**“Premenstrual Syndrome Etiology (PMSe)”**

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| AUDIT | Alcohol Use Disorders Identification Test |
| CEDAR | Clinical and Experimental Drug Addiction Research Lab |
| CCTS | Center for Clinical and Translational Science |
| COI | Conflict of Interest |
| COP | College of Pharmacy |
| DRSP | Daily Record of Severity of Problems |
| DSM-5 | Diagnostic and Statistical manual of Mental Disorders, 5th Edition |
| E3G | Estrone-3-Glucuronide |
| FDA | Food and Drug Administration |
| FSH | Follicle Stimulating Hormone |
| hCG | Human Chorionic Gonadotropin |
| HIPAA | Health Insurance Portability and Accountability Act |
| ICD | Informed Consent Document |
| IRB | Institutional Review Board |
| LH | Luteinizing Hormone |
| OHRP | Office of Human Research Protections |
| OPRS | Office for the Protection of Research Subjects |
| PMSe | Premenstrual Syndrome Etiology |
| PHI | Protected Health Information |
| PI | Principal Investigator |
| PMDD | Premenstrual Dysphoric Disorder |
| PMS | Premenstrual Syndrome |
| QA/QI | Quality Assurance/Quality Improvement |
| SAE | Serious Adverse Event |
| SOP | Standard Operating Procedure |

## 1.0 PROJECT SUMMARY/ABSTRACT

Premenstrual syndrome (PMS) is an important quality-of-life issue that affects approximately 30% of women. The cause of the disorder is poorly understood. It has been hypothesized that individual gonadal (i.e. ovarian) hormone kinetics - reflecting trajectories of hormone concentration over time - are critical for understanding the etiology of PMS. Another important factor in the etiology of PMS is stress.

The purpose of this study is to thoroughly evaluate how individual hormone kinetics and reactivity to stress contribute to the etiology of PMS. The study will enroll healthy women with regular menstrual cycles. They will chart their symptoms, menstruation timing and ovulation during the **two menstrual cycles while in the study.** This data will form the basis for PMS/PMDD diagnosis**.** In the **second menstrual cycle**, participants will complete the following study procedures:

- Blood draws and salivary sample collection at 8 different times of the menstrual cycle
- Psychosocial stress testing

If the second menstrual cycle is anovulatory, blood draws and salivary sample collection will be repeated in the third menstrual cycle. Knowledge gained from this experiment will increase our understanding of the underlying etiology of PMS.

## 2.0 BACKGROUND/SCIENTIFIC RATIONALE

Premenstrual syndrome is characterized by the presence of affective and physical symptoms that begin in the late luteal phase of the menstrual cycle and resolve in the early follicular phase. Most women of reproductive age experience one or more mild emotional or physical symptoms for one to two days before the onset of menses. In contrast, clinically significant PMS is defined as at least one symptom associated with economic or social dysfunction that occurs during the five days before the onset of menses and is present for at least three consecutive menstrual cycles (American College of Obstetricians and Gynecologists). Though women with PMS experience a wide variety of recurrent physical and cognitive symptoms, the core symptoms include affective symptoms, such as depression, irritability, and anxiety, and somatic symptoms, such as breast pain, bloating and headache.

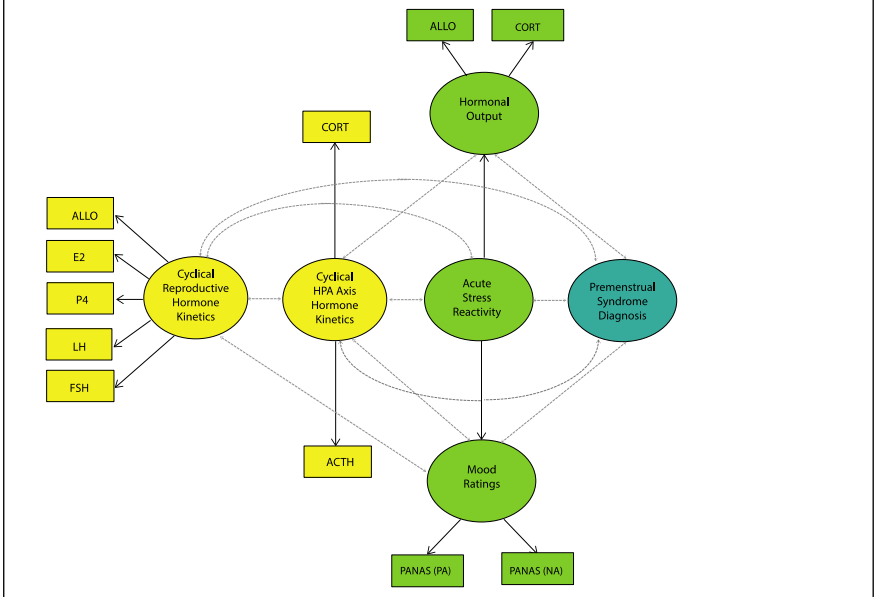



Figure 1. Graphic presentation of study measures designed to investigate gonadal, HPA axis and acute stress reactivity as causal PMS factors.

Our study will evaluate reproductive and HPA axis hormonal changes over the course of the menstrual cycle. Study participants with and without PMS/PMDD diagnosis will provide blood and saliva samples at 8 specific, ovulation-guided time points in the menstrual cycle (Figure 1, left side, yellow color). Saliva is collected to measure cortisol levels, as cortisol is a biological marker of stress. Additionally, they will complete the Trier Social Stress Test (Figure 1, middle, green color) to assess how acute stress exacerbates PMS. The main hypothesis is that variability in cyclical reproductive hormone kinetics will

indirectly affect PMS/PMDD diagnosis (Figure 1, right side, teal color) via a single pathway running through cyclical HPA axis hormone kinetics and acute stress reactivity.

## 3.0 OBJECTIVE/AIMS

Specific Aim 1 will establish case and control study cohorts with individualized timing of menstrual cycle phases as well as cycle-related psychological and physical symptoms. Participants with regular menstrual cycles will chart their symptoms and menstruation timing during **two menstrual cycles**. In addition, they will self-test LH surge for the purpose of estimating ovulation timing. This will generate two study cohorts: one with PMS/PMDD diagnosis and a healthy control with predictable bounds of menstrual cycle phases.

Specific Aim 2 will test differences in the gonadal and HPA axis hormones (measured at 8 individualized time points **in the second menstrual cycle**) between women with *vs.* without PMS/PMDD diagnosis.

Specific Aim 3 will test differences in stress reactivity between women with *vs.* without PMS/PMDD diagnosis. The stress reactivity procedure will be scheduled **in the second menstrual cycle**.

The duration of this research study is 4 years, starting November 2018 – November 2022.

