SCOR Grant:

Project I

Sex Differences and Progesterone: Association with Impulsivity and Smoking Cessation

"Hormones & Smoking Cessation"

Principal Investigator:

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Study Protocol

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A. SPECIFIC AIMS

Cigarette smoking persists as the leading cause of preventable morbidity and mortality (Centers for Disease Control and Prevention (CDC), 2010). Although there have been many advancements in smoking cessation interventions, the majority of smokers relapse soon after a quit attempt (CDC, 2010; Benowitz, 2009). Despite being more likely to develop a smoking-related disease, females are at a higher risk for smoking relapse compared to males (U.S. Department of Health and Human Services (USDHHS), 2001; Perkins & Scott, 2008). While the specific causal mechanisms associated with the sex difference in relapse rates remain unknown, increasing evidence suggests sex hormones may drive this disparity.

Overall, research to date indicates that estrogen is associated with the facilitation of drug-abuse behaviors, whereas progesterone is associated with reduction of these behaviors (Carroll & Anker, 2010; Lynch & Sofuoglu, 2010). While the clinical literature is mixed, our work offers additional support for this theory as the luteal phase (high progesterone) of the female menstrual cycle appears to be associated with decreased smoking-related symptomatology (Allen et al 2009b) and improved smoking cessation outcomes (Allen et al 2008; Allen et al 2009c) relative to the follicular phase (low progesterone).

Cigarette smokers appear to be more impulsive than non-smokers (Bickel et al 1999), and higher levels of impulsivity are associated with increased risk for smoking relapse (Doran et al 2004). Sex differences have been observed in this association such that females are more susceptible to the effects of impulsivity on smoking (Nieva et al 2011). Preliminary evidence suggests sex hormones may play a role as females who have recently quit smoking have less impulsive behavior while in the luteal phase than in the follicular phase (Allen et al 2009a). Further, within the animal literature, delivery of exogenous progesterone has been shown to decrease impulsive behavior (Llaneza & Frye, 2009).

Taken together, these data suggest that progesterone may improve smoking cessation outcomes perhaps by reducing impulsive behavior. However, the clinical literature on this topic is lacking. Therefore, in Project I we are proposing a double-blind randomized controlled trial to assess the role of exogenous progesterone on impulsivity and smoking cessation in a sample of males and females who are motivated to quit smoking. Subjects (n=200) will be stratified by sex and then randomly assigned to active progesterone (PRO; n=50 males and 50 females) or placebo (PBO; n=50 males and 50 females) to address the following specific aim:

Aim 1: Investigate sex differences in the effect of exogenous PRO compared to placebo on impulsivity and smoking cessation

Hypothesis 1: For both males and females, a lower proportion of subjects randomized to PRO will relapse by 4 weeks after quit date compared to those randomized to PBO.

Hypothesis 2: For both males and females, subjects randomized to PRO will have more days to relapse compared to those randomized to PBO.

Hypothesis 3: There will be a sex difference in smoking relapse such that females, regardless of randomization assignment, will have fewer days to relapse compared to males.

Hypothesis 4: Impulsivity will be a stronger relapse predictor in females than males.

Hypothesis 5: Among those with higher levels of serum PRO the influence of impulsivity on smoking relapse will be dampened.

Given that less than three percent of those who attempt to quit smoking remain abstinent six months later (Benowitz, 2009), there is an urgent need to gain a better understanding of the dynamic process involved in smoking cessation. This project will provide new knowledge regarding the possible protective role of progesterone against smoking relapse in males and females.

B. RESEARCH STRATEGY

B.1. SIGNIFICANCE

Cigarette smoking continues to be the number one cause of preventable morbidity and mortality in the United States (CDC, 2010). Compared to males, females are at an increased risk for development and maintenance of nicotine addiction (USDHHS, 2001). Preclinical and clinical studies have offered evidence to explain these observed sex differences, suggesting that sex hormones may modulate the reward system and related nicotine response (Lynch & Sofuoglu, 2010). Specifically, high levels of estrogen are associated with a heightened response to nicotine; whereas, high levels of progesterone are associated with a blunted response (Carroll & Anker, 2010; Lynch & Sofuoglu, 2010). Further, within the animal literature the administration of progesterone has been shown to be associated with reduced reinforcing effects of drugs, as well as a decrease in self-administration and drug-seeking behavior (Carroll & Anker, 2010).

