

**Protocol Title:**

EnBrace HR for Depression Treatment and Prevention in Women Trying to Conceive and Early Pregnancy

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**I. BACKGROUND AND SIGNIFICANCE**

**a. Historical background**

Major depressive disorder (MDD) occurs twice as often in women as in men, with an age of onset that coincides with the childbearing years. As over 20% of reproductive-age women experience an episode of depression, identifying safe and effective treatments for depression before, during and after pregnancy has become a critical public health issue.

Historically, pregnancy has been viewed as a protective time with respect to risk for psychiatric illnesses such as MDD. This assumption has resulted in a lack of prospective systematic investigations on the subject of acute treatment and prevention of MDD while women are planning to conceive and during pregnancy. Contrary to previous assumptions, recent large-scale studies demonstrate that new onset and recurrence of depressive episodes occur commonly during pregnancy and the postpartum period. The current standard of treatment for recurrent MDD is maintenance antidepressant (AD) therapy(1). These guidelines are derived from the high risk of recurrence among patients who discontinue maintenance AD therapy. Although ADs are frequently used during pregnancy, concerns remain regarding a spectrum of adverse outcomes associated with fetal exposure to these medications including: increased risk for teratogenicity, compromised obstetrical outcomes, and a variety of negative neonatal clinical syndromes(2). Given these concerns, reproductive age women treated with ADs frequently elect to discontinue their medications proximate to pregnancy or immediately after becoming pregnant despite the known increased risk for relapse or recurrence. Women who experience depressive episodes during pregnancy or while trying to conceive often forgo antidepressant use. With the exception of observational data that demonstrate that women who discontinue medication around the time of conception are at high risk of recurrence, no previous studies are available to inform clinical treatment regarding medication discontinuation for a planned pregnancy(3).

This leaves women in the difficult clinical dilemma of weighing the risks of fetal exposure to medication against the potential impact of untreated maternal depression during pregnancy. Clinical decisions are made even more complex by the fact that most studies are far from definitive in terms of comparing the risks of in utero exposure to ADs to the risks of untreated antenatal mood disorder. Given this level of uncertainty, many women and their health care providers would welcome evidence-based non-psychotropic interventions as an alternative to ADs in order to treat or prevent depressive episodes in women who are pregnant or planning pregnancy.

However, the potential efficacy of non-psychotropic interventions for the purposes of acute treatment and recurrence prevention following AD discontinuation among women who plan to conceive or for those who are pregnant has received limited study.

**b. Previous pre-clinical or clinical studies leading up to and supporting the research**

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In the following sections we review literature in several critical areas pertaining to the proposed investigation: evidence confirming that depression is often a recurrent illness; knowledge of the prevalence and outcomes of depression and its treatment across pregnancy; studies examining the reproductive safety of AD use during pregnancy, data suggesting that women often discontinue maintenance AD use proximate to conception despite an increased risk for relapse and recurrence; and investigations specific to the use of methylfolate in the treatment of MDD and for improved pregnancy outcomes.

### Depression is a Recurrent Illness

A growing body of literature indicates that MDD is most often a recurrent illness. The clinical term used to describe a depressive episode that reappears within six months of acute response is a relapse while symptoms that occur after six months of euthymia are called recurrences(4). Relapses are considered a return of the original episode, whereas recurrences represent a new episode. Although these distinctions are based on limited data, the phases of treatment to prevent relapse and recurrence have been differentiated correspondingly into continuation and maintenance phases, respectively.

Observational Studies. Data derived from the National Institute of Mental Health Collaborative Program on the Psychobiology of Depression (n=380) were examined to investigate the proportion of patients experiencing a recurrence of MDD up to 15 years after recovery from the index episode(5). The vast majority of patients (85%) experienced a recurrence during this time period, with those remaining well 5 years after recovery experiencing a rate of recurrence of 58%. Results from the Collaborative Program study (n=359) revealed a 20% relapse rate and an overall 88% recurrence rate (within five years of recovery)(6). These findings are even more compelling as these patients had received “high levels of somatic treatment” during the entire observation period. Other observational studies have confirmed high rates of relapse and recurrence in patients with and without optimal psychopharmacologic management(7-9).

Randomized Controlled Trials. Data from randomized controlled trials, typically using a double-blind discontinuation method, reveal that long-term treatment with ADs lowers the risk for relapse and recurrence when compared with placebo substitution (9-11). However, even while taking ADs for prophylaxis, up to 20-80% of patients develop another depressive episode within five years after treatment for the initial episode (6, 12-14). One recent meta-analysis pooled data from 31 randomized trials and found that maintenance AD therapy (following acute treatment) reduced the odds of relapse and recurrence by 70% compared with treatment discontinuation(15). The average rate of relapse on placebo was 41% compared with 18% on active treatment. The proportional risk reduction was found to be similar in patients with short (6 months) and long (36 months) follow-up periods, which suggests that time since response does not affect risk.

Guidelines for preventing recurrence. The observational studies and randomized controlled trials above have informed the development of recognized clinical treatment guidelines, which support the use of long term AD treatment to prevent relapse and recurrence, especially for patients described as at high risk due to clinical factors(1, 16, 17). These risk factors include a history of three or more depressive episodes, two or more depressive episodes within five years, a family history of bipolar disorder or recurrent depression, early-onset depression, and previous recurrence within one year of medication discontinuation. Additionally, individual risk factors including patient preference, suicide risk, episode severity, social support, and life stressors, influence every treatment response.

### Course and Treatment of Depression during Attempts to Conceive and During Pregnancy

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Prevalence of Depression during Pregnancy. MDD is not only a seriously debilitating illness affecting many people worldwide, but it is particularly critical in the field of women's health. MDD is twice as prevalent in women as in men, with incidence clusters during the reproductive years, as over 20% of women experience an episode of depression during this time(18, 19). Despite a lack of supportive data, pregnancy has historically been considered protective against both the emergence and recurrence of depressive symptoms. Contrary to this belief, both epidemiological data and a recent naturalistic study suggest that, pregnancy may be a time of great risk for recurrence and new onset of depression. The limited epidemiological studies conducted in pregnant adults reveal prevalence rates of moderate and severe depressive symptoms ranging from 6.9% to 20%(18, 20). The risks of untreated depression during pregnancy are significant and include poor nutrition, inadequate weight gain, poor prenatal care, inability to care for oneself, the use of cigarettes, alcohol, or other substances, ambivalence or even termination of the pregnancy, and an increased risk for postpartum depression(21-23). Postpartum depression, a condition only recently understood, is best predicted by the presence of depression during pregnancy, thus it is of critical importance to prevent the emergence of depressive symptoms during pregnancy(24).

Depression during pregnancy is a major public health concern, given its prevalence, and the implicit treatment dilemma of weighing the unknown effects of fetal AD exposure against the effects of untreated depression on 1) maternal well being, 2) obstetrical and neonatal outcomes, and 3) long term development of the child.