## 4.0 ELIGIBILITY

Women between the ages of 18 and 35, with regular menstrual cycles lasting 21 to 35 days (Gingnell et al., 2013; Deng et al., 2018; Solis et al., 2008; Sohda et al., 2017) will be recruited for the study. They will be non-illicit drug using healthy individuals. Potential study participants who are not currently taking medications that affect central nervous system (CNS) or hormonal levels are eligible to participate in this study. They will also be asked to provide a breath sample to rule out smoking. They will be without past or current Axis 1 disorder (except anxiety or depression) or current anxiety or depressive disorder. Section 4.2 lists all the exclusionary criteria. Study participants will be recruited from the general population using electronic media (ex: Craigslist, UIC classifieds), flyers, and word-of-mouth referrals.

Research staff will assess eligibility criteria in an in-person screening visit based on a detailed flowsheet created specifically for this study. All research staff will be trained by the PI on assessing inclusion/exclusion criteria. Training logs will be securely stored and kept on file in the PI's laboratory. As the final approval of subject enrollment, study PI will sign off on all study participants who passed the screening session.

After completing each step of the screening and session flowsheet, research staff will mark time of completion and his/her initials. The PI will document approving participants for study participation on the flowsheet.

### 4.1 INCLUSION CRITERIA

- Female
- Aged 18-35 years
- Average menstrual cycle 21-35 days
- Access to smartphone compatible with Clearblue® Connected application for daily use

### 4.2 EXCLUSION CRITERIA

- Lifetime DSM-5 Axis 1 disorder (except anxiety and depression), as documented in the Mental Health Interview
- Current DSM-5 Axis depressive or anxiety disorder, as documented in the Mental Health Interview
- Positive urine drug screen test
- AUDIT > 8
- Self-reported smoker or carbon monoxide concentration ≥ 6 ppm
- Irregular menstrual cycle
- Current pregnancy (urine test-verified) or lactation, or a plan to become pregnant

- Moderate or high suicide risk
- Shipley IQ (vocabulary standard score) > 80
- Prescription medications that affect CNS and/or hormone levels
- Hormonal contraception (i.e. IUD or implant)
- Illicit Drug Use

### 4.3 EXCLUDED OR VULNERABLE POPULATIONS

Vulnerable populations will not be included in the study. Participants who don't speak English are not included in the study because the questionnaires and study instructions have been developed in the English language.

## 5.0 SUBJECT ENROLLMENT

Study participants will be recruited from the general population using electronic media (ex: Craigslist, UIC classifieds, social media), flyers, and word-of-mouth referrals. One paper flyer and one electronic flyer (attached to this application) will be distributed. The telephone number and email of the CEDAR Lab will be included in paper and electronic advertisements. Prospective participants will contact the lab to complete an initial screening survey in REDCap (see attached "Initial Survey"). All contact with participants will be conducted through the lab's UIC email address or UIC office phone number. Participants who email the lab will be sent an introductory email outlining study goals and directed to fill out the REDCap survey. Participants who phone the lab will be asked to provide an email address, following which lab personnel will send the introductory email.

Additionally, CEDAR Lab will obtain identified data from CCTS CRDW - UIC CIRCLE specifically for the purpose of recruiting potential participants with premenstrual dysphoric disorder (PMDD). The requested data set will include names, email addresses, telephone numbers, street address, city, and state for females between ages 18-35 with PMDD diagnosis (ICD-10-CM F32.81 or ICD-9-CM 625.4). Lab personnel will telephone or send an introductory email to potential participants outlining study goals and inviting those interested to fill out the REDCap survey. If lab personnel are unable to reach potential participants by email or telephone, a letter will be sent out through mail with information regarding the study using the address provided in the data set. Study personnel will follow the attached "Screening Script" for communications with participants that occur prior to their in-person consent.

CEDAR Lab will use the following online research study posting systems for recruiting participants: ResearchMatch.org, UI Health Research Registry, and The New Normal Match. Interested volunteers may communicate through the online research study posting systems. Volunteers of interest will be contacted with an introductory email via the respective portal.

The first question of the initial survey is an auxillary consent question. Individuals who answer "No" to the question "Does the CEDAR Lab have your consent to ask you questions regarding the PMSe Study?" will not be allowed to complete the initial survey. The initial survey contains questions about their substance use history to determine eligibility for the study as outlined in Sections 4.1 and 4.2. In the version 12 of the Protocol, the ACOG question was removed and included in the initial survey. Prospective participants who pass the initial survey will be scheduled for an in-person screening to determine eligibility for the study as outlined in Section 4.1 Inclusion Criteria and Section 4.2 Exclusion Criteria.

Data gathered from participants who fail to meet inclusion criteria will be kept with all study documentation in the event the same participant returns with information different than previously reported. In this event, research staff will be able to compare responses and optimize subject protection and study integrity. Following study completion, all data gathered from participants who failed screening criteria will be shredded with remaining study documentation.

The consent procedure is detailed according to processes established in the Code of Federal Regulation and the University of Illinois Institutional Review Board. All research staff responsible for screening participants will be trained by the PI and document screening protocol in the Screening Flowsheet. The informed consent procedure will be carried out in a private and a quiet setting. Prior to initiating the procedure, the person consenting will ensure that the individual is an adult, is able to read, and understands the English language. The most recent version of the ICD will be used. The individual obtaining consent will briefly summarize each section of the ICD. Non-resident alien status will be ascertained and will be confirmed during the consent process. Study participants will be informed that the payments must be processed in accordance with the section "Will I be reimbursed for any of my expenses or paid for my participation in this research study?" of the informed consent form. Non-resident aliens who cannot provide the appropriate documents to receive payments will not be eligible to participate in the study. Study participants will be given ample time to review the document and encouraged to ask clarifying questions. Questions will be noted in the ICD by research staff. Participants who do not accept the use of the Clearblue Connected application on their compatible smartphone will not be allowed to participate in the study. The participant will be provided with a signed copy of the ICD.

## 5.1 PARTICPANT COMPENSATION

Participants will be compensated up to $330-525 for completed activities. Completion of menstrual cycle 1 will be compensated as $35. In the menstrual cycle 2, participants will be compensated $15 for visits 1-5 and $20 for visits 6-8 completed during cycle 2. Participants who did not reach LH peak in cycle 2 will return to complete additional visits in cycle 3 and will be compensated $25 for blood draw visits 1-5 and $30 for blood draw visits 6-8. Participants will be compensated $20 only if computerized tasks of cognition are completed on both blood draw visit 2 or blood draw visit occurring on same day as peak LH and blood draw visits 7 or 8. Participants will be compensated with $140 for completion of the Trier Social Stress Test. Depending on immigration status in the United States and UIC employment status, participants will receive compensation as a combination of cash and a check in the mail, as a combination of cash and through the payroll system, only as a check in the mail, or only through payroll system.

