remission of sNVP. Remission is defined as a PUQE score of 3 (no symptoms) or 4 (1 hour or less of nausea without retching or vomiting). Side effects assessment will occur the day after each dose increase to evaluate tolerability. Reduction to the previous dose will occur if side effects are burdensome. Although the modal dose of mirtazapine from case reports is 30 mg, tolerability studies in persons with NVP have not been published. Steady-state plasma concentrations of mirtazapine occur within 5 days[32] and will be achieved across the week prior to dose escalations. Weekly plasma concentrations will be obtained to confirm absorption of mirtazapine and explore associations with side effects. Sampling will occur at a consistent time of day for each woman; ideally, the time will be in the late afternoon during the drug elimination phase as close to the trough concentration as feasible. Adverse events will be reviewed by the DSMB after every 5 subjects to determine whether a protocol or dosing change is warranted.

Both compliance with treatment and vomiting within an hour of the dose will be recorded in REDCap (along with the daily PUQE score) to evaluate these factors in the interpretation of

plasma concentrations. Mirtazapine treatment will continue unless the participant withdraws consent, experiences a limiting side effect or an obstetrician decides that the health risk to the patient compels discontinuation. At the end of the 3-week trial, subjects will be asked whether they prefer to continue mirtazapine, which will also serve as a measure of treatment satisfaction. Pregnant persons who choose to stop treatment will be given a taper regimen in reverse order of the dose escalation required for the 3-week trial. For example, if a patient is taking 45 mg at the end of week 3, she will begin a taper (by week) of 30 to 15 to 7.5 to 0 mg. If she relapses or has discontinuation symptoms, the previous effective dose will be given. She may attempt to taper again with the same approach. Participants who continue to be treated with mirtazapine in the continuation phase will be followed monthly throughout pregnancy unless they withdraw consent.

Maintenance Drug Treatment (Figure 4). For pregnant persons who choose to continue treatment, mirtazapine will be prescribed at the dose achieved at the end of the 3-week trial. The duration of treatment will be decided by the patient with a study obstetrician based upon her response and comfort with drug discontinuation. These data will be novel since no information on the duration of treatment with mirtazapine in persons with sNVP is available. For persons treated until delivery, maternal and cord blood will be obtained for plasma mirtazapine concentration measurement to evaluate placental transfer. If postpartum mirtazapine treatment is desired, it will be coordinated with our Collaborative Care Perinatal Services (COMPASS - the integrated mental health program in the Obstetrics department), or in the Asher Center in the Department of Psychiatry, which Dr. Wisner directs.

Figure 4: Data Collection: Continuation Treatment

Maintenance (every 4 weeks)	**Delivery**
Wt, Ht, BP	PES Maternal and umbilical cord blood
PUQE GH	
Plasma	
PHQ-9 GAD-7 C-SSRS	
ASE SS	
Medication Log	

PUQE=Pregnancy Unique Quality of Emesis;
PHQ-9=Patient Health Questionnaire;
GAD-7 =Generalized Anxiety Disorder;
C-SSRS=Columbia-Suicide Severity Rating Scale;
ASE=Asberg Side Effects;
SS=Screen for Serotonin Syndrome.
PES, Peripartum Events Scale.

Other Drug Exposure. All prescription and over-the-counter drugs, alcohol and substances used by subjects will be recorded at intake and weekly visits in the Medication Log. We also will record integrative therapies such as ginger and acupuncture. First-trimester use of cannabis for sNVP is increasing as the number of states declaring it legal rises.[45] In Illinois, cannabis use became legal on January 1, 2020. First-trimester cannabis use in pregnant persons with and without sNVP in the Kaiser-Permanente system was 11.1% and 5.8%, respectively.[45] Cannabinoid agonists such as tetrahydro-cannabinol, nabilone, dronabinol and medical marijuana have potent anti-nauseant and anti-emetic activity.[46] Cannabinoid hyperemesis syndrome, with cyclic severe nausea and vomiting relieved by hot baths, is a rare, paradoxical problem in individuals with long-term, high cannabis use.[47] However, both ACOG[48] and FDA[49] advise against the use of cannabis in pregnancy due to concerns about its impact on fetal neurodevelopment. The obstetrical evaluation of inclusion criteria will include cannabinoid hyperemesis syndrome in the differential diagnosis of HG.

Although we will not have the power to evaluate the effect of additional drug exposures in this preparatory R21 grant mechanism, we will assess the type and frequency of these exposures to inform the approach to statistical adjustment in the adequately powered Phase 3 randomized controlled trial.