Prevalence of AD Use during Pregnancy. As previously demonstrated, based on data derived from health insurance and hospital records, investigators found that ADs were prescribed to nearly 8% of all pregnant women(2). The investigators found that AD use during pregnancy increased from 2.0% of all deliveries in 1996 to 7.6% of all deliveries in 2004 and 2005, with consistently more women dispensed an AD during the first trimester of pregnancy than in either the second or the third trimester. Clinicians must weigh the morbidity associated with depressive relapse and recurrence in the mother against the risk of adverse birth outcomes that may be associated with medication exposure for the fetus. In order to avoid fetal exposure to ADs where attendant risks of in utero exposure is incompletely delineated, many women discontinue these medicines regardless of risk for recurrence.

High Risk of Relapse of Depression during Pregnancy among Women who Discontinue Maintenance AD Therapy. Studies conducted over the last decade have demonstrated that prevalence of depression during pregnancy is similar to age-matched non-pregnant women, replacing previously held ideas that pregnancy was protective against psychiatric illness. Left untreated, depression can negatively impact both the mother and the fetus. For women with histories of MDD who discontinue AD medication to avoid fetal drug exposure, the risk of depressive relapse is high. In a multi-site NIMH funded collaborative study, the rate of depressive relapse among women with a history of MDD who discontinued ADs (68%) was significantly higher than the rate (26%) for women who maintained AD treatment(3). In this study, continued AD treatment during pregnancy significantly reduced the risk of maternal depressive relapse. Data from this large scale, multi-site study also demonstrated that there is a broad distribution of AD use early in pregnancy that is not wholly determined by severity of illness as defined by number of episodes of MDD. In fact, there was no association between the decision to discontinue medication during pregnancy and duration of illness, number of previous episodes, or frequency of co-morbid psychiatric illness.

### **Risks Associated With Fetal Exposure to ADs**

The following studies, though conflicting and methodologically limited, raise concern that prenatal AD use impacts risk for teratogenic outcomes, perinatal withdrawal symptoms, and obstetrical complications and have prompted clinicians and patients to avoid AD exposure during pregnancy.

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Teratogenicity. Though recently more data have become available through several large birth defect surveillance programs, study limitations including small sample size, variation in outcomes reported, and inconsistent conclusions, have made using these sources to inform clinical decisions regarding pharmacologic management during pregnancy challenging for both patient and clinician. For example, two large case-control studies published recently questioned the safety of selective serotonin reuptake inhibitors (SSRIs) with respect to teratogenic risk using large records from a managed care organization and the Swedish Birth registry(25, 26). Based on their size, these studies might be expected to refine the risk estimate for congenital malformations following fetal exposure to SSRIs, but they produced divergent results.

The National Birth Defects Prevention Study compared 9,622 infants with birth defects with 4,092 control infants born in the United States from 1997 to 2003 and found no overall significant association between use of any SSRI in early pregnancy and congenital heart defects or most other birth defects analyzed. The exception was a significantly increased risk, particularly with paroxetine, for anencephaly (odds ratio 2.4), craniosynostosis (OR 2.5), and omphalocele (OR 2.8), birth defects that have not been associated with in utero exposure to SSRIs in previous studies(25). Yet in the accompanying data from the case-control Sloane Epidemiology Center Birth Defects Study (9,849 infants with birth defects and 5,860 infants without), no associations were identified between overall maternal SSRI use in early pregnancy and these three anomalies or congenital heart defects(26). There was, however, a significant association between paroxetine exposure and right-ventricular outflow tract obstruction defects (odds ratio of 3.3), as well as between the use of sertraline specifically and both omphalocele (odds ratio 5.7) and septal defects (2.0). It should be noted that the number of actual exposures in these studies to a specific SSRI was particularly small (<10). Thus, despite larger amounts of data which appear to be reassuring with respect to fetal exposure to SSRIs and risk for organ malformation, these inconsistent conclusions make patients and clinicians vigilant about use of ADs during pregnancy.

Recently, studies have raised concerns about whether prenatal AD use is associated with an increased risk of autism, although studies have been inconsistent in whether there is an increased risk or not among children who have been exposed to ADs in utero.

Perinatal Outcomes. Some(27-31), but not all(22, 32, 33)studies have noted an association between fetal exposure to SSRIs and adverse perinatal outcomes, including decreased gestational age, low birth weight, and poor neonatal adaptation, leading to increased rates of newborn complications and subsequent special care nursery admissions(27, 34-38). Several recent reports have noted an increased incidence of neonatal jitteriness, tachypnea, cyanosis, and tremulousness with late pregnancy exposure to SSRIs, while other studies have inconsistently reported an increased risk of persistent pulmonary hypertension of the newborn (PPHN)(27, 28, 34). While these associations deserve further study, the seriousness of the condition has led many women and their health care providers to attempt to discontinue AD prior to or during pregnancy. These analyses have led some authors to suggest AD discontinuation prior to delivery to presumably minimize the risk of neonatal toxicity. Additionally, FDA mandated labeling across the SSRIs also recommends discontinuation prior to delivery. While the recommendation is intuitive, the data are not conclusive and withdrawing treatment from patients just as they are about to enter the postpartum period, a time of heightened risk for affective illness, may carry significant clinical risk.

Although concerning, these studies vary greatly in the method of assessment, have limited blinded assessments, and include confounding factors such as other medication use or other psychological disorders and retrospective design, limiting their clinical significance. Moreover, research is required regarding if these short term symptoms have long-term effects.

Obstetrical Outcomes. Preterm birth (< 37 weeks gestation) is an obstetrical outcome of significant

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clinical relevance, as it affects up to 15% of all births in the US and remains a leading cause of perinatal morbidity(39). Premature infants are more likely to suffer from cerebral palsy, respiratory difficulties, and learning difficulties than infants who are born at term(39, 40). In addition to emotional and social burdens to society, preterm birth poses significant financial burdens: in 2003 the March of Dimes reported that total hospital costs related to preterm birth were in excess of \$18 billion in the US(41). While the costs per case decrease with each advancing week of gestation, the number of preterm births increases, resulting in comparable total expenses for early and late preterm birth. Neonatal morbidity is most concerning with early preterm births; however recent studies have examined neonatal medical problems in premature infants between 35 and 37 weeks, and have found increased cases of temperature instability, hypoglycemia, respiratory distress, jaundice, evaluations for sepsis, and treatment with intravenous infusions(42).

Several studies have shown an association between fetal exposure to various medications and preterm birth(22, 33, 37, 43-47). Serotonin is a potent vasoconstrictor of the umbilicoplacental circulatory bed and circulatory levels of serotonin have been shown to be markedly increased in preeclampsia(48, 49). The net effect of most clinically available ADs is increased serotonin neurotransmission as well as alterations in beta-adrenergic receptors. Though all but one of these negative studies(35) included prospectively followed subjects, they were limited by the fact that AD exposure occurred only during early pregnancy for the majority of subjects(33, 37, 43-47), by small sample sizes(22, 32, 35, 38, 47, 50), and by the lack of a comparison unexposed control group(51). The exact mechanism by which ADs may impact pregnancy duration is not known.