See Table 1 for details.

Table 1. Participant Compensation

| | **Permanent resident or a US citizen (UIC Employees)** | | **Permanent resident or a US citizen (non-UIC Employees)** | | **Nonresident alien eligible to receive payment*** | |
|---|---|---|---|---|---|---|
| **Compensation for Study Part** | **Amount** | **Timeline** | **Amount** | **Timeline** | **Amount** | **Timeline** |
| Menstrual Cycle 1 | $35 in cash | $35 on visit 1 of Menstrual Cycle 2 | $35 in cash | $35 on visit 1 of Menstrual Cycle 2 | $35 as a check | Check within 4 to 6 weeks |
| Menstrual Cycle 2 ** | $15 per visit for visit 1-5<br>$20 for visit 6-8<br>$140 for completion of | $100 in cash on visit 8.<br>Payroll within 4 to 6 weeks | $15 per visit for visit 1-5<br>$20 for visit 6-8<br>$140 for completion of | $100 in cash on visit 8.<br>Check within 6 to 8 weeks | $15 per visit for visit 1-5<br>$20 for visit 6-8<br>$140 for completion of | Check within 6 to 8 weeks |

| | | | | | | |
|---|---|---|---|---|---|---|
| | the 4-hour task session. | | the 4-hour task session. | | the 4-hour task session. | |
| Menstrual Cycle 3) *** | $25 per visit for visit 1-5<br><br>$30 per visit for visit 6-8 | Payroll within 4 to 6 weeks | $25 per visit for visit 1-5<br><br>$30 per visit for visit 6-8 | Check within 6 to 8 weeks | $25 per visit for visit 1-5<br><br>$30 per visit for visit 6-8 | Check within 6 to 8 weeks |

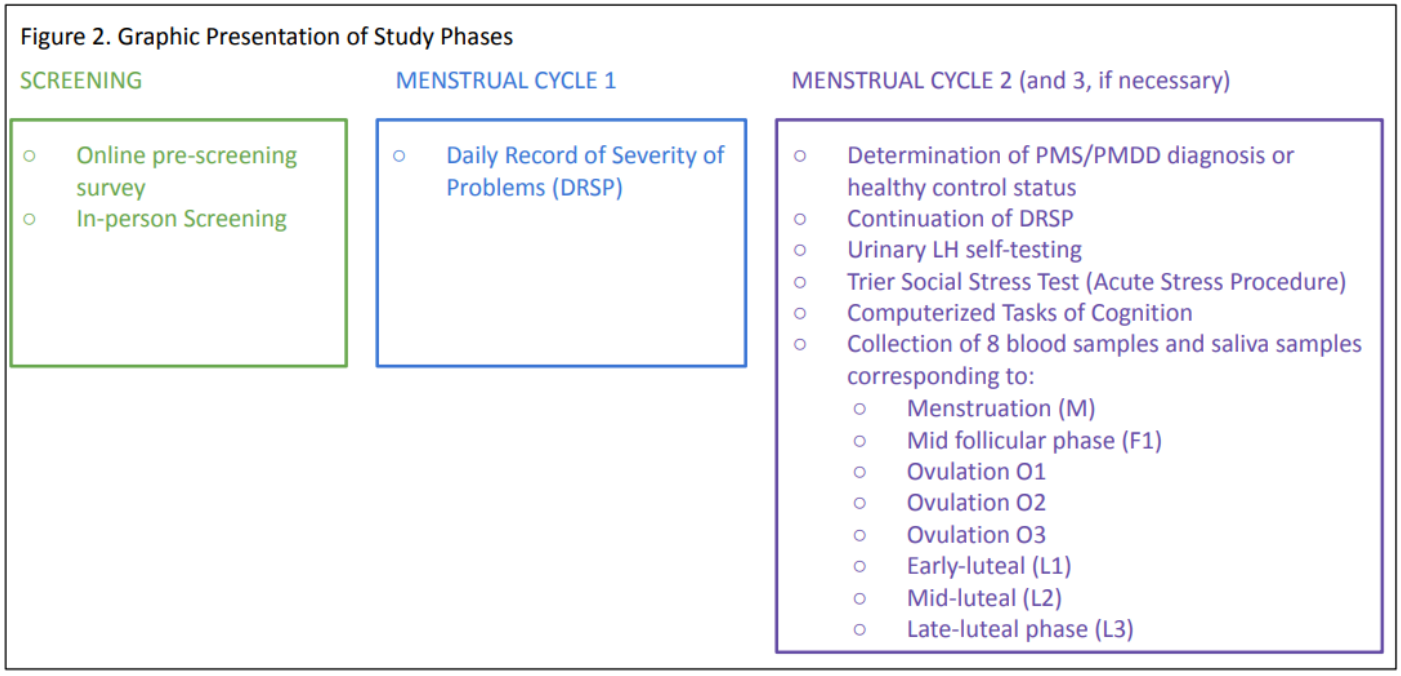
## 6.0 STUDY DESIGN AND PROCEDURES

This study will be conducted only at the University of Illinois. Study spaces will be rented at the Center for Clinical and Translational Science. Research staff working out of the PI's laboratory will ensure regulatory compliance, recruit participants, and collect and analyze data. The PI's lab is located on the first floor of UIC College of Pharmacy. Study materials, equipment, and all paper documentation will be locked in the office of research staff affiliated with the study. This is a cohort design study. Participants' data will be shared in a de-identified manner with a National Institute of Health (NIH) NIMH data repository.

## 6.1 PROCEDURES AND ASSESSMENTS

Procedures and assessments occurring in each study phase is outlined in figure 2.

Figure 2. Graphic Presentation of Study Phases




### 6.1A. SCREENING

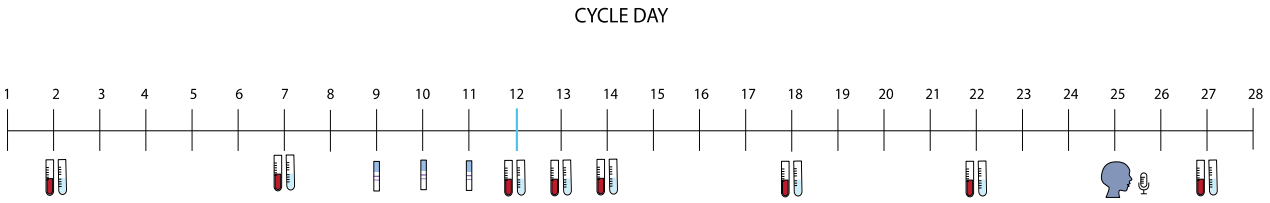
Following the completion of the online survey, study participants will be scheduled for an in-person screening interview, at which time all the criteria listed in sections 4.1 and 4.2 will be assessed. Participants will also be instructed to complete a Demographics Survey during the screening. The purpose of the Demographics Survey is to compare the makeup of each experimental group and ensure that there is no significant demographic difference in the composition of the PMS/PMDD case vs. control group.