Recent studies suggest that progesterone may play a key role in the observed sex differences in addictive behaviors. A review by Lynch & Sofuoglu (2010) concluded that progesterone (PRO) may counter the enhanced vulnerability in females by altering the biological response to nicotine's reinforcing effects. Other clinical research on smoking cessation by menstrual phase has indicated that the follicular phase (low PRO) may be associated with more favorable outcomes when paired with nicotine replacement therapy (Franklin et al 2007; Carpenter et al 2008); whereas the luteal phase (high PRO) may be associated with more favorable outcomes when either no medication or non-nicotine medications (i.e. bupropion) are used (Allen et al 2008; Mazure et al 2011). However, the specific mechanisms as to how PRO may assist with smoking cessation efforts remain unknown. Given that PRO has been shown to reduce impulsive behaviors in animals (Llaneza and Frye, 2009) one theory is that PRO blunts impulsivity in humans and, therefore, protects against smoking relapse.

Further clinical research has focused on association of various personality traits, primarily impulsivity. Impulsivity has four factors including a lack of premeditation regarding the consequences of behavior, lack of perseverance when tasks are boring or aversive, sensation seeking and urgency, and the tendency to behave impulsively while experiencing negative affect (Doran et al 2009). Sex differences in the association between impulsivity and smoking behavior have been observed. For example, one recent study observed that high levels of impulsivity were associated with increased nicotine use in females, but not males (Stoltenberg et al 2008). A second study observed a positive association between two factors of impulsivity – sensation seeking and general activity – and number of cigarettes smoked per day in females, but not males (Nieva et al 2011). The role of sex hormones in these associations is unclear; however, taken together this offers evidence for a possible interaction between PRO, impulsivity and smoking behavior.

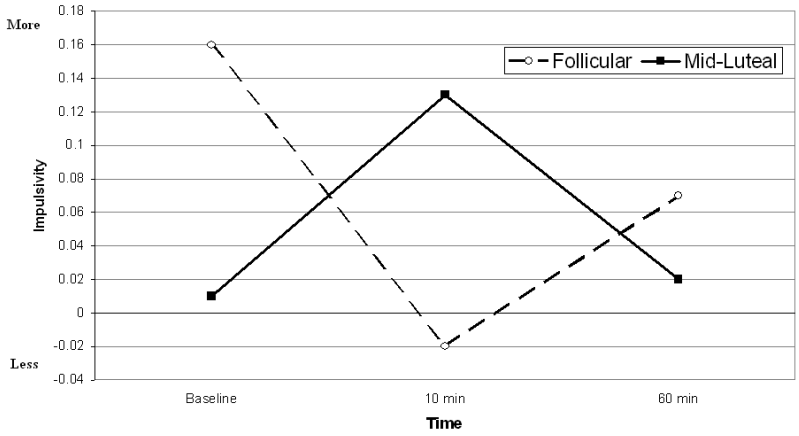
This SCOR application proposes robust comparisons of hormonal influences in clinical and preclinical studies. Here, in Project I, we propose direct and additive conditions. Specifically, we will assess the effects of PRO, compared to placebo (PBO), as well as the sex differences on impulsivity and smoking cessation outcomes in females and males who are motivated to quit smoking using a 12-week double-blind randomized clinical trial.

This project, especially in the context of the other projects, is highly significant in several domains. First, the proposed work directly compares female and male subjects with respect to PRO modulation of smoking cessation. Second, because PRO and impulsivity both have a role in smoking cessation and relapse, a direct comparison of PRO versus PBO on impulsivity is important. Third, these data will directly address (a) the role of PRO on smoking cessation outcomes, (b) the role of sex differences on smoking cessation outcomes, (c) the role of impulsivity on smoking cessation outcomes, and (d) interactions of sex, PRO and impulsivity on smoking cessation outcomes. Fourth, while Project I will focus solely on nicotine and PRO effects on nicotine, Project II, using similar design features, will focus on cocaine with co-morbid nicotine use in humans and the combined effects of PRO and atomoxetine. Project III will conduct parallel preclinical studies to both projects. Therefore, the complete data set will provide unique and significant insights into sex differences as well as, translational data. Finally, the combined expertise of the assembled named investigators is unique and greatly enhances the probability that the work will be completed as proposed and that significant findings will be forthcoming.