### **Treatment Decisions during Pregnancy Are Not Driven by Illness Severity**

In a naturalistic prospective study, investigators found that over 43% of women discontinuing AD medications due to pregnancy concerns relapsed, over 50% during the first trimester(3). It could be expected that without random assignment to participation in the study, the participants who elected to enroll would be those with the least severe depression histories. This presumes patients with a history of multiple episodes would disproportionately choose to continue pharmacologic treatment, as compared to women with histories of fewer or more mild illness. However, data from a large scale, multi-site study conducted Cohen, et al. show that there is a broad distribution of AD use early in pregnancy in patients that is not wholly confounded with severity of illness as defined by number of episodes of major depression. We found no association between the decision to discontinue medication during pregnancy and duration of illness, number of previous episodes, or frequency of co-morbid psychiatric illness(3).

### **Selection of Intervention (EnBrace prenatal supplement)**

The current study will provide evidence regarding the efficacy, tolerability, feasibility and acceptability of a selected non-psychotropic treatment alternative to AD use while women are trying to conceive or during pregnancy. We hypothesize that rates of MDD relapse coinciding with AD discontinuation proximate to pregnancy may be attenuated if there are other effective treatments available to women.

### **Candidate Non-psychotropic Treatments for Women Trying to Conceive and During Pregnancy**

Ideally, a candidate treatment for MDD in pregnant women and those trying to conceive would: 1) demonstrate efficacy for MDD, 2) have a good safety profile in pregnancy and lactation, and 3) benefit the pregnancy beyond its impact upon MDD. The decision to continue an AD may be appropriate for some women who suffer from a history of highly recurrent disease, although most wish to have alternatives. Integrative, or Complementary and Alternative Medicine (CAM) treatments, have been increasingly used by individuals with MDD, particularly women, making the study of the efficacy of these interventions that much more compelling and urgent. Demonstrating the attractiveness of non-

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psychotropic options, a recent report demonstrated that over 40% of the adult population in the U.S. used at least one CAM treatment over the past year, with women more likely than men to use CAM(52, 53). This pattern of utilization highlights the need for more research with integrative treatments for depression in women, as they are more likely than men to both suffer from MDD and to use CAM treatments(52). MDD is a common indication for nutritional supplement use, particularly among women, underscoring the attractiveness of these treatments to patients and the urgent need for systematic study of these interventions(54-58).

### **L-methylfolate and Other Folate-related Compounds**

There is consistent and growing evidence of a role for various folate forms in the prevention and treatment of depression. In fact, there is compelling evidence that treatment with a methylfolate agent would not only avoid the potential risks of ADs in pregnancy, but would also confer important benefits to pregnancy and child outcomes as well, such as prevention of congenital birth defects and longer term neurodevelopmental outcomes. To date, there is an evidence base for AD effects for folic acid, folinic acid, and methylfolate, and similar findings may be attributable to the fact that these folate forms share an interconversion potential in the complex set of pathways that comprise the one-carbon cycle(59-62). These reactions, which depend on B12 and homocysteine availability, are postulated to exert an AD effect by impacting the synthesis of neurotransmitters such as norepinephrine, dopamine, and serotonin.

Some but not all studies suggest efficacy of folate monotherapy for MDD, but this intervention may be limited by the common occurrence of polymorphisms in the general population that make folate a less efficient one-carbon cycle constituent than L-methylfolate. Since certain polymorphisms that impair methylation processes and the conversion of folate into its active form, methylfolate, have been found to be common in individuals with MDD, methylfolate may be a more effective form of folate supplementation to target MDD(63). Also, methylfolate may be more readily absorbed in the brain compared to other folate forms(64).

Recently, Fava and colleagues demonstrated that adjunct L-methylfolate is significantly superior to placebo for the treatment of MDD in patients who had failed to respond to AD therapy alone (65). In addition, several other open and blinded studies of methylfolate monotherapy in a variety of depressed populations have found that patients experienced significant improvement in depressive symptoms with no drug-related adverse events(66-70). Although more controlled data are needed, initial studies indicate that methylfolate may be a safe and effective option for the treatment of MDD, especially in populations that are vulnerable to medication-related adverse events, and those who are folate deficient or whose folate needs are elevated, such as pregnant women.

### **Omega-3 Fatty Acids, Depression, and Pregnancy**

**Omega-3 Fatty Acids:** Omega-3 fatty acids are nutritional compounds with well established benefits for human health, and particular benefits for fetal and infant development. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are two important omega-3 fatty acids found in fish and most fish oil or omega-3 supplements. The majority of randomized controlled trials demonstrate a significant AD benefit of omega-3 fatty acids in mood disorders overall, although they are best studied as an augmentation treatment rather than a stand-alone therapy.

**Perinatal Depression Considerations:** The benefits of maternal omega-3 fatty acid intake have been established for infant outcomes, although women are often afraid to eat fish during pregnancy since the U.S. FDA mercury advisories. Only a few treatment studies have specifically looked at omega-3 fatty

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acids as a primary treatment for MDD during pregnancy and postpartum depression, and they have been small studies with mixed outcomes. Omega-3 fatty acid supplements have been well tolerated by pregnant and postpartum women. The exact dose still needs to be determined for optimal benefits for MDD, but modest doses of EPA and DHA (with a higher ratio of EPA:DHA) have shown the most promise, and is a reasonable dose for general health benefits, infant outcome benefits, and as an add-on treatment for MDD.

**EnBrace HR** is a prescription prenatal/postnatal dietary management product that contains vitamins and minerals, including folic acid and methylfolate. It meets the above criteria as a potential ideal candidate for the prevention of MDD in pregnancy. It contains L-methylfolate and other folate derivatives, and is optimal for a population with high rates of polymorphisms that affect folic acid metabolism. It also contains omega-3 fatty acids, primarily EPA, which shows promise for the treatment of depression. Importantly, these components are crucial for healthy pregnancies. Folic acid supplementation has been associated with the reduced risk of neural tube defects and is recommended for use in women of reproductive potential to reduce the risk of birth defects. Given that a substantial proportion of the population are poor folic acid metabolizers, methylfolate compounds may provide a more efficient delivery of folate-related compounds. Also, folate-related compounds supplemented in utero (folic acid, methylfolate) are associated with a lower risk of subsequent autism in children(71, 72).

### **Rationale behind research and potential benefits to patients and/or society**

Women who experience depression while trying to conceive and during a pregnancy often seek to minimize exposure to psychotropic medications. Likewise, women in remission from depression who are currently taking maintenance AD treatment and who are planning to conceive or are pregnant will often discontinue treatment out of concern over known and unknown risks of fetal exposure to these medications, regardless of clinical evidence showing that this puts them at a higher risk of relapse. The decision to avoid or discontinue maintenance AD treatment during pregnancy is also often made despite the risk of recurrence of MDD, which may result in a range of negative outcomes for both the mother and her newborn.