### 6.1B. MENSTRUAL CYCLE 1

The purpose of menstrual cycle 1 and 2 are to establish Premenstrual Syndrome diagnosis, Premenstrual Dysphoric Disorder diagnosis, or the healthy control status. Every day, participants will be asked to complete

the Daily Record of Severity of Problems (DRSP) (Endicott et al., 2006) in which they will chart their menstruation timing as well as give a score of 1 to 6 for affective or somatic symptoms according to their severity. Study physician, Dr. Christopher Holden (Assistant Clinical Professor of Psychiatry/Director of Addiction Psychiatry at UIC) will review DRSPs and provide Premenstrual Syndrome diagnosis when mean score 5 days before menstruation exceeds 50, mean luteal phase score is at least 30% higher than that of the follicular phase, and at least 3 symptoms score more than 3 in the 2-month period (see Deng et al., 2018, supplement). Otherwise, study participants will be classified as healthy controls. Dr. Holden's role on the project is to provide the PMS or PMDD diagnosis as well as help with the recruitment of study participants. In addition, the study physician will be responsible for suicidality risk assessment (see Section 8.0).

Figure 3. Graphic Presentation of Menstrual Cycle 2 Procedures




## 6.1C. MENSTRUAL CYCLE 2

Table 2. Original Schedule of Study Visits According to Average Cycle Length

| Average cycle length (days) | Visit 1 Menses | Visit 2 Mid follicular | Visit 3 Periovulatory 1 | Visit 4 Periovulatory 2[a] | Visit 5 Periovulatory 3 | Visit 6 Early luteal | Visit 7 Mid luteal | Visit 8 Late luteal |
|---|---|---|---|---|---|---|---|---|
| 21 | 2 | 4 | 5 | 6 | 7 | 11 | 15 | 20 |
| 22 | 2 | 4 | 6 | 7 | 8 | 12 | 16 | 21 |
| 23 | 2 | 5 | 7 | 8 | 9 | 13 | 17 | 22 |
| 24 | 2 | 5 | 8 | 9 | 10 | 14 | 18 | 23 |
| 25 | 2 | 6 | 9 | 10 | 11 | 15 | 19 | 24 |
| 26 | 2 | 6 | 10 | 11 | 12 | 16 | 20 | 25 |
| 27 | 2 | 7 | 11 | 12 | 13 | 17 | 21 | 26 |
| 28 | 2 | 7 | 12 | 13 | 14 | 18 | 22 | 27 |
| 29 | 2 | 7 | 13 | 14 | 15 | 19 | 23 | 28 |
| 30 | 2 | 8 | 14 | 15 | 16 | 20 | 24 | 29 |
| 31 | 2 | 8 | 15 | 16 | 17 | 21 | 25 | 30 |
| 32 | 2 | 9 | 16 | 17 | 18 | 22 | 26 | 31 |
| 33 | 2 | 9 | 17 | 18 | 19 | 23 | 27 | 32 |
| 34 | 2 | 10 | 18 | 19 | 20 | 24 | 28 | 33 |
| 35 | 2 | 10 | 19 | 20 | 21 | 25 | 29 | 34 |

In the menstrual cycle 2 (Figure 3), study participants will continue daily DRSP completion. Study participants will use the Clearblue Connected smartphone application (free to download) during menstrual cycle 2 which

records results from daily Clearblue Connected Ovulation Test System urine tests in order to capture LH surge. A participant will start the testing according to the manufacturer's instructions. Only one sample (i.e. the first daily urine sample) is tested per day before 7:00 AM. Participants will take a photo of the result and upload it to REDCap, to measure adherence.

**Based on the average menstrual cycle length from cycle 1, participants will be provided with a blood draw schedule outlined in Table 2 on their first day of menses, though blood draw visits 3, 4, and 5 may change depending on the results of the ovulation test. If the ovulation monitor indicates "peak" fertility outside of blood draw visits 3, 4, or 5, study participants will be required to come to the CCTS the same day and the subsequent 2 days. For example, a participant with 32 day-cycle is tentatively scheduled for blood draws on 16$^{th}$, 17$^{th}$, and 18$^{th}$ of the month. However, if the monitor indicates LH peak on the 14$^{th}$, the participant will need to undergo blood draw on the 14$^{th}$, 15$^{th}$ and 16$^{th}$. ELISA analysis of LH hormones requires fasted blood samples, so participants will be informed that they must plan to fast for the morning of each blood draw session, with the possibility of having to fast for one unscheduled visit. If a participant does not reach an LH peak by blood draw visit 7 during cycle 2, blood draw visit 8 will be canceled. The participant will be required to complete blood visits 1-8 during the subsequent month, cycle 3. If a participant does not reach an LH peak by blood draw visit 7 during cycle 3, the participant will be ineligible to complete remaining visits or remain in the study. The In-Person Blood Draw sessions are broken down into two parts. The first part of the session will begin at 8:00am during 6 visits at CCTS (the remaining 2 visits are described below). Participants will be asked to rinse their mouth thoroughly with water and wait for 10 minutes. During this time, the heart rate monitor will be placed for the purpose of measurement of heart rate variability. The measurement will take 5 minutes. After the heart rate monitor is removed, participants will complete a sleep diary. Next, a saliva will be collected via passive drool. Participants may tilt the head forward, allowing the saliva to pool on the floor of the mouth, then pass the saliva through the SalivaBio Collection Aid (SCA) into a polypropylene vial. After this, a needle will be placed in participants' arm and they will be asked to remain still while their blood is drawn. The study session will end at 8:30am.**

In addition, participants will be randomly assigned to perform the second part of the session on both blood draw visit 2 or blood draw visit occurring on same day as peak LH and blood draw visit 7 or blood draw visit 8. Peak LH visit will be the day of peak fertility of participants. The study session will begin at 8:00am. Participants will be asked to rinse their mouth thoroughly with water and wait for 10 minutes. During this time, the heart rate monitor will be placed to measure heart rates for 5 minutes. Then, participants will be asked to provide saliva samples. Following this, study participants will take three computerized tests of cognition, measuring working memory, response inhibition and attention. The tests will be administered using Psytoolkit (https://www.psytoolkit.org/), an online platform for running psychology experiments. The duration of the tests is 15 minutes. Next, blood draws will occur from 8:35-8:45. The session will end at 8:50am.