B.2. PRELIMINARY STUDIES

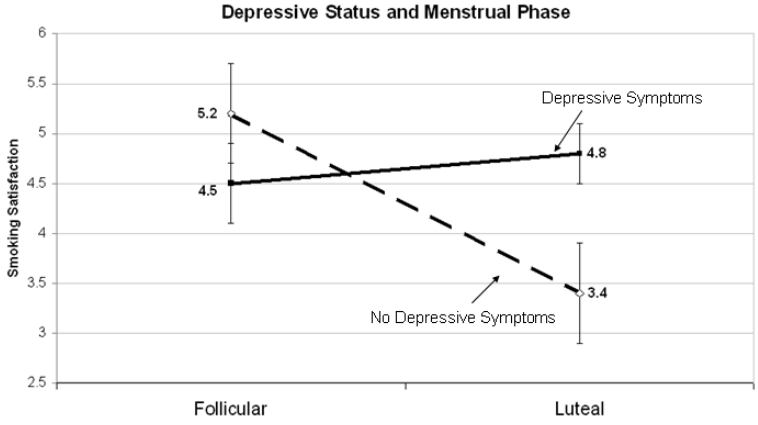
B.2.1. Impulsivity Varies by Menstrual Phase after Exposure to Nicotine. *Goal*: This cross-over study aimed to measure differences in nicotine response between follicular (F) and luteal (L) menstrual phases in a sample (n=20) of female smokers between the ages of 18 and 40. *Results*: After exposure to nicotine nasal spray, subjects in the F phase became significantly more impulsive on the Immediate Memory Task computer program (Doughtery et al 2002) compared to subjects in the L phase (Figure 1). *Relevance*: Sex hormones appear to impact the level of impulsivity, such that high levels of progesterone are associated with less impulsivity after exposure to nicotine. The association between progesterone and impulsivity may be associated with risk for relapse.

Figure 1. Changes in Impulsivity by Menstrual Phase



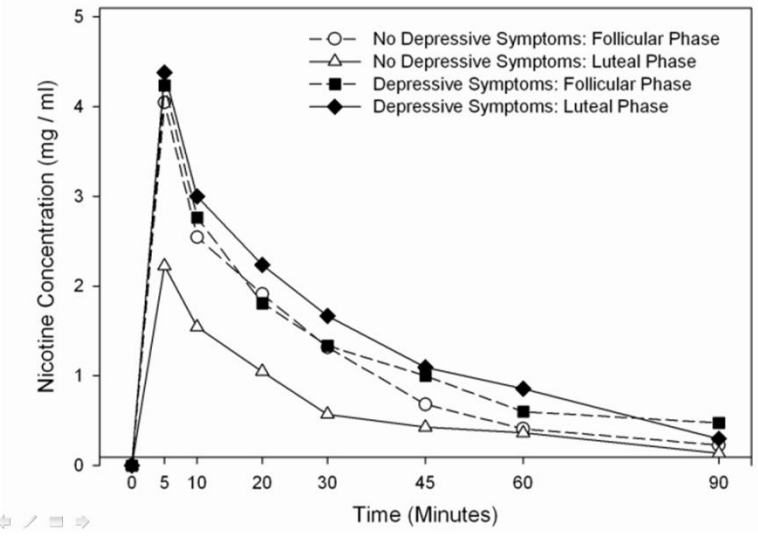
B.2.2: Smoking Satisfaction & Enjoyment Vary by Menstrual Phase during Ad Libitum Smoking. *Goal:* The purpose of this cross-sectional study was to investigate the differences in reinforcing effects (mCEQ) [24] of smoking by menstrual phase and depressive symptoms in a sample of female subjects (n=39) who were classified into four groups: no depressive symptoms follicular phase (NDS-F), no depressive symptoms luteal phase (NDS-L), depressive symptoms follicular phase (DS-F) and depressive symptoms luteal phase (DS-L). *Results:* Smoking Satisfaction varied by menstrual phase in the NDS group but not the SDS group (F-NDS: 5.2±0.5; L-NDS: 3.4±0.5; F-SDS: 4.5±0.4; L-SDS: 4.8±0.3; p=0.016; Figure 2) and a similar trend was observed within the Enjoyment subscale (F-NDS: 4.4±0.6; L-NDS: 1.7±0.6; F-SDS: 3.6±0.5; L-SDS: 2.9±0.5; p=0.089). *Relevance*: Among those without depressive symptoms, sex hormones appear to impact the level of reinforcing effects of smoking, such that high levels of progesterone are associated with less smoking satisfaction and less enjoyment.