However, few studies have examined folate treatment specifically to assist patients who wish to avoid or discontinue ADs, and none have examined this during the time proximate to attempts to conceive, or during pregnancy, which is particularly relevant due to safety concerns. The adaptation of a non-psychotropic treatment for use in women who are pregnant or planning pregnancy who choose to avoid or discontinue maintenance AD treatment would broaden treatment choices available during this important time in the female life-cycle.

## **II. SPECIFIC AIMS**

### **a. Specify objectives and hypotheses to be tested**

**Objective:** The overarching goal of this investigation is to assess EnBrace as a treatment for the acute treatment and prevention of depression in women with a history of major depressive disorder who decide to avoid or discontinue their maintenance AD treatment for pregnancy. After completing this protocol, we plan to use the preliminary data for the development of a randomized controlled trial protocol. We will include two groups of women who are interested in minimizing medication exposures while trying to conceive or during pregnancy: 1) women who have histories of depression and are not depressed, and would like to stop antidepressants for pregnancy, 2) women in depressive episodes who are pregnant or trying to conceive (on or off of antidepressant medications).

**Specific Aim 1a:** To evaluate the efficacy of EnBrace when used as maintenance treatment for MDD in a group of women (N=10) who are trying to conceive or are early in pregnancy and who

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have decided to stop ADs (Group 1). Relapse rates for women in this context have been demonstrated to be high, with 68% relapse rates in a large multisite NIMH-funded trial.

**Specific Aim 1b:** To evaluate the efficacy of EnBrace when used as an acute treatment for MDD in a group of women (N=10) who are trying to conceive or are early in pregnancy (Group 2). Women will have major depressive episodes in this group, and may receive EnBrace as monotherapy, or as an adjunct to current pharmacotherapy.

*Hypothesis 1a:* We hypothesize that relapse rates will be lower for women who receive EnBrace compared to historical controls. MDD relapse will be determined by the Mini-International Neuropsychiatric Interview (MINI) mood module that will be administered by a study clinician at each visit.

*Hypothesis 1b:* We hypothesize that the majority of women who receive EnBrace will experience a response (50% improvement in depressive symptoms) to EnBrace therapy.

**Specific Aim 2:** To identify biological markers as potential predictors of response to EnBrace.

*Hypothesis 2:* We hypothesize that pre- to post-treatment changes in homocysteine, folate, B12, IL-6 and CRP will be associated with response to EnBrace. We hypothesize specifically that levels of folate and B12 will increase and homocysteine will decrease temporally with treatment and be predictive of prevention of depressive episodes. We hypothesize that treatment will lower IL-6 and CRP levels due to the anti-inflammatory components of EnBrace (i.e., omega-3 fatty acids) and that decreased levels of inflammatory markers may predict lower risk of depressive relapse in participants who enter the study while not on a depressive episode (Group 1), and will predict response to treatment in women who enter the study while in a depressive episode (Group 2).

**Specific Aim 3 (Exploratory):** To identify factors influencing adherence to and tolerability of treatment. This will be achieved by using qualitative methods to explore (a) perceived risks and benefits of treatment; (b) perceived side effect profile; (c) treatment convenience; (d) knowledge of, attitudes towards, and preferences for depression treatment while attempting to conceive or early pregnancy.

*Hypothesis 3:* We hypothesize that EnBrace will be perceived by patients as 1) an acceptable and attractive treatment with a favorable risk/benefit profile in the context of pregnancy or while trying to conceive, 2) well tolerated, 3) convenient and easy to adhere to, 4) will be a treatment that women who are trying to conceive or who are pregnant find intuitive and preferable to prescription antidepressant medication (or for women on antidepressant treatment in Group 2, who prefer the augmentation with EnBrace rather than an increase in antidepressant dose or augmentation with a prescription psychotropic medication).

### III. SUBJECT SELECTION

#### a. Inclusion/Exclusion Criteria

##### Group 1

**Inclusion Criteria:** Subjects will include women 18 years and older who meet the following criteria:

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1. Planning pregnancy or pregnant < 28 weeks gestation
2. Currently meet criteria for stable remission from MDD, defined as a baseline score of  $\leq 10$  on the Montgomery-Åsberg Depression Rating Scale (MADRS)
3. Current or recent treatment with an AD
4. Have elected to discontinue AD medication for pregnancy (may have already begun or completed taper)
5. Have a history of a major depressive episode/ Previous Episode of MDD, as verified using the MINI Structured Clinical Interview for DSM-5; have MDD as one of their primary diagnoses
6. Has a treating prescribing clinician for the treatment of MDD

**Exclusion Criteria:** The presence of any of the following criteria will exclude subjects from participation:

1. Current major depressive episode, as diagnosed on the MINI mood portion
2. Significant risk for self-harm or harm to others
3. Psychotic symptoms
4. Meeting criteria for a primary diagnosis of schizophrenia, an active eating disorder, dementia, delirium, or other cognitive disorder
5. Presence of an active substance and/or alcohol abuse disorder within six months prior to screening
6. Pernicious anemia or history of gastric bypass surgery
7. Seizure disorder and/or on anticonvulsant medications
8. Allergy to beeswax, soy, fish, nuts, peanuts, egg, wheat, milk, and/or shellfish
9. Non-English speaking

### **Group 2**

**Inclusion Criteria:** Subjects will include women 18 years and older who meet the following criteria:

1. Planning pregnancy or pregnant < 28 weeks gestation
2. Currently experiencing clinically significant depressive symptoms, defined as a baseline score of  $\geq 15$  on the Montgomery-Åsberg Depression Rating Scale (MADRS)
3. Experiencing a major depressive episode, as verified using the MINI Structured Clinical Interview for DSM-5; have MDD as one of their primary diagnoses
4. Has a treating prescribing clinician for the treatment of MDD

**Exclusion Criteria:** The presence of any of the following criteria will exclude subjects from participation:

1. Significant risk for self-harm or harm to others
2. Psychotic symptoms
3. Meeting criteria for a primary diagnosis of schizophrenia, an active eating disorder, dementia, delirium, or other cognitive disorder
4. Presence of an active substance and/or alcohol abuse disorder within six months prior to screening
5. Pernicious anemia or history of gastric bypass surgery
6. Seizure disorder and/or on anticonvulsant medications
7. Allergy to beeswax, soy, fish, nuts, peanuts, egg, wheat, milk, and/or shellfish

8. Non-English speaking

**b. Recruitment Sources**

We plan to enroll 10 women who meet criteria for history of MDD, have decided to stop AD medication while trying to conceive or during early pregnancy (< 28 weeks), and are eligible to receive treatment with EnBrace prenatal supplement. We also plan to enroll 10 women who meet the criteria for a current major depressive episode who are trying to conceive or pregnant (< 28 weeks), and are eligible to receive treatment with EnBrace prenatal supplement.