Side Effect Assessment**.** Before mirtazapine treatment, a comprehensive metabolic profile and urinalysis will be obtained as standard of care. An ECG also will be performed. The degree of QT prolongation observed with both 45 mg (therapeutic) and 75 mg (supra-therapeutic) doses of mirtazapine was not clinically meaningful,[47] and QTc ≥500 msec was not observed among mirtazapine-treated patients.[50] The drug regimen to which mirtazapine may be added will be reviewed by Dr. Stika, a fellowship-trained clinical pharmacologist and obstetrician, for QTc prolongation risk prior to mirtazapine administration, or Dr. Goslawski, an attending obstetrician-gynecologist in Obstetrical Triage, or Dr. Wisner, the PI, a perinatal psychopharmacologist. Side effects will be assessed with the 14–item Asberg Side Effects (ASE)[51] scale, which was adapted by our team for SSRI-treated pregnant persons.[52,53] The ASE quantifies discomforts from mild to severe and a summary of overall distress. Serotonin hyper-stimulation will be reviewed with Hunter's Decision Rules for Diagnosis of Serotonin Toxicity (SS).[54] SS is characterized by tachycardia, diaphoresis, myoclonus and tremor.[55] The incidence of SS is infrequent (9/10,000) as shown in a retrospective cohort study[56]; however, ondansetron, metoclopramide and mirtazapine have been associated with SS during monotherapy and with other serotonergic drugs[57], although rarely in young persons.[58] Treatment includes drug discontinuation, benzodiazepines and the anti-serotonergic drug cyproheptadine.

Specific Instrument Use

Pregnancy Unique Quality of Emesis (PUQE) [43] **scale (Figure 2):** We will utilize the PUQE scale to capture the severity of nausea and vomiting in pregnancy based on three physical symptoms: nausea, vomiting, and retching over the previous 24 hours. A PUQE score of < 6 is considered mild, a score from 7-12 is moderate, and a score of 13+ is considered severe. This scale will be entered daily in REDCap directly by the participant.

Self-Administered Comorbidity Questionnaire (SCQ)[59]: The Comorbidity Questionnaire (CQ) assesses comorbid conditions in clinical and health services research. The questionnaire is self-administered, short, easily understood, and can be completed by individuals without any medical background. It also allows the subject to note the severity of each comorbid conditions and their perception of its impact on their function.

9-Item Patient Health Questionnaire (PHQ-9)[60]: The 9-Item Patient Health Questionnaire (PHQ-9) is a self-administered instrument based on the nine DSM-5 criteria listed under criterion A for Major Depressive Disorder. The questionnaire includes criteria based diagnosis of depressive symptoms, assists in identifying treatment goals, determining severity of symptoms, as well as guiding clinical intervention. When considering a diagnosis, the clinician will use clinical interviewing skills to determine whether the symptoms are causing clinically significant distress or impairment and those symptoms are not better explained or attributed to other conditions, such as substance use, medical conditions, or bereavement.

Generalized Anxiety Disorder Scale, 7-item (GAD-7)[61]: The Generalized Anxiety Scale is a 7-item self-report for symptoms consistent with the Diagnostic and Statistical Manual of Mental Disorders of generalized anxiety disorder.

Peripartum Events Scale (PES)[62]: The Peripartum Events Scale (PES) captures data from several categories in the birth record. The following categories of events are included: medical and obstetric risk factors, time in operating room, fetal monitoring, surgical complications, infant anthropometrics and outcome, NICU admission, and postpartum complications (such as infection, hemorrhage). Admission to the special care nursery will also

be noted. We have modified the original measure to align with current obstetrical practices. The PES will be completed for all enrolled participants.

PROMIS Global Health[63]: The PROMIS Global Health item scale assesses overall health. The global health items include ratings of the five primary PROMIS domains (physical function, fatigue, pain, emotional distress, social health) as well as perceptions of general health that cut across domains. Global items allow respondents to weigh together different aspects of health to arrive at a "bottom-line" indicator of their health. Similar global health items have been found predictive of future health care utilization and mortality. The PROMIS Global Health items include the most widely used single self-rated health item ("In general, would you say your health is . . ."). Previous research has shown that this item taps physical and mental health about equally but reflects physical health more than mental health among respondents at lower income levels. PROMIS Global Health items include specific ratings of physical health and mental health, as well as a rating of overall quality of life. The remaining items provide global ratings of physical function, fatigue, pain, emotional distress, and social health. The PROMIS Global Health items can be administered as individual items or combined to produce separate physical and mental health summary scores.

Columbia-Suicide Severity Rating Scale (C-SSRS)[77]: The Columbia-Suicide Severity Rating Scale (C-SSRS) is a questionnaire used for suicide assessment that was developed with NIMH support. The scale is evidence-supported and is part of a national and international public health initiative involving the assessment of suicidality. Suicidal ideation will be assessed at baseline, during, and 28 days after treatment cessation if there were any abnormalities during the trial.

DATA AND SPECIMEN BANKING

Subject plasma and blood for DNA extraction will be stored in a -70ºC freezer in the Northwestern Core Laboratory. All samples will be de-identified and labeled with the Northwestern Medicine clinical research unit ID, the subject ID, the date of collection, the type of sample collected (e.g. plasma), and the corresponding timepoint. Samples will not contain protected health information or any other type of identifiable information.
Mirtazapine Assay. Michael Avram, PhD, Scientific Advisor of the Clinical Pharmacology Core, will analyze plasma for concentrations of mirtazapine and desmethylmirtazapine by high-performance liquid chromatography-tandem mass spectrometry after sample preparation by solid-phase extraction (see letter of support).[64 65] the lower limit of quantitation will be 0.5 ng/mL. The linear range of the calibration curve will be 0.5--250 ng/mL. Accuracy will be within ±10% and precision 10% or less. Dr. Avram will model the serial concentration data for analyses to determine associations with variables (tolerability, side effects, pharmacogenetic data, adverse events) and whether remission is associated with mirtazapine concentration, with statistician Amy Yang, MS, and our team.