### 6.1d. Trier Social Stress Test

During the second or third menstrual cycle (depending on whether an LH peak occurs in the second menstrual cycle), study participants will also attend a procedure designed to test their stress reactivity (Figure 4). The stress procedure will be scheduled in between blood draw visits #7 and #8 (See Table 2). Laboratory study session will begin at 11:00 at CCTS. First, a urine drug screen will be collected for the purpose of ruling out drug intake, along with CO testing for the purpose of ensuring absence of smoking. Around 11:15, participants will be offered a choice of snack – a granola bar or crackers. An intravenous catheter will be placed at 11:30. Participants will enter the relaxation phase from 11:30 to 13:00, during which they will read neutral materials or watch a neutral

movie. The relaxation phase is necessary for any stress encountered as the result of catheter insertion to subside.

The Trier Social Stress Test (Kirschbaum et al., 1993) will begin at 13:30 in order to minimize circadian variations in cortisol levels. Participants will be given verbal instructions for the TSST speech and mental arithmetic performance tasks. The document "TSST.Instructions.doc" is attached. Participants will be told that they will be taking on the role of an applicant for their ideal position and that they must deliver a 5-min speech which will convince a panel of interviewers that they are the best candidate for a self-identified ideal job. They will also be told that they will be performing another task, which will be given by the panel. Please note, per consent form, that participants already consented to give a public speech as part of the study.

Study participants will be given 10 minutes to prepare for the task, and then escorted to another room, with three interviewers in white coats sitting at a table. The interviewers will follow a strict protocol by exhibiting unemotional neutrality and avoiding any oral or mimic feedback. Participants will be instructed to step in front of a microphone, which permits the study subjects to have a clear view of the panel. Participants will be expected to utilize the entire 5 minutes for the speech and will be prompted as needed by the interviewers. For the second 5-minute task, participants will be asked to subtract 13 from 1,022 as fast as possible and speak their answer aloud. They will be asked to start again if they made a mistake. After the tasks, participants will be escorted back to the study room for the collection of various samples as shown in Figure 4 through 14:50. The discharge procedure will include removal of the intravenous line, completion of adverse event form and debriefing. The study procedure will end at 15:00.

## 6.2 SPECIMEN CONSIDERATIONS

### 6.2.1 URINE SPECIMEN (IN-PERSON SCREENING)

Urine drug specimens will be collected from participants during In-Person Screening. The purpose of the specimen is two-fold: 1. urine drug screen and 2. pregnancy test. Specimens will be collected and tested at the UIC College of Pharmacy. The label will include the information that will be on the urine collection cup during urine drug screen and urine pregnancy testing. Research staff will document test results on the study flowsheet.

For the drug screening, research specialist will verify the temperature strip on the collection cup is between 90 – 100°F within 4 minutes of urine collection. The research specialist will read drug of abuse test results by pulling label from right to left to remove expose test results in 5 minutes. For pregnancy testing, the research specialist will use Serum/Urine hCG-STAT chromatographic immunoassay by transferring 3 full drops of urine to the specimen well of the test device. The result will be read at 3 to 4 minutes when testing a urine specimen.

### 6.2.2 MENSTRUAL CYCLE 2 (SPECIMEN COLLECTION ACROSS THE MENSTRUAL CYCLE)

Participants will collect first morning urine specimens during menstrual cycle 2. Urine specimens will be used for daily hormone testing with the Clearblue Connected Ovulation Test System. Participants will dispose of their specimen in the sink or toilet upon completion of daily testing. Specimens will not be stored.

Blood and saliva specimens will be collected by research staff from participants during in-person blood draw visits (totaling 8 visits across the menstrual cycle) as outlined in Table 3. Research staff will extract plasma and peripheral blood mononuclear cells (PBMCs) from whole blood. Neuroactive steroid biosynthesis will be determined by levels in the plasma using gas chromatography-mass spectrometry and real time PCR (qPCR) for measuring the mRNA levels of key enzymes involved in the neuroactive steroid biosynthetic pathway.

| Table 3. Specimen collected at each of the 8 blood draw visits across the menstrual cycle | | | | | | |
|---|---|---|---|---|---|---|
| **Collection tube (no. tubes x volume)** | **Specimen type** | **Volume to be drawn** | **No. aliquots x volume** | **Analytes** | **Test Lab** | **Storage Location** |
| Red top Serum Separation tube (2 x 6.0 mL) | Serum | 9 mL | 1 x 0.6 mL | LH/FSH/Estradiol | ARUP | Hamidovic Lab |
| | | | 1 x 0.4 mL | Progesterone | UIC RRC | Hamidovic Lab |
| | | | 1 x 0.5 mL | Allopregnanolone | UIC RRC | Hamidovic Lab |
| | | | 2 x 0.5 mL | Extra stored | UIC RRC | Hamidovic Lab |
| | | | N/A | Plasma | UIC RRC | Hamidovic Lab |
| Purple top EDTA tube (1 x 6.0 mL) | Whole blood | 6 mL | 1 x 6 mL | Peripheral blood mononuclear cells | UIC RRC | UIC RRC |
| Salimetrics Collection Tube | Saliva | 1.5 mL | 1 x 0.5 mL | Cortisol | Salimetrics | Hamidovic Lab |
| | | | | | | |

### 6.2.3 MENSTRUAL CYCLE 2 (ACUTE STRESS PROCEDURE)

Blood and saliva specimens will be collected by research staff from participants during the Trier Social Stress Session as outlined in Table 4.

| Table 4. Acute stress visit blood and saliva sample collection | | | | | | |
|---|---|---|---|---|---|---|
| **Collection tube (no.tubes x volume)** | **Specimen type** | **Volume to be drawn (per one blood draw*)** | **No. aliquots x volume** | **Analytes** | **Test Lab** | **Storage Location** |
| Red top Serum Separation tube (1 x 5.0 mL) | Serum | 5 mL | 1 x 0.5 mL | Extra stored | UIC RRC | Hamidovic Lab |
| | | | 1 x 0.5 mL | Allopregnanolone | UIC RRC | Hamidovic Lab |
| | | | N/A | Plasma | UIC RRC | Hamidovic Lab |
| Salimetrics Collection Tube | Saliva | 1.5 mL | 1 x 0.5 mL | Cortisol | Salimetrics | Hamidovic Lab |

*There are total 7 blood draws and saliva collections during the Trier Social Stress Test session

## 6.3 PROSPECTIVE DATA

Participants will report symptoms of PMS online through REDCap (DRSP). The DRSP refers to symptoms experienced in the past day and will be conducted every evening during 2 menstrual cycles ( We anticipate that approximately 5-10% of study participants will not ovulate in the 2nd menstrual cycle, and will need to enter the 3rd menstrual cycle. In this case, participants who enter the third menstrual cycle will complete DRSPs.). Data will not be collected retrospectively.