Potential subjects will be enrolled from four major sources:

- 1) Women who have had a previous interaction with the MGH Center for Women's Mental Health, either through research or clinically, and have consented to be contacted about future studies for which they may be eligible.
  - a. These women will be contacted by e-mail, postal mail, and phone, based on how each indicated she would prefer to be contacted by our program.
- 2) Women who are currently seen in consults who indicate to the MGH Perinatal Psychiatrist with whom they have a consult that they would be interested in adjunct or alternative medication for pregnancy
  - a. These women will be given information about the study at the end of their consult with a Perinatal Psychiatrist and asked to schedule a separate appointment for a screening interview with a member of the study staff
- 3) Women who are seen in the MGH outpatient Obstetrics department
  - a. These women will be pre-identified through preliminary screening, and approached during their clinic visit by a provider in the Obstetrics department who will introduce the study and obtain permission to be contacted by study staff.
- 4) Physicians in the community

As a group, clinicians at the MGH Center for Women's Mental Health (CWMH) have extensive experience over the last 25 years providing these consultations to women presenting for the most current information regarding both risks of AD exposure during pregnancy and risks of recurrence of underlying disorder in the setting of AD discontinuation either while planning to conceive or during pregnancy. This group, under the direction of Dr. Cohen, has a longstanding record of recruiting women for federally funded studies of depression before, during and after pregnancy derived from a potential subject pool of 900 pregravid women per year who are seen for consultation regarding the risks of psychotropic use during pregnancy. Approximately half (450) of these women are euthymic on maintenance AD therapy and are referred by their community clinicians for consultation about maintaining, changing, or discontinuing their medication for pregnancy.

During consultations by perinatal psychiatrists, the relative risks of fetal exposure to ADs are explained, as are the attendant risks of relapse/recurrence of depression in the setting of AD discontinuation. Information about the relative risks of various treatment options is provided to both the patient and the referring clinician; referring psychiatrists are contacted both by phone and in writing. Available information informing patient decisions about treatment options and the associated risk/benefit analysis is also available to patients/potential subjects through a web driven Perinatal Information Resource Center ([www.womensmentalhealth.org](http://www.womensmentalhealth.org)), run by the MGH Perinatal and Reproductive Psychiatry Program. Patients and clinicians are consistently referred to this dynamic website, which is constantly updated with the most recent data.

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As part of MGH IRB approved protocol 2002P001596, patients seen in consultation may consent to be contacted over time to monitor their plans and ultimate treatment decisions regarding AD use prior to and during pregnancy. Over the course of several years, we have established a very large cohort of women with perinatal depression and euthymic women on AD treatment of whom ultimately 50% decide to discontinue treatment prior to and during pregnancy. The pool of study-eligible subjects for the current investigation is therefore substantial; given this system, accessioning an adequate number of subjects for the pilot is assured.

At the point of enrollment, potential subjects will have already reviewed risks of perinatal treatment in a consultation with a non-study psychiatrist in the CWMH program and in collaboration with the patient's psychiatrist in the community, decided to discontinue AD treatment (Group 1) or begin antidepressant monotherapy or supplement current AD treatment (Group 2).

Consultations presenting to the CWMH are reviewed on a weekly basis by the team of the CWMH perinatal psychiatrists to provide consistency in what information is conveyed. *No subject will be referred to the study for potential inclusion until she has made an informed decision regarding AD therapy.*

Potential subjects will also be recruited through outpatient centers of the Department of Obstetrics at the Massachusetts General Hospital. Study staff will first identify potentially eligible patients prior to their appointments in the clinic and inform their health care provider that they may be eligible. The provider who is known to the potential subject and has firsthand knowledge of the patient's medical history will initially introduce the study to the patient and obtain the patient's verbal consent to be contacted or approached by study staff.

### IV. SUBJECT ENROLLMENT

#### a. Methods of enrollment

Potential subjects will be recruited from the Massachusetts General Hospital (MGH) Center for Women's Mental Health (CWMH) clinic, outpatient Obstetrics clinic, and from referrals from health care providers in the community. Interested potential participants will be referred to study staff for a pre-screening phone call. Patients potentially eligible for Group 1 will continue on in the screening process only if the patient explicitly states that she has decided to discontinue antidepressant treatment in the context of pregnancy (planning or during). Patients potentially eligible for group 2 will only continue the screening process if they state that they do not wish to start therapy with an antidepressant medication.

After a preliminary phone screening, a research coordinator working within the CWMH will schedule the patient for a baseline visit. This baseline visit will be conducted by either the principal investigator (PI) or another clinician trained in all study assessment procedures, along with trained clinical research coordinators. After an explanation of the study procedures, written informed consent will be obtained from patients prior to execution of any study assessments or procedures.

#### b. Informed Consent procedures

The study coordinator will briefly discuss the main eligibility criteria and study protocol with each woman who inquires about the study at the time of a brief phone screen. At the baseline visit, a study coordinator and licensed study physician will review the consent form in its entirety with prospective subjects. Women enrolling in this study must be capable of understanding the nature of this study as well as the discomforts and potential benefits. Any questions or areas of concern regarding the protocol

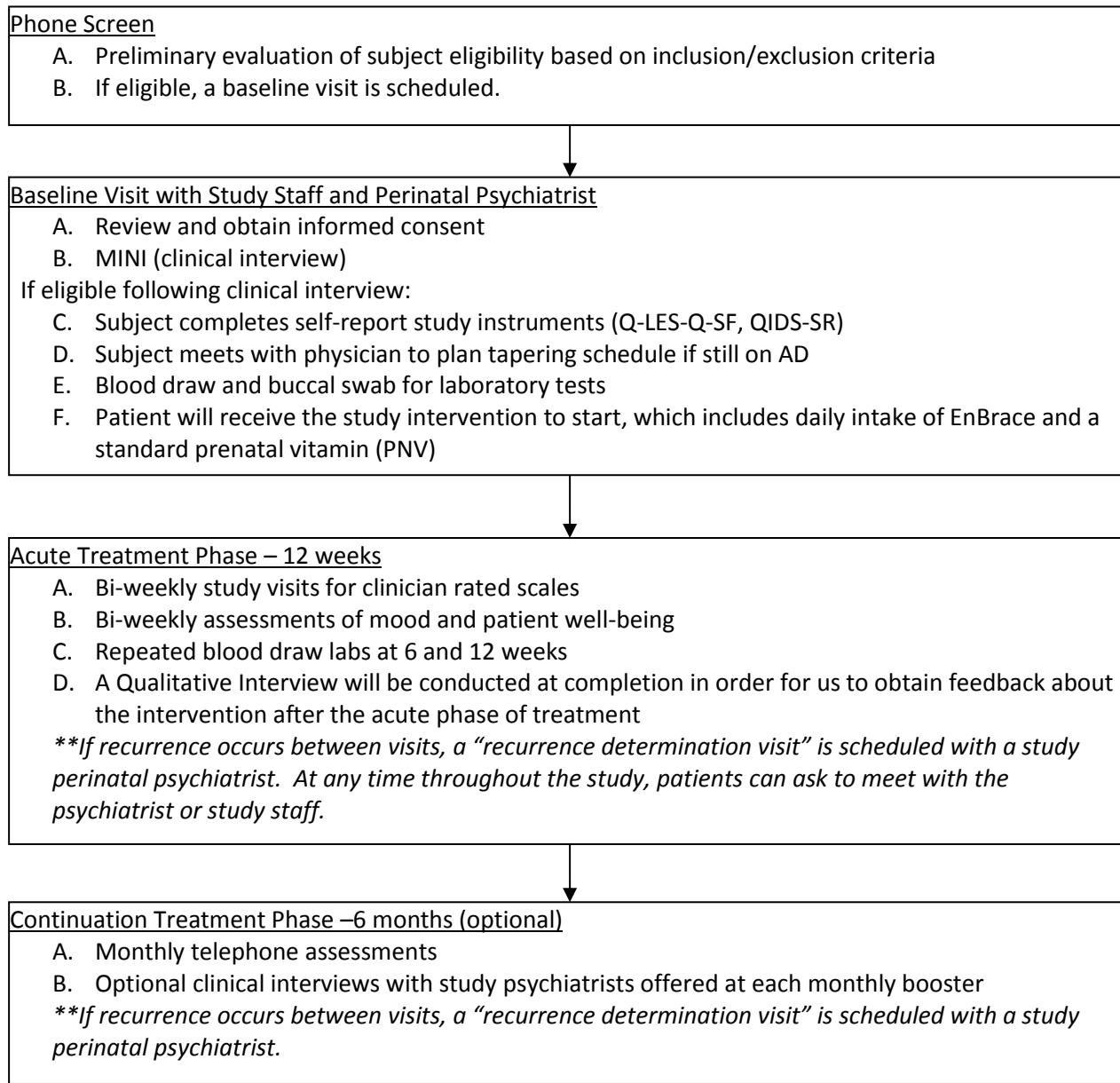
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or alternative treatment options will be addressed by one of the study physicians. If a woman feels comfortable with the study procedures, she will sign two copies of the consent form along with the study physician.