We will seek consent from our subjects to have their fully de-identified data and biospecimens included in the NICHD Data and Specimen Hub (DASH-https://dash.nichd.nih.gov/) for future studies.

SHARING RESULTS WITH PARTICIPANTS

No research data will be shared with participants. Because this is an open trial of a marketed drug, the participants will have direct knowledge of clinical information that may be useful in the

future, such as their response to mirtazapine, the efficacious dose, and the duration of treatment required.

STUDY TIMELINES

It will take approximately 18 months to enroll all study participants (Figure 5). We will evaluate subject flow and safety analyses in weekly research meetings, which will be conducted throughout the project.

Figure 5. Project Time Line

Year	Study Months	Study Tasks	Cum. Enroll
Pre-Award	10/21-02/22	Submit IRB and IND applications, finalize manual of operations, develop recruitment tools, inform obstetrical practices of upcoming E-SNAP study startup	0
02/22	01-03	Finalize and test REDCap database; open recruitment	0
	04-12	Enroll 1-2 new subjects/month; DSMB review after every 5 subjects are enrolled	15
02/23-12/23	13-18	Enroll 1-2 new subjects/month; DSMB review after every 5 subjects are enrolled	10
	19-24	Plasma conc and DNA Analyses; Summary Variables and Statistical Analyses; Manuscript finalization and submission; Final IRB, DSMB and IRB reviews; Draft R01 Phase 3 submission if warranted.	25= target

INCLUSION AND EXCLUSION CRITERIA

Figure 6: Inclusion and Exclusion Criteria

Inclusion Criterion	Rationale
Ages 18-49 years	Age of adult childbearing persons
Singleton pregnancy	Appropriate for initial Phase 2 trial
Inpatient or outpatient status	Target is pregnant persons with refractory sNVP
Care within Prentice Women's Hospital maternity practices	Retain subjects through pregnancy; coordinate with obstetrical care
English speaking	Measures in English, staff are English speaking
Obstetrician's evaluation and diagnosis of sNVP or HG	Differentiate from medical disorders (i.e. pancreatitis, appendicitis)
Tolerance of oral disintegrating tablet at bedtime	Preparation is appropriate for persons experiencing emesis
PUQE score of 10-15; moderate/high or severe	Pharmacotherapy is appropriate for this level of severity
Refractory sNVP	Inadequate response to two commonly used drugs
Anti-emetics may be continued as in real-world practice	Focus is mirtazapine for sNVP non-responsive to other medications
Exclusion Criterion	**Rationale**
Allergic or adverse reaction to mirtazapine	Inappropriate treatment
Patient has bipolar disorder without anti-manic drug treatment	Risk for hypomania/mania induction
Subjects with active depression, or history of or current active suicidal ideation or attempt	Mitigate risk for suicidality

VULNERABLE POPULATIONS

The disease studied, sNVP, is specific to pregnant individuals. Case series studies of pregnant persons with sNVP or HG and who were treated with mirtazapine are reviewed in the Research Strategy section. Mirtazapine is FDA-indicated for the treatment of depression, and data on reproductive outcomes are available from treatment of this group of people. Additional information on pregnancy outcomes and neonates will be collected from the delivery record.

The potential risk to the fetus is due to the drug intervention, which also holds the prospect of direct benefit for the woman through control of her NVP/HG with mirtazapine treatment. This Phase 2 trial is to assess maternal tolerability, dosing, adverse effects and preliminary efficacy. No reproductive risks to the fetus have been described but studies are relatively small in terms of sample size (about 500 subjects). Outcomes for longer-term reproductive risks are not available. However, pregnant persons with NVP/HEG suffer consequences of this disabling disorder, and up to 14% of pregnant persons request terminations due to their distress. This research will provide important biomedical knowledge which cannot be obtained by any other means. The risk is the least possible for achieving the objectives of the research. Because the research holds the prospect of direct benefit to the pregnant woman through disease control, the interventions also hold benefit for the fetus who is dependent upon maternal health and nutritional sustenance.

No inducements, monetary or otherwise, will be offered to terminate a pregnancy. Investigators and staff engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy, which will be the responsibility of the patient's obstetrician. Individuals engaged in the study will have no part in determining the viability of a fetus or neonate.

Elucidation of the impact of pharmacogenetics on our capacity to individualize dosing would have major impact upon clinical care of pregnant persons who suffer sNVP.