Figure 2. Smoking Satisfaction Subscale by Depressive Status and Menstrual Phase



B.2.3. Pharmacokinetics of Nicotine varies by Menstrual Phase in Women without Depressive Symptoms. *Goal*: This cross-over study aimed to measure menstrual phase differences in pharmacokinetics after exposure to nicotine nasal spray within a sample of abstinent female smokers with regular menstrual cycles who either had depressive symptoms (n=23) or did not (n=24). *Results*: There was a significant interaction between depressive symptoms status and menstrual phase such that those without depressive symptoms had a significant menstrual phase difference in their maximum nicotine concentration levels (p=0.020; Figure 3). *Relevance:* In women without depressive symptoms high

Figure 3. Mean Plasma Nicotine Concentrations Following Nicotine Nasal Spray Use



progesterone levels are associated with lower nicotine response; this may be associated with risk for relapse.

B.2.4. Changes in Estradiol/Progesterone (E2/P) Ratio are Associated with Changes in Craving. *Goal*: This cross-over study aimed to assess the influence of the E2/P ratio on smoking-related symptoms of withdrawal (MNWS), smoking urges (Brief-QSU), and reinforcing effects of smoking (mCEQ) using a within subject analysis in a sample of female smokers (n=50) with regular menstrual cycles between the ages of 18 and 40. *Results*: During ad libitum smoking, an increase in the E2/P ratio was associated with an increase in craving on two independent items of measurement: mCEQ (t=2.38, p=0.02) and MNWS (t=1.92, p=0.06). *Relevance*: Changes in sex hormone levels are associated with changes in craving for cigarettes.

B.3. INNOVATION

This project offers the following two highly innovative features. First, directly comparing PRO effects on impulsivity, as well as smoking cessation and relapse in females and males is highly innovative. Second, chronic use of PRO as a smoking cessation aid has not yet been investigated. Overall, the high level of innovation stems from (a) reliance on previously obtained data from human and animal studies by the experienced study team, (b) the translational strategies of furthering direct comparisons in the proposed clinical and preclinical research, (c) combining extant data to address a unique series of questions regarding determinants and modulators of drug cessation, and (d) use of rigorous multidisciplinary methods (such as thorough neurocognitive assessment of impulsivity, and detailed hormone and menstrual cycle measurement) to implement the projects and answer the questions posed.

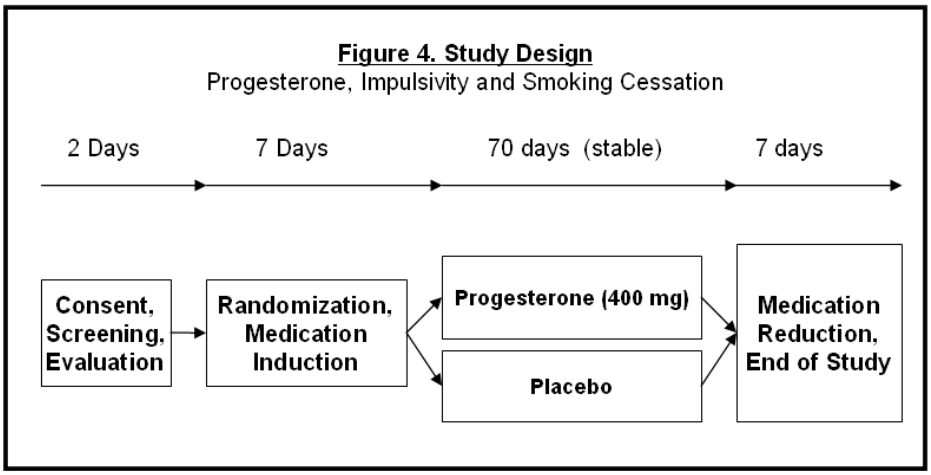
B.4. APPROACH

The two clinical projects - Projects I (Allen) and II (Specker) - will use parallel methods and measures, deviating only as appropriate for the differences in the populations. The details are described below.