Enrolled subjects will be given a copy of the completed consent form before any study procedures are completed. If subjects have reservations about study participation at the first visit, they have the option to take the consent form home to review the decision to participate in the study with their family and health-care providers, and then return at a later date to discuss the study again with research physicians and coordinators before signing the consent form and initiating study procedures. Subjects may also elect to participate in the study remotely by phone for visits 2, 3, 5, and 6, for which verbal consent will be recorded in the subject binder. Subjects will be made aware that visits 1, 4, and 7 must be in person before signing the consent form.

### **STUDY PROCEDURES**

Patient Flow through Study Procedures:



Procedures/Data Collection

For the acute treatment phase, visits will include a baseline visit (2-3 hours), and every other week assessments (thirty minutes to one hour each). Please note that the schedule of independent outcome assessments and in-person visits may vary depending on patient scheduling issues. Furthermore, research personnel will attempt to schedule all assessments as in-person visits, however to accommodate subjects, assessments may be done over the phone.

Participants may elect to participate in visits 2, 3, 5, and 6 via phone interview rather than in-person visits. All participants must participate in visits 1, 4, and 7 in person. Study physicians will perform clinician-administered questionnaires by telephone for participants who elect to participate remotely for visits 2, 3, 5, and 6. Verbal consent will be obtained from the subject to conduct visits by phone and will be recorded in the subject's research file. Those subjects who choose to participate in visits 2, 3, 5, and 6 will receive the study drug by mail using first-class shipping to ensure appropriate dispensing and supply of the study drug over the course of the study.

Additionally, patients may request a physician meeting at any visit. Please see table below for listing of assessments at each visit.

**Schedule of Assessments: Acute Phase (12 weeks)**

Visit #	V1	V2	V3	V4	V5	V6	V7
Week #	0	2	4	6	8	10	12
MINI: full MINI at V1; depression module at follow-ups	X	X	X	X	X	X	X
Demographics, medical & psychiatric history	X						
Labs: genetic sample	X						
Labs: folate, homocysteine, B12, IL-6, CRP	X			X			X
Vital Signs: Height only at V1, weight, blood pressure	X	X	X	X	X	X	X
MADRS	X	X	X	X	X	X	X
CGI-Clinician	X	X	X	X	X	X	X
EPDS	X	X	X	X	X	X	X
QIDS-SR	X	X	X	X	X	X	X
Q-LES-Q-SF	X			X			X

A Qualitative interview will be conducted by study staff after completion of the acute treatment phase in order to obtain feedback on the intervention.

Instrument Descriptions:

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*Mini-International Neuropsychiatric Interview (MINI)*: The MINI is a widely used clinician-administered, structured interview used to diagnose psychiatric patients. It was designed to rapidly and accurately assess psychiatric illness, and has been found to be reliable and valid in making a diagnosis of MDD and other psychiatric diagnoses(73-75). The MINI can be administered by non-clinicians who are trained to administer it and the MDD section takes up to 10 minutes to complete.

*Montgomery-Åsberg Depression Rating Scale (MADRS)*: The MADRS is a widely used 10-item clinician-rated scale that describes the severity of depressive symptoms (range  $\geq 60$ , higher score indicates more depression symptoms)(76). The MADRS has good internal consistency (Cronbach's  $\alpha = 0.82$ ), test-retest reliability (correlation 0.90), and validity and is highly sensitive to changes with treatment(76-78). Remission of depression in clinical trials has been defined loosely as a final MADRS score  $<10$  or, more strictly, as a score  $<5$ (79).

*Clinical Global Impressions Scale (CGI)*: The CGI contains 7-point global severity and change (improvement) scales and will be used as an overall outcome measure(80).

*Quick Inventory of Depressive Symptoms (QIDS-SR)*: The QIDS-SR is a 16-item self report rating scale for depressive symptoms. This instrument was used in the STARD effectiveness trial, in which  $>4000$  depressed patients were enrolled. In a recent paper, Trivedi and colleagues reported on the psychometric properties of the QIDS-SR, including documentation of high concurrent validity and internal consistency(81).

*Edinburgh Postnatal Depression Scale (EPDS)*: This measure is a 10-item self-report used to measure postpartum depressive symptoms and takes  $<5$  minutes to complete(82). This scale will be one of our outcome measures for depressive symptoms. It has been validated in community and obstetrical samples. A score of  $\geq 10$  is suggestive of perinatal depression. Because it measures symptoms and is not diagnostic of a relapse, we will use the MINI to assess the recurrence of a major depressive episode. The EPDS is widely utilized in multidisciplinary settings and de-emphasizes somatic symptoms that are common in pregnancy and postpartum. The EPDS is validated for use in pregnancy as well as postpartum with good specificity and sensitivity(83).

*Quality of Life Satisfaction Questionnaire Short Form (Q-LES-Q-SF)*: The Q-LES-Q asks questions in 8 modules of 6-16 questions each, about physical health/activities, general feelings of well being and relaxation, function at work, household duties, school or course work, leisure activities, social relations, and general activities over the past week(84). The "short form" includes only the General Activities section. Patients are asked to rate the answers on a scale of 1-5, from "not at all or never" to "frequently or all the time." Answers in the "frequently" range indicate greater satisfaction with life. A total score for the "short form" is calculated by simply totaling answers to all 16 items of the General Activities section.