PARTICIPANT POPULATION(S)

Figure 7. Recruitment Targets

Accrual Number:	Category/Group: (Adults/Children Special/Vulnerable Populations)	Consented: Maximum Number to be Consented or Reviewed/Collected/ Screened	Enrolled and samples collected: Number to Complete the Study or Needed to Address the Research Question
Local	Pregnant persons	100	25

RECRUITMENT METHODS

Authorized research personnel will work with clinicians from the Northwestern Obstetrics and Gynecology services and the Obstetrical Triage program to identify potentially eligible individuals and approach them about their interest in participating. We have defined several eligibility criteria to allow participants to be screened by our study team. Subject burden can be reduced and study efficiency improved by asking only those subjects likely to be eligible to undergo a full baseline assessment. The screen includes: 1) age 2) gestational age of the fetus, 3) confirmation of plan to receive care and deliver at Prentice Women's Hospital (PWH), 4)

PUQE score of 10-15, 5) has been treated with at least two anti-emetic/antinauseant drugs with inadequate response; and 8) English speaking.

The inclusion/exclusion criteria will be reviewed in the patient's chart and documented on the screening log. If a patient meets all the inclusion criteria for enrollment, does not have any of the exclusion criteria, she will be approached about the study by authorized personnel. Her primary obstetrician will be contacted to review the patient's participation.

Brochures will be available to provide potential subjects with additional information. We will also post information about this study on our Asher Center and Northwestern Medicine websites, as well as post on the NCT site.

COMPENSATION FOR PARTICIPATION IN RESEARCH ACTIVITIES

Participants will be compensated with $35 for each week of the three-week trial. If a participant wishes to participate in the continuation period or a mirtazapine tapering regimen, they will continue for 5 additional weeks and compensated with $35 each week.

If a participant enters into the study early in pregnancy (gestational age of 5 weeks), they will have monthly visits after the 8 weeks is completed, for a maximum total of 10 visits.

Compensation will be provided in a form of a check at the end of each week during their follow-up visit.

WITHDRAWAL OF PARTICIPANTS

A participant will be withdrawn from the research without their consent if there is: 1) refusal to follow the medication protocol, and/or 2) refusal to answer study questionnaires, 3) the participant fails to respond to contact attempts from the study team.

RISKS TO PARTICIPANTS

The potential risks of this study include exposure to an additional medication, mirtazapine, which has antiemetic/antinauseant properties. People eligible for this study will have already accepted two drugs to treat sNVP. This plan mirrors clinical practice since commonly prescribed antiemetic/ antinauseant drugs prescribed in standard practice will be given before mirtazapine.

Reproductive Exposure Data. Djulus et al.[66] and Winterfeld et al.[67] conducted prospective studies of the rate of birth defects in infants exposed to mirtazapine in utero. Djulus et al. included three groups (104 women per group) of pregnant women with depression and exposure to mirtazapine, other antidepressants or non-teratogenic drugs. The malformation rate did not significantly differ by either drug exposure group compared to the non-teratogen group. Birth weights were similar across groups. As anticipated, the preterm birth rate was higher in both antidepressant-treated groups compared to the non-teratogen exposure group. The relationship between antidepressant exposure and preterm birth is attributable to factors associated with the underlying depression (confounding by indication) rather than the drug exposure.[68] In Winterfeld et al.'s study, mirtazapine-exposed women were compared to two groups including women exposed to selective serotonin reuptake inhibitors (SSRI) and without mental illness (all groups with N=357). No significant differences in rates of birth defects were observed across the three groups. Gestational age at birth, birth weight, and miscarriage rates were similar across groups. In a case series of 56 women by Smit et al.[69], no malformations

were observed in the newborns of 26 women exposed to mirtazapine in the first trimester. Of 54 infants exposed in the third trimester, 14 (26%) had poor neonatal adaptation, similar to the rate observed after SSRI exposure. Birth weights were within the normal range. Preterm births occurred in 9% of exposed newborns vs. 7.7% of the general population. In summary, although the total number of women with first-trimester exposure to mirtazapine is relatively small (N=487), the results do not suggest a signal for birth defects. The majority of large-scale studies of populations of women who have taken antidepressant medications similar to mirtazapine, neither birth defects nor neurodevelopmental problems (including autism[70]) have been associated with the use of these drugs[71]. Additional data on pregnancy and newborn outcomes associated with mirtazapine exposure in the context of sNVP will be obtained in the proposed R21 study and included in the later Phase 3 RCT, if such a trial is supported by data from this R21 study.

Pharmacotherapy with any drug for NVP is associated with benefits and harms that must be balanced by the physician and patient. Commonly used drugs, such as ondansetron, metoclopramide, and prochlorperazine also have treatment benefits and harms that must be balanced against the risks associated with sNVP. Ondansetron use increased from less than 1% prior to 2000 to 13% in 2014.[72] Data from the National Birth Defects Prevention and Slone Birth Defects Studies showed that ondansetron exposure was not associated with an elevated risk for the majority of defects; however, increased risks were observed for cleft palate (adjusted OR=1.6, 95% CI 1.1-2.3) and renal agenesis-dysgenesis (OR=1.8, 95% CI 1.1-3.0) in the Birth Defects Study.[72] Huybrechts et al [73] evaluated 1,816,414 pregnancies with 88,467 (4.9%) and reported that first-trimester exposure to ondansetron was not associated with overall congenital or cardiac malformations but with a small increased risk of oral clefts (RR=1.24 (95% CI, 1.03-1.48).