REDCap will only be accessed by the PI and her research team on password protected computers in the PI's lab located on the first floor of UIC College of Pharmacy. This research project will be shared amongst the research team in REDCap and each member will be able to access the information by logging into the REDCap database under their individual profiles. Participants' personal information will be stored in REDCap to ensure

protection of personal identifiers. Software needed to collect study data from research devices during testing sessions will be downloaded on PI's research laptop. As discussed, the PI's laptop is password-protected and only available to members of the research team. No identifiers will be stored on the laptops. Hard copy files will be stored in locked cabinets inside the locked offices in the PI's lab located in the UIC College of Pharmacy - 833 South Wood Street – Chicago, IL 60612. The PI's lab consists of two rooms within UIC College of Pharmacy – room 117A and 115. The Principal Investigator and her designated research team will have access to the research study information.

## 7.0 EXPECTED RISKS/BENEFITS

There are no expected benefits to the participants of this research study, however, it is expected that a better understanding of hormone kinetics and stress will lead to a more sophisticated understanding of Premenstrual Syndrome. We do not anticipate any risks of particular severity or seriousness.

There is a risk of distress from answering personal questions about participants' mental health history during the Mental Health Interview. Saliva collection via passive drool may be uncomfortable for participants. Blood draw side effects include discomfort, bruising and/or bleeding at the needle site (>20%); dizziness and infection (<2%). These side effects are generally benign and reversible. Also, study subjects may feel discomfort and distress from Trier Social Stress Test.

Additionally, there is a potential risk of loss of confidentiality. Information that identifies subjects will only be shared between research staff involved in this particular study. The research team will make every effort to protect subject's private health information and guard against any loss of privacy. Participant information will be securely stored and only accessible to authorized personnel as described in section 8.0 "Data Collection and Management Procedures".

There is a potential risk of discomfort or awkwardness associated with at-home urine testing with the Clearblue Connected Ovulation Test System. Additionally, there is a risk of discomfort or stress from revelations and concerns regarding failed ovulation detection or infertility.

## 8.0 DATA COLLECTION AND MANAGEMENT PROCEDURES

Data collection will occur throughout the 2-menstrual cycle study procedure. Table 5 outlines each of the data collection tools along with information when in the study they are collected.

Table 5. Questionnaires and physical measurements by visit type

| Data Collection Tool | PRE-SCREENING | SCREENING | Menstrual Cycles 1 and 2 (DAILY) | Menstrual Cycle 2 VISIT 1 | Menstrual Cycle 2 VISIT 2 | Menstrual Cycle 2 VISIT 3 | Menstrual Cycle 2 VISIT 4 | Menstrual Cycle 2 VISIT 5 | Menstrual Cycle 2 VISIT 6 | Menstrual Cycle 2 VISIT 7 | Menstrual Cycle 2 VISIT 8 | ACUTE STRESS REACTIVITY STUDY |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Initial Survey | ✓ | | | | | | | | | | | |
| Medication and Health Review | | ✓ | | | | | | | | | | |
| Shipley IQ Test | | ✓ | | | | | | | | | | |
| Mental Health Interview | | ✓ | | | | | | | | | | |
| Demographics Survey | | ✓ | | | | | | | | | | |
| Substance Use Survey | | ✓ | | | | | | | | | | |
| Physical Activity | | ✓ | | | | | | | | | | |
| State-Trait Anxiety Inventory (Y-2 only) | | ✓ | | | | | | | | | | |
| Beck's Depression Inventory | | ✓ | | | | | | | | | | |
| Personality | | ✓ | | | | | | | | | | |
| Physical Measures* | | ✓ | | | | | | | | | | |
| Daily Record of Severity of Problems | | | ✓ | | | | | | | | | |
| Adverse Event Questionnaire | | | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Adverse Event Tracking Form | | | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Task Perception Rating | | | | | | | | | | | | ✓ |
| Heart Rate | | | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Computerized Cognition Tasks | | | | | ✓ | ✓ | | | | ✓ | ✓ | |
| Visual Analogue Scale | | | | | | | | | | | | ✓ |
| Blood Pressure | | | | | | | | | | | | ✓ |
| Sleep Diary | | | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |

*Includes: height; weight; blood pressure; pulse; sitting knee and abdominal height; waist, hip, abdominal, arm and thigh circumference.

Responses from Demographics, Physical Activity, Strait-Trait Anxiety Inventory (Y-2), Becks Depression Inventory, Personality, Physical Measurement, DRSPs, Task Perception Rating, VAS, Blood Pressure, Date of blood draws, Date of day 1 of cycle, and Date of ovulation surveys will be de-identified and submitted to NIH NIMH data repository. The repository will only be accessed by the PI and an assigned research staff on password protected computers.

*The Mental Health Interview will be administered verbally and includes a question about suicide risk. This question is a not part of an evaluation of suicide risk* per se. Study coordinator will call Dr. Hamidovic regarding any person reporting that he/she is suicidal (as part of Depression assessment). Dr. Hamidovic will conduct an assessment by asking further questions related to suicidality using the attached MINI-International Neuropsychiatric Interview. Individuals scoring "low suicidality" and without imminent threat will be given referral to UIC Adult Psychiatry Service (312-996-2200). Dr. Hamidovic will contact Dr. Holden for an in-person assessment for individuals with moderate/high suicidality. For those exhibiting an immediate danger, authorities may be called if Dr. Holden or Dr. Hamidovic view it necessary.

Participants who consent to the study by signing the ICD will be assigned a unique Subject ID, consisting of 7 numbers. Screening flowsheets will be labeled with Subject ID only. Only the consent, which will be locked in the PI's laboratory will have study participant's identifier (name and signature). All paper copies – with and without identifiers - will be stored in the PI's UIC lab located on the first floor of the UIC College of Pharmacy.

Participants will perform computerized tasks from the PsyToolkit website. Only subject ID will be entered and task performance results will be downloaded from the website. The Clearblue Connected application may collect personal information about users including name, age, gender, birth date, health-related information, email address, fertility information, social media account names, authentication information, inventory of other installed information, cookies (application use), and microphone and camera data. The Clearblue Connected application uses industry standards (security and vulnerability scans, software audits, firewalls, data encryption) to protect user privacy, and will not willfully share user information without user consent. Participants are informed of the Clearblue Connected application's security features in the Informed Consent Document. The research team will not download any personal data from the application and will only collect relevant information about hormone changes from the application.