B.4.1. Study Design

This double-blind, clinical trial (Figure 4) will prescreen an estimated 600 potential subjects, consent and evaluate approximately 300 potential subjects and ultimately enroll 250 subjects to ensure 200 subjects provide a primary relapse outcome measure at four weeks after quit date. Subjects will be stratified by sex then randomized to one of two groups (n=100 per group / 50% female): Progesterone (PRO) or Placebo (PBO). Telephone screening and visit invitation (20 minutes) leads to the consent process and in-person screening including medical-psychiatric evaluation for inclusion/exclusion (two visits, two hours each), then randomization and medication induction (seven days), stable medication (70 days) with medication reduction and final evaluation for secondary outcomes (over the last seven days). These procedures will be conducted as described below.

Figure 4. Study Design
Progesterone, Impulsivity and Smoking Cessation



B.4.2. Setting, Recruitment, Subjects

Setting**:** This project will be conducted at the Delaware Clinical Research Unit (DCRU). The DCRU has both inpatient and outpatient resources for the spectrum of biomedical research including special capabilities that were developed for study of substance use disorders. The Clinical and Translational Sciences Institute (CTSI), runs the DCRU and functions parallel and support the activities of the NIH funded CTSA, which it predated.

The DCRU includes: reception area, examination rooms, meeting rooms, clinical interview rooms, testing rooms for computer based performance tasks, a wet lab for handling bloods and other specimens, freezers (to -80°C), all essential staff offices, each with multiple telephone and computer lines through the University of Minnesota servers, a locked limited access protocol, equipment and medication rooms, as well as secure cabinets for study files and essential supply and support areas and services.

Recruitment**:** To meet recruitment goals, we aim to enroll a total of 250 subjects (~6 subjects/month) to ensure a final sample size of 100 females and 100 males. Our primary recruitment method will be advertising in the mainstream media. While this type of recruitment can be challenging, our team has been successful with this form of recruitment. For example, our current study recruiting females between the ages of 18-40 has had success with Facebook advertising. Specifically, over the past seven months we have advertised on Facebook resulting in 6,483 clicks to our website, an estimated 180 phone calls to our clinic and an enrollment of 29 subjects (~4 subjects/month). We regularly use television, radio, mailings, and other internet sources to identify study subjects with similar success. Using all of these methods, we have successfully enrolled ~8 subjects/month over the past year in our two ongoing tobacco use research studies.

Subjects and Eligibility: Females 18-50 years of age with regular menstrual cycles and males, 18-60 years of age, (n=300; 50% females) will be enrolled who are current smokers and are motivated to quit smoking.

Inclusion Criteria**:** • Male 18 to 60 years old or female between 18 and 50 years old; •Self-report smoking ≥ 5 cigarettes/day for at least the past year; • Motivated to quit smoking (self-report ≥ 7 on 10-point Likert-type scale); • In stable physical/mental health; • Self report of regular menstrual cycles (female only) • Willing to use double-barrier contraception method if sexually active and not surgically sterilized; • English fluency; • Understand the study procedures and able to provide informed consent; •Ability to participate fully in research elements for the duration of the trial.