In a large retrospective cohort study, infants exposed to metoclopramide in the first trimester were compared to unexposed infants. No significant differences in congenital malformations, birth weight, preterm delivery or perinatal death were observed.[74] Although data for prochlorperazine are limited[14], no consistent evidence of teratogenesis exists for the use of phenothiazine drugs in the treatment of NVP. Chronic maternal use of metoclopramide and prochlorperazine increase the risk for maternal extrapyramidal movement disorders and neonates have experienced agitation, hyper- or hypotonia, tremor, somnolence and respiratory distress.

Blood sampling will be done to allow the plasma assay for mirtazapine concentrations. The phlebotomy services will be obtained from the Diagnostic and Treatment Center on the second floor of Arkes Pavilion, Prentice Women's laboratory services, or the Asher Center clinical research laboratory. All are accessible through indoor walkways from Prentice Women's Hospital. There are minimal risks to phlebotomy, which are rare and include bruising, pain, infection and mild maternal anxiety. The amount of blood that will be drawn at enrollment for study purposes is 3 ml (thyroid hormones) and 5 ml (DNA sample), for a total of 8 ml, and 5 ml at each follow up assessment for plasma concentrations of mirtazapine.

POTENTIAL BENEFITS TO PARTICIPANTS

There is no definitive benefit to participants from whom data will be collected. Pregnant persons may benefit from the additional education about the disorder and possibly from treatment with the promising drug mirtazapine. The additional monitoring by study staff may be perceived as supportive.

The dearth of information about the treatment of sNVP has been identified in systematic reviews, meta-analyses and the recent NICHD-led Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC). Data to inform the acceptability, tolerability, dosing and design of a subsequent randomized controlled trial to expand pharmacotherapy would be a major contribution in the care of pregnant persons.

According to the Code of Federal Regulations, Title 45 Part 46, Subpart B, research may be conducted in people when preclinical studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant persons, have been conducted and provide data for assessing potential risks to pregnant persons and fetuses. This is the case for mirtazapine, which is FDA-indicated for the treatment of depression. This Phase 2 trial will be submitted for review prior to implementation to our IRB and to the FDA for an IND. Additionally, research is acceptable when the risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus. The purpose of this Phase 2 study is the development of important biomedical knowledge which cannot be obtained by any other means.

DATA MANAGEMENT AND CONFIDENTIALITY

Data will be collected and managed using Research Electronic Data Capture (REDCap) housed at Northwestern University's Clinical and Translational Sciences Institute (CTSA), NUCATS. REDCap is a secure, web-based application designed for research studies that provides an intuitive interface for validated data entry, audit trails for tracking data manipulation and export procedures, and automated export procedures for seamless data downloads to common statistical packages, and procedures for importing data from external sources.

Multiple procedures will be used to protect the confidentiality of the participants in this study. Names of participants will not appear on any written records, which include interview forms, self-report forms, or checklists. Code numbers will be used for all computerized data. Confidentiality will be preserved by using numbers (different than medical record numbers) rather than names in the computer files. A separate file (stored in a secure file with limited access) will map patient names and numbers. Access to files will be restricted to appropriate personnel as designated by the PI. All persons on the study team who have access to any subject-related data are required to complete training and testing for research certification. Hard copy files, such as written consent forms, are double-locked and separate from research data for the subject.

Data communication between data entry computers and database servers will be encrypted via a VPN client. Access to the VPN connection will require user authentication via username and password. Firewall software will restrict communication to traffic to the database server that is absolutely critical for conducting research. All unwanted inbound traffic will be blocked at the firewall. Anti-virus software will guard against the intrusions that typically attack through malicious email and removable media. Privacy protection and malware detection software will be active in real-time as additional assurance that unwanted cookies or browser plug-ins are not slowing performance of the device. The data management and information technology staff (data managers, programmers, statisticians) will have access to the database, but not information linking the study ID to the subject's name.

Subject plasma will be stored in a -70ºC freezer in the Northwestern Core Laboratory. These samples will be labeled with the Northwestern Medicine clinical research unit ID, the subject ID, the date of collection, the type of sample collected (e.g. "plasma"), and the corresponding timepoint. Only study personnel will have access to data and will be responsible for

transmission of data. Approved study personnel and Clinical Research Unit Core Lab staff will have access to specimens and will be responsible for transmission of specimens. Deidentified specimens will be transported to Purdue University using FedEx delivery services for analysis.

Multiple procedures will be used to protect the confidentiality of the participants in this study. Names of participants will not appear on any written records, which include interview forms, self-report forms, or checklists. Code numbers will be used for all computerized data. Confidentiality will be preserved by using numbers (different than medical record numbers) rather than names in the computer files. A separate file (stored in a secure file with limited access) will map patient names and numbers. Access to files will be restricted to appropriate personnel as designated by the PI. All persons on the study team who have access to any subject-related data are required to complete training and testing for research certification. Hard copy files, such as written consent forms, are double-locked and separate from research data for the subject.

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We will seek consent from our subjects to have their de-identified data and biospecimens included in the NICHD Data and Specimen Hub (DASH-https://dash.nichd.nih.gov/) for future studies.