REDCap will only be accessed by the PI and her research team on password protected computers in the PI's lab located on the first floor of UIC College of Pharmacy. This research project will be shared amongst the research team in REDCap and each member will be able to access the information by logging into the REDCap database under their individual profiles. Participants' personal information will be stored in REDCap to ensure protection of personal identifiers. As discussed, the PI's laptop is password-protected and only available to members of the research team. No identifiers will be stored on the laptops. Hard copy files will be stored in locked cabinets inside the locked offices in the PI's lab located in the UIC College of Pharmacy - 833 South Wood Street – Chicago, IL 60612. The PI's lab consists of two rooms within UIC College of Pharmacy – room 117A and 115. The Principal Investigator and her designated research team will have access to the research study information. There will be no collaborators involved in this study.

## 9.0 DATA ANALYSIS

The study will recruit approximately 1500 participants over a 4-year period. This recruitment number accommodates screen failures, with the total number of participants completing the study at 120.

The primary evaluation is a repeated measure analysis, testing for differences in study outcomes by PMS/PMDD diagnosis. General Estimating Equations will be implemented to analyze all repeated measures. Time will be modeled as a categorical, dummy variable in order to avoid an *a priori* shape assumption, as is otherwise encountered with the use of a mathematical function to model development over time (Twisk, 2013). As shown in a GEE model in a study involving administration of TSST (Xin et al., 2017), every subsequent measurement (coded as a dummy variable) after the baseline measurement is used as a time indicator. An interaction between group (with *vs.* without PMS/PMDD diagnosis) and categorical (dummy) time variable will be added to the model in order to detect a difference in study outcomes over time between the two groups.

## 10.0 QUALITY CONTROL AND QUALITY ASSURANCE

For each survey done on REDCap, the software does not allow the participants to submit the survey unless every pertinent question for each individual participant has been answered (ex. once a participant answers that he or she does not smoke, the questions regarding frequency of smoking are skipped.) In this way, quality control is assured in that none of the participants can submit incomplete surveys or are forced to fabricate answers for questions that do not apply to them.

Visit attendance will be monitored by research staff by marking on testing flowsheets whether participants attended or scheduled appropriate In-Person Blood Draw visits.

The CEDAR Lab research team will evaluate data quality both as it is collected and during the later data processing stages. Therefore, data quality evaluation will be done every time data is collected from the participants and also at least once afterwards for each data recording. The ultimate responsibility for data quality rests with the Principal Investigator.

## 11.0 DATA AND SAFETY MONITORING

Subjects will be asked to report any adverse events by specific questioning. The questions will specifically refer to symptoms of blood draw, but they will include additional questions about general adverse events as specified in the ICD. In addition, subjects will be asked to report any adverse events not listed on the ICD. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. If any serious events are detected, they will be followed up to determine the final outcome. Following completion of the study, participants will be instructed to report any adverse events and if the Principal Investigator determines that it is possibly related to the study treatment or participation, will be recorded and reported.

Per policy of UIC OPRS, depending on the seriousness of the event, an adverse event will be reported either within 5 business days (in case of a serious event) or 15 business days (in an event the serious criteria is not met) as outlined in the UIC HSPP form “Prompt Reporting to the IRB”. Clinical course of each event will be followed until resolution, stabilization or until it has been determined that the study treatment or participation is not the cause. The following events will be reported within 5 business days as well: 1) Breach of confidentiality, 2) Change to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant, 3) Complaint of a participant when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team, or 4) Major protocol violations that are unplanned and unintentional, and 5) Apparent serious or continuing noncompliance.

This form will be reviewed and signed first by the research team member, and also by the study PI. At that time, the PI will determine whether the reported events fall in the category of unanticipated AEs. Depending on the seriousness of the event, it will be reported either within 5 business days (in case of a serious event) or 15 business days (in an event the serious criteria is not met) as outlined in the UIC HSPP form "Prompt Reporting to the IRB". Clinical course of each event will be followed until resolution, stabilization or until it has been determined that the study treatment or participation is not the cause.

All research staff will be responsible for collecting AEs and UPs, but the ultimate responsibility and classification determination will rest with the PI. Whereas the study coordinator/postdoc will sign the completed Adverse Event form, that form will be given to the PI who will use the "Adverse Event Tracking Form" for final classification of the AE. It will be documented on the form whether the event listed in the blank space on the Adverse Event form falls into anticipated/unanticipated and whether the nature of the event is serious/non-serious. In the event of unanticipated and/or serious event, the resolution of the AE will be tracked by the PI and all communications will be related to the Institutional Review Board.

At the end of menstrual cycle 2, and following each Blood Draw visit, participants will be asked to complete "Adverse Event Questionnaire". One Adverse Event Questionnaire is designed to be administered during the last blood draw visit and contains events that participants may experience during use of the Clearblue Connected Ovulation Test System and Clearblue Connected smartphone application. Participants who drop out at any point during the study will be asked to complete this form prior to receiving payment. A second Adverse Event Questionnaire is designed with blood draw events. The research member facilitating the session and the PI will review and sign the form. The PI will record the determination of expectancy and seriousness of each event in the "Adverse Event Tracking Form", and will communicate the result of this determination using UIC HSPP form "Prompt Reporting to the IRB".

This research study will not include a Data and Safety Monitoring Board (DSMB). Safety concerns, including adverse events, related to the research study will be managed by the PI and the research team, as directed. The Principal Investigator will oversee the safety of the study by a careful assessment and appropriate reporting of adverse events as noted above.

Adverse events and unanticipated problems will be monitored after each testing session as described above. Per policy of HSPP, expedited reporting of those events related to study participation that are unforeseen and indicate that participants or others are at an increased risk of harm, will occur within 5 working days from the time the investigator became aware of the event. This is the case for any adverse that occurs any time during or after research study, which in the opinion of the Principal Investigator is unexpected and related to the study procedures. The reporting process will consist of sending a written report to the IRB that includes a description of the event with information regarding the fulfillment of expedited reporting, follow-up/resolution and need for revision of the ICD and/or other study documentation. Copies of each report and documentation of IRB notification and receipt will be kept in the Principal Investigator's study file.

More rapid reporting requirements will be followed when deaths occur during the course of the research study. The event will be reported within 24 hours when the death is unforeseen (unexpected) and indicates participants (or others) are at an increased risk of harm. Report of the event within 72 hours will be filed for all other deaths, regardless of whether the death is related to study participation.

Less serious events (1. Local adverse events or problems that are unanticipated and, while not meeting the criteria of serious, indicate research is associated with a greater risk of harm to participants or others than previously known, 2. External adverse events that are unanticipated, indicate research associated with a greater risk of harm to participants or others than previously known and more likely than not to have been caused by

the procedures associated with or subject's participation in the research 3. New information indicating an unexpected change to the risks or benefits of the research (i.e., an unanticipated problem), and 4. Administrative hold by investigator, sponsor, regulatory authorities or other entities) will be reported within 15 business days.