Exclusion criteria**:** • Current use of other types of tobacco, nicotine replacement therapy, or smoking cessation medications; • Current or recent (< 3 months) breastfeeding (females only), • Current or planned pregnancy within the next three months (females only); • DSM-IV diagnoses for psychotic disorders, bipolar disorder, ADHD, major depressive disorder within the last 3 months, • Substance dependence within the last 3 months with the exceptions of nicotine dependence and non-daily use of marijuana.; •Unstable psychotropic medications (< 3 months); • Current use of exogenous hormones, finasteroid (propecia), efavirenz, red clover, ketoconazole and other drugs that are CYP3A4 inhibitors; •Conditions contraindicated to progesterone treatment (including, but not limited to, thrombophlebitis, deep vein thrombosis, pulmonary embolus, clotting or bleeding disorders, heart disease, diabetes, history of stroke, allergy to peanuts, hypersensitive to progesterone and liver dysfunction).

B.4.3. Visit Sequence & Procedures

Screening Visits (Visits 1 and 2): Initial screening procedures for Project I and II will be identical except for drug use related criteria, testing and evaluation. Candidates completing the consent process will be screened in a two-visit process. For males, this two-visit process will be scheduled within two weeks of completion of the phone interview. For females, this two-visit process will be completed during the follicular phase of their menstrual cycle to avoid any potential menstrual phase effects on smoking behavior or mood measures, as well as to limit wait time for initial study procedures (details below). Therefore, after the phone screen females will be told to call with the first day of their next period, and then the two-part screening visits will be scheduled during days 1-7 (where Day 1 is the onset of menses) of the menstrual cycle. We have used this procedure with success in our ongoing trial on menstrual phase and depressive symptoms.

At the first of two screening visits (Screening Visit 1), the study will be described in detail to candidates by the study coordinator, and informed consent will be obtained. Subjects agreeing to participate will undergo medical, psychiatric and other evaluation to determine eligibility. The medical evaluation will include: brief physical exam (height, weight, blood pressure, heart rate, and medical history interview), audiotaped psychiatric interview, carbon monoxide level and a blood draw (for measurement of serum hormone levels and liver function via ALT and AST measurement) and a urine pregnancy test (females only). Trained staff will conduct all interviews including the Structured Clinical Interview for DSM-IV (SCID; First, 1995) and instrument administration with audiotapes reviewed regularly to sustain fidelity. Self-report instruments measuring

impulsivity, personality characteristics, stress, caffeine use, smoking withdrawal and behavior will be completed. At the second screening visit (Screening Visit 2; scheduled within three days of the first screening visit), baseline impulsivity tasks will be completed. Females will then be provided with urine luteinizing hormone (LH) testing kits with instructions for daily use. The quit date will be set based on LH testing results (details below). The investigators will review the data to determine eligibility. Subjects meeting eligibility criteria will be given instructions on when to come back for their Baseline Visit (details below).

Quit Date Assignment: This procedure will be identical to Project II and is described in detail here (Table 1). For *female subjects* the quit date will be assigned during the luteal phase. We have selected the luteal phase (typically the last 14 days of the menstrual cycle; Yee et al 1999) for quit date given that our prior work has demonstrated that this menstrual phase is associated with improved smoking cessation outcomes (Allen et al 2008). Therefore, using identical techniques from our prior work (Allen et al 2008) the quit date will be set as follows: First, to determine date of ovulation, female subjects will use LH tests. Several studies by our group and others have shown that ovulation can accurately be predicted by urine LH testing (e.g. Allen et al 1999, Allen et al 2000, Allen et al 2008, Grinsted et al 1989, Luciano et al 1990). Using the First Response urine testing kit (Carter Products), subjects will determine their LH peak with daily urine testing during specific days of the cycle (See Appendix A for instructions). The testing will be done for ten consecutive days starting on Day 8-12 (depending on cycle length). Although the surge may last up to three days, the first day of the surge is most important, because it predicts ovulation 24-48 hours later. In our prior studies, as well as our current study, subjects found the test easy to use and have been compliant. If no LH surge is identified in the first two months, that female subject will be labeled anovulatory and dropped for ineligibility (estimated < 5% occurrence). Second, once ovulation is detected, the baseline appointment and quit date will be scheduled. The baseline appointment will occur within three days of ovulation. Quit date will be set for seven days after the baseline appointment (i.e. seven to ten days after ovulation).