PROVISIONS TO MONITOR THE DATA TO ENSURE THE SAFETY OF PARTICIPANTS

The primary patient and safety monitoring function is the responsibility of the PI, Katherine L. Wisner, MD, MS. She was a founding member of the NIMH Data Safety and Monitoring Board for multi-site clinical trials. Co-Investigators are Catherine S. Stika, MD, and Melissa Goslawski, MD. Dr. Stika is a co-PI with Dr. Wisner on the Obstetric-Fetal Pharmacology Center and Medical Director of the Obstetrical Triage Service, where pregnant persons seek urgent care for sNVP. Dr. Goslawski is an obstetrician who works in the Obstetrical Triage Service. They will support recruitment, assessment and monitoring of subjects for the E-SNAP protocol.

The research team has the responsibility to respond to information that affects the well-being of the subject (such as severe dehydration from NVP) consistent with Good Clinical Practice. The proposed study does not limit any interventions that would be prescribed for any subject. If a subject's condition worsens during the study and her clinical status dictates removal from the study, a study physician will provide the rationale for removal. The study team will confer with the patient's primary obstetrician and to develop a treatment plan for the participant.

Adverse Events. The adverse event definitions required for an FDA IND will be applied by the study team. The occurrence of adverse events will be tracked in the study data base by

manager Mr. Erickson and statistician Dr. Kim, who will be responsible for ensuring the accurate, timely and secure incorporation of information into the study data base.

In the Data Safety and Monitoring Plan, Drs. Wisner, Stika and Kim will evaluate safety at several levels: 1) the individual subject, 2) the group of subjects as the study data accrue through review of all adverse events for patterns, and 3) the integrity of the data and data monitoring procedures. The team will evaluate the progress of the study and provide quarterly assessments of data quality, timeliness and completion; participant recruitment; accrual and retention; participant risk versus benefit; and other factors that affect study outcome. Monitoring will include factors external to the study, such as scientific developments that could have an impact on the therapeutic options, safety of the participants or the ethics of the study. All adverse events will be reported to the Northwestern IRB, DSMB and FDA as required.

A Data Safety and Monitoring Board (DSMB) will be constructed for this project. The E-SNAP project includes pregnant persons being treated with mirtazapine, which meets the definition of a NIH clinical trial. It will also be submitted to the FDA for review for an IND, since the investigation involves pregnant persons, "a patient population that significantly increases the risk (or decreases the acceptability of the risk) associated with the use of the drug product (21 CFR 312.2(b)(1)(iii))."

The DSMB will include external academic faculty members in the following areas: one maternal-fetal medicine specialist who has expertise in reproductive outcomes associated with drug exposure; an obstetrician-gynecologist with an interest in sNVP; and a reproductive pharmacoepidemiologist. The board will conduct quarterly phone conferences to review study materials relevant to data integrity and safety as defined above. Flow through the study, side effects and adverse event frequency, withdrawals and post-enrollment hospitalizations will be reviewed. A formal Consort Chart will be generated as the study evolves.[75]

The DSMB will review specifically the frequency of adverse study-associated events in all subjects as follows: 1) acceptability data; 2) the tolerability of the mirtazapine dosage regimen; 3) mirtazapine discontinuation and reason(s) for discontinuation; 4) emergency room visits; 5) post-enrollment hospitalizations, durations and interventions; 6) additional medication exposures during the three week and optional maintenance study periods; 7) the adequacy of the tapering regimen to mitigate discontinuation symptoms, the number of pregnant persons who experience recurrence of sNVP and the number tapers that are attempted; 8) patient complaints to the study team or IRB; and, 9) reproductive outcomes for both the mother and the neonate on the Peripartum Events Scale, which will be compared to the outcomes of data from in-utero SSRI antidepressants. These findings will be evaluated and summarized by neonatology consultant Malika Shah, MD.

The DSMB meetings will occur by teleconference. The data will be summarized and provided prior to the phone consultations to the DSMB members. The tables below summarize the activities of the DSMB.

YEAR 01	YEAR 02
Prior to initial meeting: discuss and sign agreement and expectations for DSMB participation; develop format for minutes at all meetings.	Continue quarterly teleconferences; adjust data delivery format as appropriate per DSMB input.

Initial meeting: Review protocol, establish the data to be reviewed by the DSMB; set additional quarterly phone conferences with option for as needed meetings. A particular focus will be assessment of the tolerability of the dosing strategy and the potential need for modification. Quarterly: Review course of study to date, summarize any untoward events, problem solve. Data summaries provided to DSMB members at least 10 days prior to quarterly conference reviews.	Final meeting: review course of study; summarize untoward events, quarterly phone; review and generate final report.

PROVISIONS TO PROTECT THE PRIVACY INTERESTS OF PARTICIPANTS

Subjects will be informed regarding staff who will have access to their data. Topics covered in questionnaires are consistent with standard of care evaluations and are not expected to induce any additional discomfort or distress.

Authorized research personnel may have access to enrolled subjects' medical records at the designation of the Principal Investigator in compliance with EDW policy.