### Laboratory Measures

Blood samples will be collected for laboratory analyses that may serve as biomarkers of treatment response. These include levels of biologic measures that are associated with folate metabolism and inflammatory markers that may be associated with omega-3 fatty acid intake (known to be anti-inflammatory). The following will be assessed at baseline, 6 weeks, and 12 weeks: folate, B12, and homocysteine levels; IL-6 and CRP, inflammatory markers. Cheek swab samples for genetic testing will be collected at baseline for polymorphisms associated with folate metabolism (i.e., genes encoding for MTHFR, methylene tetra-hydro folate reductase).

### Drop criteria:

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1. Participant experiences severe worsening of depression symptoms, as indicated by a CGI-I of 6 or 7 on 2 consecutive visits determined by a licensed study psychiatrist. Subjects with a CGI-I of 6 or 7 on 2 consecutive visits will be terminated from the study and referred for additional clinical treatment as needed.
2. A Group 1 participant who is not experiencing depression symptoms decides to restart antidepressant treatment while they are well
3. A Group 2 participant who enrolled during a current depressive episode has either started a new antidepressant or increased the dose of an antidepressant they were already taking
4. Emergence of suicidal ideation, homicidal ideation, or psychotic symptoms. The anchors for suicidality will include the QIDS-SR, Question 12 (with an answer of 2 or 3) and the MADRS, Question 10 (with an answer of 4, 5, or 6). Acute suicidality, based on these measures and the licensed psychiatrist's clinical assessment, will result in termination of participation in the study and swift triage to the Acute Psychiatry Service at Massachusetts General Hospital.
5. Evidence of abuse or misuse of study medication
6. Evidence of current alcohol and/or drug abuse
7. Any severe or unstable medical illness that includes concern regarding safety of continued use of study medication
8. Intolerance to study medication as determined by research clinician
9. Significant hypersensitivity reaction
10. Inability or unwillingness to complete the study procedures

## V. BIOSTATISTICAL ANALYSIS

We will compare the rates of depressive relapse and duration of time out of a depressive episode for Group 1 participants, and compare these data to historical controls that were also assessed prospectively. For Group 2, we will compare depressive response rates (response defined as 50% reduction in depressive symptoms on the MADRS, our primary outcome) to response rates in studies of SSRIs for the treatment of depression.

In addition, we will monitor depressive symptom burden with continuous variables across the treatment study for both groups.

To control for prenatal vitamin (PNV) use, we will supply a standard PNV to each participant to take daily in combination with EnBrace. The Sponsor has offered to supply the PNV, such that each participant will take the same PNV; this will lower the risk of inconsistencies between participants. In the statistical analysis, the data collected in this preliminary study will be compared to historical controls with a history of MDD who discontinued AD maintenance therapy during pregnancy, most of which were taking standard PNVs, but not EnBrace. This reference will allow us to estimate the relative efficacy of EnBrace in relapse prevention of women who discontinue maintenance ADs for pregnancy.

### Exploratory Analyses

We will also explore the collected laboratory tests as potential biomarkers.

## VI. RISKS AND DISCOMFORTS

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Subject burden for participation includes the time spent participating in study visits. Visits will include a baseline visit (2-3 hours), follow up visits (30 min to one hour each), and three blood draws over the course of the study. The total time burden for subjects is similar to our previous investigations involving very similar populations. Risks of this study include potential psychological distress that may occur during treatment and assessment visits, during which history, current symptoms and life stressors are discussed. Participation in this study does not directly affect risk for recurrence or worsening of depression. To be eligible, subjects must have already made an informed decision regarding antidepressant treatment in the context of pregnancy. Study assessment and treatment visits may increase recognition of symptom worsening and ensure that appropriate treatment is provided. Patients who experience worsening of depressive symptoms will be presented with options for treatment, including antidepressant medications.

According to the NIH National Library of Medicine, adverse reactions to EnBrace that have been reported include: allergic sensitization associated with folic acid; paresthesia, somnolence, nausea, and headaches associated with pyridoxine; and mild transient diarrhea, polycythemia vera, itching, transitory exanthema and the feeling of swelling of the entire body associated with cobalamin. Finally, EnBrace may cause allergic reaction. If patients have any side effects, they will be instructed to report them immediately to the study doctor. If any subject develops an adverse event, the adverse event will be reported to the MGH IRB consistent with Human Research Committee (HRC) guidelines. EnBrace carries no known risks to an embryo, fetus, or breastfeeding infant.

This research study poses the potential risk of subjects consuming higher than recommended doses of B vitamins, iron, and folate when taking EnBrace in combination with a standard prenatal vitamin. The 1.5 milligrams of iron contained in EnBrace is very minimal such that when combined with iron in the typical PNV, there would be little to no risk of exposure to higher than recommended levels of iron. This is also the case for certain B vitamins, which are present in minimal level in EnBrace. Finally, there is potential risk for consumption of higher than recommended doses of folic acid, which can mask vitamin B12 deficiency. To minimize this risk, we will exclude patients with known pernicious anemia or who have had gastric bypass, which may lead to a vulnerability to vitamin B12 deficiency.

As with any clinical research study, there is a potential risk for loss of confidentiality. We will make every effort to keep personal health information confidential.

### Risks of Blood Draws

Phlebotomy can cause pain, bleeding or bruising at the site where the needle enters the vein. Some subjects may feel dizzy or light-headed during a blood draw. There is a very small risk of infection at the site from which we take the blood. A suspected infection would be treated with antibiotics and the subject would be encouraged to follow up with their primary care physician.

### Adequacy of Protection against Risks

Salient safety issues that we address in this section include: 1) ensuring that patients do not feel obligated to enroll in the study, but elect to participate by their own volition 2) caring for patients who may experience a recurrence of their depression during the course of the study 3) maintaining the confidentiality of the study subjects, and 4) ensuring that staff are sensitive to issues of beneficence, justice, race, ethnicity, and gender. The following elements of our proposal are designed to reduce risk for human subjects.

### Recruitment and Informed Consent

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Subjects will be recruited through the MGH Center for Women's Mental Health and clinician referrals, under the direction of Dr. Marlene Freeman and Dr. Lee Cohen. At the outset of the proposed investigation, staff psychiatrists and research assistants of the MGH Center for Women's Mental Health will participate in a one-hour meeting with the study PI and co-PI for the purpose of reviewing the aims, design and selection criteria for the proposed investigation.

This clinical and research group sees 900 women annually who are seeking consultation for expert guidance in evaluating the risks and benefits of discontinuing psychotropic medication proximate to pregnancy. Over the last five years, half of these women have suffered from recurrent major depression and have presented on maintenance AD therapy.

We have spent the last decade recruiting a sample of women for perinatal depression (e.g. Prospective Pregnancy Study, n=201, Postpartum Study, n= 129). Under a separate MGH IRB approved protocol we have permission for ongoing dynamic contact with these patients as they proceed through their reproductive life cycles. Through this system, we have recruited participants for two large scale research studies involving pregnancy.