Stopping rules for the study will apply to expedited cases in which the probability of study treatment causality is high or a case of a change to the risks or potential benefits of the research (such as safety monitoring indicates that a particular side effect is more severe, or more frequent than initially expected). In the case of an expedited event, the study will be stopped until further information is gathered and a potential plan is formulated through consultation with the IRB.

The PI and an appointed research team member will provide guidance to participants on the most appropriate method of discontinuation based on where they are in the study protocol. Recommendations will be given based on what procedures the subject has completed. Researchers will provide a discharge summary of the session based on what the participant has completed. The team will provide supportive care to subjects as needed following all premature discontinuations.

## 12.0 STATISTICAL CONSIDERATIONS

**Power Calculation:** The primary hypothesis is that study participants with the PMS/PMDD diagnosis will have a blunted acute stress cortisol response compared to participants without the diagnosis. Means and standard deviation from Table 2 of Huang et al. (2015) were entered into GLIMMPSE for all the time points. Base correlation was estimated as 0.7, with decay rate as 0.2. Means were scaled as 0.8, 1 and 1.2. Alternative values for variability were derived by scaling the calculated covariance matrix by 0.5, 1, and 2. Results are presented in Figure 5. With 90% power, alpha level set at 0.05 variability scale factor of 2 and mean scale factor of 1.2, 120 study participants in total are needed to detect a time by group interaction.

## 13.0 REGULATORY REQUIREMENTS

## 13.1 INFORMED CONSENT

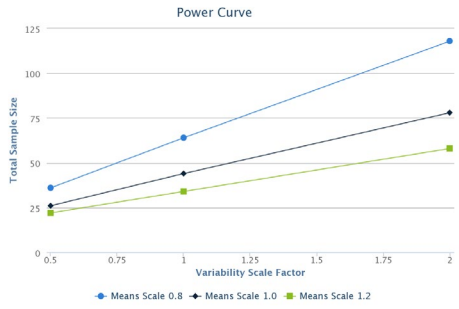



Figure 5. Power curve showing the total sample size according to variability scaling. The calculations are based on 90% power, 0.05 alpha value, base correlation of 0.8 and decay rate of 0.2.

If a participant passes the initial REDCap survey, he/she will be contacted by a member of the research team to schedule an in-person screening session. In-person screenings will take place in a private room located in the College of Pharmacy. Informed consent will be obtained at the beginning of the screening session. The "Screening Flowsheet" was developed by the PI including all the sections that need to be checked by the member of the research team obtaining the consent.

Study participants will be given ample time to review the form. The consent procedure will be carried out in a private and quiet setting. Prior to initiating the procedure, the person consenting will ensure that the individual is an adult by reviewing the participant's government-issued ID. Additionally, the person consenting will ask the individual if they are able to read and understands the English language. The most recent version of the ICD will be used. The individual obtaining the consent will summarize each section of the ICD. Study participants will be told the following: "Take as much time as you need to read the entire consent document. Please inform me when you are done reading the form so I may answer any questions you have." All the questions the subject had will be written on the coordinator flowsheet.

As of December 2019, the Trier Social Stress Test was added to the protocol. Therefore, participants will be invited to complete this procedure. There are 2 categories of participants who may wish to be included in the Trier Social Stress Test session:

- Category 1: Actively participating subjects – those who will be coming in the near-future for their menstrual cycle blood draws, and
- Category 2: Participants who completed the study (i.e. only the menstrual cycle phase blood draws) and indicated on the discharge paper that they may be contacted in the future for any additional research studies

Actively participating subjects will be contacted for the newly added components of the study on the first day of their in-person blood draw. The study subjects who have already completed the study will be contacted through email.

The research team will retain the original ICD and store the document in a locked cabinet in a locked office within the PI's lab. Only designated research team members appointed to this research study will be granted approval by the PI to obtain informed consent. Study personnel have completed the required CITI Training for Human Subject Protection. In addition to completion of the online training modules, study personnel will practice obtaining informed consent in the PI's lab. The PI will provide feedback and expert tips to the research team for the ICD process. The PI has over 10 years of research experience and has lead numerous clinical research studies involving obtaining informed consent from human subjects. The record of training of all research members will be kept on file in the laboratory.

Informed consent documents will be stored as hard copy files in the PI's lab located in the UIC College of Pharmacy. Only the PI and her designated research team for this study will have access to the ICD. The research team is committed to being vigilant in the protection of patient information.

### 13.2 Subject Confidentiality

Research personnel will take all feasible measures to ensure subject information remains secure and protected at all times. Paper files will be stored in a locked cabinet located in the PI's UIC lab located in the College of Pharmacy located at 833 South Wood Street, Chicago, IL 60612. Electronic files will be stored on a password protected computer that will only be accessible to the research team for this study. REDCap, a widely used secure web application, will be the storage location for electronic files for this study. The details of the research project will be shared electronically in REDCap amongst the study team. Patient identifiers will be stored in REDCap, however, to ensure confidentiality subjects will be tracked by subject ID number throughout the study. Researchers will refer to subjects by their assigned ID number instead of using personal identifying information in research discussions. Unauthorized individuals who are not affiliated with the research study will not have access to sensitive subject information.

The PI and her appointed research team will have access to the study data. Study generated data and sensitive participant information will only be accessible to researchers affiliated with this study. Study data will be stored on password-protected computers in the PI's lab. Sensitive patient identifiers will be stored in REDCap on password protected computers only accessible to authorized individuals.

The REDCap database used for this research will include identifiable information in order for researchers to track participants for both research and safety purposes. Upon enrolling in the study, participants will be assigned a subject ID number. Throughout the study, participants will only be tracked by their subject ID number, not any personal identifiers. Hard copy files including screening documents for each participant, will only list the subject ID number. The exception to this are the forms which the subjects will have to sign (for example, the ICD and adverse event form). Those forms will be locked in a filing cabinet in a lab office which will also be locked.

Researchers will destroy participant identifiers after all analyses, publications, reports, and presentations are complete – i.e., 6 years following study completion. Identifiable information will not be used in these discussions. Following completion of the study, the research team will submit a final report to the UIC IRB as directed by the Office of the Vice Chancellor for Research.

A Certificate of Confidentiality will be required and obtained for this research study. Participants will be asked personal questions about their substance use history. Researchers are committed to protecting study participants' confidentiality. The research team will inform participants about the purpose of the Certificate of Confidentiality prior to asking questions about substance use.

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