COMPENSATION FOR RESEARCH-RELATED INJURY

The university or researchers will not pay for medical care required because of a bad outcome resulting from participation in this research study. This does not keep participants from seeking to be paid back for care required because of a bad outcome.

ECONOMIC BURDEN TO PARTICIPANTS

There is no cost to subjects to participate in this study.

CONSENT PROCESS

Written informed consent will be obtained in the place in which the subject was recruited (the Obstetrical Triage Unit, Prentice Women's Hospital or the Asher Center), or with electronic consent through REDCap. We have integrated this flexible approach due to the unpredictable effects of the pandemic. The time devoted to the consent discussion is estimated to be 30 minutes, but study personnel will provide as much time as is necessary for the participant to review the consent and ask questions.

When the participant agrees to enroll in this study, her electronic signature with time stamp and certification will be collected through REDCap. A digital PDF copy of the signed consent form will be offered to the participant after consent is signed. REDCap will serve as the central repository of signed consent forms. Only authorized study personnel will have access to REDCap via VPN.

The REDCap electronic consent will use the same language as the IRB stamped consent, will have a version stamp in the footer, and will contain the same required signature fields:

participant's initials on pertinent fields; participant's full name, signature and signature date; and person obtaining consent's full name, signature and signature date.

NON-ENGLISH SPEAKING PARTICIPANTS

Participants must speak English, as the clinicians conducting this study are English-speaking and measures and assessments are in English.

WAIVER OR ALTERATION OF CONSENT PROCESS

Participants must be able to provide written consent. Required information will be disclosed, and the research does not involve deception.

TRIAL STOPPING CRITERIA

This clinical trial will stop in the instance of any of the following:

- Death of a subject during the trial
- Grade 3 or higher toxicity in any organ system per the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 developed by the National Cancer Institute
- Grade 2 or higher allergic/hypersensitivity reaction
- If there are two identical unexpected treatment-related toxicities that are Grade 3 or higher, we will suspend accrual pending further review by the Institutional Review Board

An individual subject will stop participating in the clinical trial in the instance of any of the following:

- New onset suicidal thoughts or behaviors
- Grade 3 or higher drug-related serious adverse event (SAE) based on the CTCAE, version 5.0
- Acute livery injury [alanine transaminase (ALT) or aspartate transaminase (AST) > 3-fold upper limit of normal (ULN), alkaline phosphatase (ALP) or total bilirubin (TBL) > 2 fold ULN]
- Subjects with serum sodium < 125 mmol/L

PROTECTED HEALTH INFORMATION (PHI AND HIPAA)

This study involves the creation, use or disclosure of Protected Personal Health Information. Protected Personal Health Information includes names, address, dates of birth and ages, telephone numbers, email addresses, social security numbers (see Compensation section), and medical record numbers. HIPAA requirements and measures to protect PHI will be implemented as described in the Data Management and Confidentiality section.

QUALIFICATIONS TO CONDUCT RESEARCH AND RESOURCES AVAILABLE

An interdisciplinary team with a strong commitment to improving care for pregnant persons collaborated in the development of this protocol. Northwestern is the sole clinical site for this study. The PI is Katherine L. Wisner, MD, MS, is the Norman and Helen Asher Professor of Psychiatry and Obstetrics and Gynecology. She has conducted nine NIMH-funded R01 observational (during pregnancy) and randomized clinical trial (postpartum) studies of mood disorders. Dr. Wisner was an author in the joint ACOG-APA Committee's consensus report for managing depression during pregnancy [76] and is the first author of *Mental Health and Behavioral Disorders*, in Obstetrics: Normal and Problem Pregnancies, edited by Gabbe S et al (2007, 2012) and *Psychotropic Drugs* (in Schaefer C et al, Drugs during Pregnancy and Lactation: Treatment Options and Risk Assessment, 2014). She is a fellow of the American College of Neuropsychopharmacology. Dr. Wisner participated in the FDA Advisory Committee to Revise Drug Labeling for Pregnancy and Lactation; FDA Pediatrics Subcommittee, Neonatal Effects of SSRI Use; Research Committee, Organization of Teratology Information Services; FDA Advisory: Perinatal Depression-Examining the Risks and Benefits of Treatment; CDC TRxeating for Two: Safe Medication Use in Pregnancy Expert Meeting. Drs. Wisner and Stika (see below) are Co-PIs on the Northwestern Obstetric-Fetal Pharmacology Research Center funded by NICHD.

The co-I is Catherine S. Stika, MD, Professor of Obstetrics and Gynecology. Dr. Stika completed a fellowship in clinical pharmacology and was a consultant for the FDA Guidance for Pharmacokinetic studies in pregnancy. She is the primary author of *Drug Therapy in Pregnant and Nursing Women*, in Principles of Clinical Pharmacology, edited by AJ Atkinson, Jr., in 2001, 2006 and 2012. This book serves as the core text for the NIH annual clinical pharmacology course. NIH is developing an on-line video program of lectures and cases, and Dr. Stika will prepare the obstetrical section. She has served on the DSMB for the OPRU network from 2005 – 2014 and was the obstetrical co-PI on the Northwestern Obstetric-Fetal Pharmacology Research Center funded by NICHD (2015-2021).