Also, for an NIMH R-21 funded study to assess depressive relapse risk in women undergoing infertility treatment, we successfully recruited 49 participants. We also recruited N=12 women for a CBT study in pregnancy, designed to utilize CBT to reduce the risk of depressive relapse in women trying to conceive and discontinuing ADs.

The Clinical Research Department has a seamless relationship with the Clinical Center. At the Clinical Center, psychiatrists see over 600 women a year for consults regarding treatment recommendations for psychotropic medication during pregnancy.

Every woman who comes to either the Research Program to participate in a clinical trial or for a consult with one of the psychiatrists in our program has the opportunity to fill out a form allowing us to enter her information into our tracking system. This is also complemented by our internet resource center ([www.womensmentalhealth.org](http://www.womensmentalhealth.org)) as well as a seasonal e-newsletter with nearly 4,000 subscribers.

These critical recruitment tools generate a constant flow of patients that may be eligible and interested in participating in the current study. If a potential Group 1 patient indicates that she is undecided on whether she wants to discontinue her antidepressant treatment or elects to stay on antidepressant treatment, she will not be informed about the current study.

Informed consent will be obtained by one of the research psychiatrists from patients at the start of the baseline visit, prior to conducting any study assessments or procedures. The PI or another member of the study team (MD or PhD-level clinician) who is trained in all study assessment procedures will review the consent form with all patients. Subjects in this study must be capable of understanding the nature of this study as well as the discomforts and potential benefits. These will be explained in full by the HRC-approved research staff. All subjects will then be asked to read, understand, and sign the informed consent prior to participation.

### **Protection Against Risk**

As discussed above, in order to (1) prevent patients from feeling obligated to participate in the study, subjects eligible for Group 1 will only be enrolled if they decide to discontinue AD treatment. Subjects eligible for Group 2 will only be included if they have decided not to accept treatment with an antidepressant medication (if not currently on an antidepressant) or opt not to increase the dose or add an adjunctive antidepressant medication (if presenting on an antidepressant). The risks and benefits of

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discontinuing maintenance AD treatment will be described to the patient in detail. Additionally, the research clinician will inform the patient that they can choose, at any point, to reinitiate AD treatment.

For (2) prompt identification of patients who experience a depressive recurrence or worsening of acute depression during the study, it is likely that over the course of the investigation some women may have significant psychiatric symptoms requiring acute intervention and/or evaluation and referral. The investigators have the clinical expertise and resources available to provide acute evaluations and, if needed, referral. The Acute Psychiatry Service of the MGH is staffed and available 24 hours/day to handle psychiatric emergencies. Because subjects are assessed for mood symptoms at each study assessment visit, the likelihood that symptom worsening will be identified in a timely manner is increased.

As in all clinical research studies, it will be critical to (3) maintain the confidentiality of the women with psychiatric illnesses and/or treatment. Data collected in the study will be used for research purposes only. All members of the research team will treat all data with strict confidentiality. All members of the research team, prior to working on a research protocol, are required to complete a designated course in the ethics and regulations governing research with human subjects. Documentation of completion of this course will be required for all study personnel at the beginning of the investigation. Subject confidentiality will be assured by use of identification numbers on pre-coded data collection sheets. Only one master log with identifying information linking the patient name and the identification number will be maintained and kept in a secure location separate from the remainder of the study data. Signed informed consent forms will be kept in a locked room for documentation purposes. Any paper data obtained during the investigation, which includes interview, symptom rating scale, and lab result forms, will be kept in a separate secure filing cabinet with access limited to the research team. After recruitment and analysis of data are complete (at the end of the funding period), all subjects' identifying information will be destroyed and will not be included as part of long-term storage of data sets. No data will be reported on an individual basis; all findings will be presented in aggregate.

Additional steps will be taken to protect confidentiality of genetic data as outlined:

1. All study staff are trained to make confidentiality of genetic data a priority.
2. No genetic research data (or any other data related to the study) will be entered into the medical record.
3. The results of the genetic analyses will only be shared with participants who elect to receive them through secure email, postal mail, or in person at study visits using an approved letter. This information will not be shared with their family members or unauthorized third parties. All questions regarding genetic results will be deferred to participants' treating providers.
4. Genetic data are encoded using coded identifiers. These codes, rather than personal identifiers, are used in any analytic datasets. The code key linking coded identifiers to personal identifiers are kept in an access-restricted, password protected electronic file and are not shared with the genetics laboratories.
5. Samples and genetic data stored in the laboratory will be identified only by the code numbers and laboratory personnel will not have access to personal identifiers.
6. The most serious risk would be identification of individuals in the publicly shared database. To prevent this, computerized data files provided to other investigators will not include any of the HIPPA-defined personal identifiers.

In order to assure that the (4) subject's personal contribution to this research study is acknowledged, all study staff will receive training in human subject research, which includes emphasis on issues of confidentiality, respect, beneficence, justice, race, ethnicity and gender.

## **VII. POTENTIAL BENEFITS**

There are many benefits that may result from participation in the proposed investigation. Subjects enrolled in the study will contribute to the base of scientific knowledge concerning effective methods to 1) discontinue AD treatment proximate to conception, 2) prevent recurrence of depression during a high-risk period, and 3) treat acute depression with alternative or adjunct pharmacotherapy. If a safety issue or mental health problem is identified during a study assessment, the subject will benefit from having the study team member facilitate management of her symptoms. If subjects do experience a depressive recurrence or other clinical deterioration during study participation, the study team will facilitate referral for coordination of care. Since contact with the study team will occur at multiple time points, subjects will have the opportunity to easily access experts in the area of depression and pregnancy. Subjects who request the results of the MTHFR genetics analysis may benefit from useful information regarding folate use in the context of pregnancy-related decision-making with their providers. Lastly, subjects will be compensated \$50 at three time points for a total of \$150 for their participation in the study. Parking validation will be provided to cover costs of parking fees during study visits. The study may additionally compensate for travel expenses for MBTA public transportation if requested.

## **VIII. MONITORING AND QUALITY ASSURANCE**

During the course of the protocol, study and non-study related events such as hospitalization or recurrence of depression may occur, therefore risk management protocols are in place to address these events as they occur. All professional and technical staff are fully trained and available to manage adverse events. Physicians are available by phone and pager to be informed of serious adverse events. These events will be promptly reported to the MGH IRB, according to the Code of Federal Regulations, and the subject's primary care and mental health providers will also be informed.

At each visit, study physicians will prompt the participant to report any occurrences of health problems beyond the subject's depression. Any serious or non-serious adverse event will be recorded in the participant's study binder at each examination. Serious and non-serious adverse events will also be reported to the Human Research Committee in accordance with Human Research Committee reporting guidelines, following the timeframes specified by the Partners Investigator's Guidelines. In case of a serious adverse event, appropriate diagnostic and therapeutic measures will be taken, as determined by the investigator. All adverse event reports will be reviewed by the principal investigator and reported to the FDA in accordance with the guidelines outlined in the Investigational New Drug application.

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