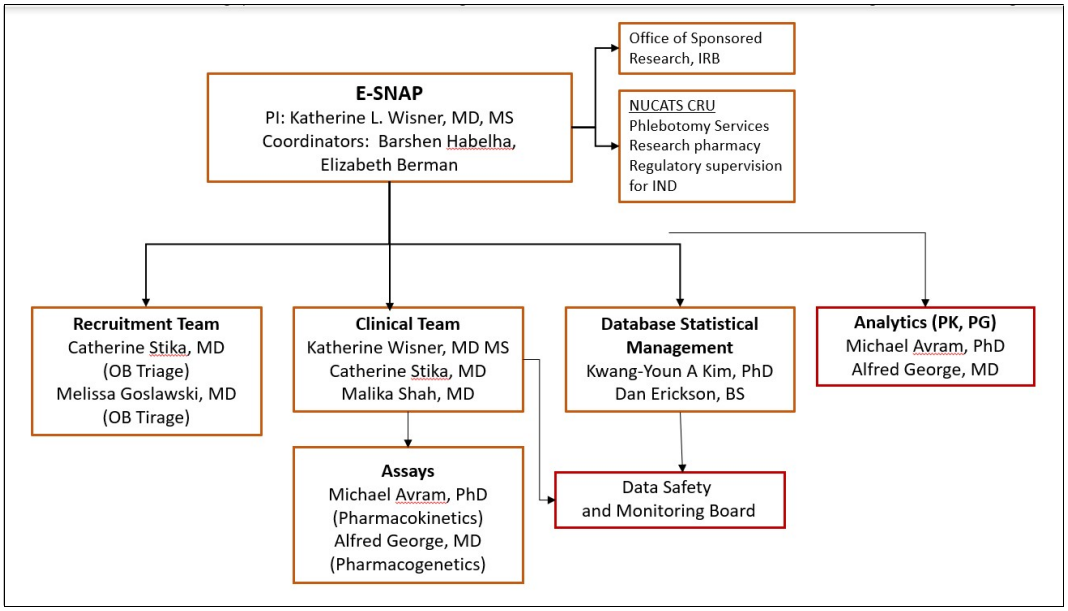
Dr. Goslawski is an obstetrician-gynecologist employed by Northwestern Medicine to work in the Obstetrical Triage Unit at Prentice Women's Hospital. She is also a perinatal psychiatry scholar in the Asher Center for the Study and Treatment of Depressive Disorders with Dr. Wisner.

Achievement of the scientific goals depends upon efficient administrative operations. The structure will support efficient communication, study processes and personnel management. Katherine L. Wisner, MD, MS, is the principal investigator and administrative leader. Dr. Wisner will supervise Ms. Berman and Ms. Habelhah, experienced research coordinators, in the overall conduct of research activities. The entire study team will meet weekly for one hour. All meetings will be documented by minutes containing a summary and task assignment list with personnel responsible for completing the task. These minutes will be available on the internal website.

Administrative Goals:

1. Manage resources equitably and efficiently, including budget, resource management and liaison to the Northwestern University Office of Sponsored Research.
2. Support clear, equitable and transparent study-wide procedures, including monitoring progress on objectives, distribution of resources, achieving milestones and providing constructive feedback.

3. Facilitate information flow across partners such as the Northwestern Office of Sponsored Research, IRB, DSMB, FDA, research pharmacy, regulatory monitors and clinical research unit staff.
4. Establish a manual of operating procedures (MOP) to ensure regulatory compliance, policy development, record-keeping practices, coordinated oversight of recruitment, management of subject data and human subject issues. The MOP will include information on all aspects of the study, such as organizational structure, screening, inclusion/exclusion criteria; treatments, collection, shipping and location of specimens, adverse events, data entry and management, statistical analysis and publications. Protocol updates and clarifications from study meetings will be included in the dynamic MOP, which will be updated weekly during the investigation. The final version of the MOP will contain all information need to construct the later definitive clinical trial to be submitted as an R01 if the data from this study are supportive.
5. A decision-making algorithm for data reporting procedures will be developed and placed in the MOP. Quality assurance procedures, such as frequent data quality reviews and direct observation of research staff conducting procedures, will be devised. Training and ongoing supervision of research staff are essential to promoting intervention fidelity. We will develop (and modify iteratively) training procedures and scripts for interacting with participants at each visit. Training will include review of the MOP, data collection and management systems, and quality control procedures. Staff will have hands-on experience with the data system by entering mock data and reviewing reporting procedures.
6. The data team will generate reports for the review of the study team (with attention to sections that must be kept blind by the clinical team), as well as for DSMB and FDA review. Criteria will include enrollment of participants, frequency of attrition, unanticipated events, and protocol violations. We will use quantitative measures compiled from screening, enrollment and study visit data entry logs. At regular study team meeting, comprehensive reports will include recruitment, retention and other performance parameters; quality control for data received; data that include missed visits and protocol violations, and participant characteristics. The organizational structure for the E-SNAP project is shown below:



MULTI-SITE RESEARCH

This is a single-site investigation at Northwestern University Institutional Review Board is the IRB of record for this study.

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