Table 1. Timing of Study Procedures by Sex

	Female Subjects	Male Subjects
Initial Phone Interview	Anytime	
Screening Visit 1	Menstrual Cycle Days 1-7	Within 2 weeks of Phone Screen
Screening Visit 2	Within 3 days of Screening Visit 1	
Baseline Visit	Within 3 days after LH Surge	Delay matched to Female Subject
Medication Start	8PM on day of Baseline Visit	
Quit Date	7 days after Baseline Visit	
Week 0	Day of Quit Date	
Week 1-Week 11	Weekly	
Medication End	Day of Week 11 Visit	
Final Visit	12 Weeks after Quit Date	

Since this entails a delay of variable duration from Screening Visit 2 to Baseline Visit (thus impacting timing of medication initiation) across female subjects, each *male subject* will be matched to a female subject for a similar delay so that, across the male and female groups, study procedures will be follow a similar chronology.

Baseline Visit (Visit 3)**:** When the LH surge occurs female subjects will be instructed to come into the clinic within three days for their baseline visit and to start medication. Male subjects will be instructed to come into the clinic according to their assigned delay (per list generated by the Biostatistics Core). This visit will occur seven days prior to quit date. At this visit, subjects will be randomized to PRO or PBO within strata defined by sex. The Statistical Analysis Core (SAC) will generate the randomization tables (one for each sex), and the Clinical Trials Research Pharmacy will use it to determine randomization assignment. Randomization assignment will be stored in a secure file in a secure location at the Clinical Trials Research Pharmacy, to be shared only with the SAC. All other project staff including PI and study coordinator, as well as the participant, will remain blinded to the randomization assignment.

At the baseline visit subjects will provide a blood sample (for hormone assessment), breath sample (to confirm smoking status via carbon monoxide breathalyzer), have their vital signs (blood pressure, heart rate, weight) measured, be informed of their quit date, and receive brief behavioral counseling to prepare for their quit date. At the end of this visit subjects will be paid for their time and given study medication along with instructions for taking the medication (beginning at 8PM that day), as well as a clinic visit schedule for the remaining clinic visits. This visit will take approximately one hour to complete.

Weeks 0-12 (Visits 4-16): The Week 0 clinic visit will occur on the assigned quit date. Subjects will attend clinic visits on a weekly basis thereafter for twelve weeks. At weeks 0-4, week 8 and week 12 blood samples (hormone measurement) will be collected. Urine samples will be collected at all visits from all participants (pregnancy tests for females; and visual inspection of urine color to confirm compliance with taking study medication via riboflavin filler). At weeks 0-4, week 8 and week 12 urine will be saved for biochemical confirmation of smoking status via nicotine/cotinine levels. Subjects will also complete several forms and questionnaires (described below). Subjects will also return the medication bottle and unused medication, be given a new two-week supply and adverse events will be assessed. At Week 11, study medication will be discontinued. Finally, subjects will receive brief smoking cessation behavioral counseling (Appendix A). At the end of each visit subjects will be paid for their time. These visits will take approximately 30-45 minutes to complete.

Study Adherence: To encourage compliance the following will occur: (1) at the Baseline Visit, subjects will be given a schedule of all remaining appointments; (2) at each visit the subjects will be given an appointment reminder card for the next visit; (3) reminder calls, texts and/or emails (per subject's preference) will be placed or sent the day before each visit; (4) subjects will be routinely reminded that regardless of their smoking status their data are valuable and important; and (5) regardless of smoking status, subjects will be compensated at each visit (described in the following). If a subject misses a visit, study staff will try to reach him/her by phone that day to reschedule for one to three days later. If that does not work, staff will contact the subject's designated 'contact person' (i.e., someone who does not live with the subject but knows how to get in touch). If a subject does not attend any visits after the screening visits, he/she will be labeled as a "*drop*" and replaced. If the subject discontinues from the study after randomization but before the final follow-up visit, he/she will be labeled an "*incomplete*" but not replaced. If a subject does not quit on their assigned quit date or relapses later, she/he will be encouraged to stay in the study and make another quit attempt; such that we will follow them for three months regardless of smoking status. Subjects who complete the four week follow-up period after quit date, regardless of smoking status, will be labeled a "*completer*" for the primary outcome and not replaced. Our sample size goal to sufficiently power the primary outcome is for 200 completers.

B.4.4. Subject Compensation

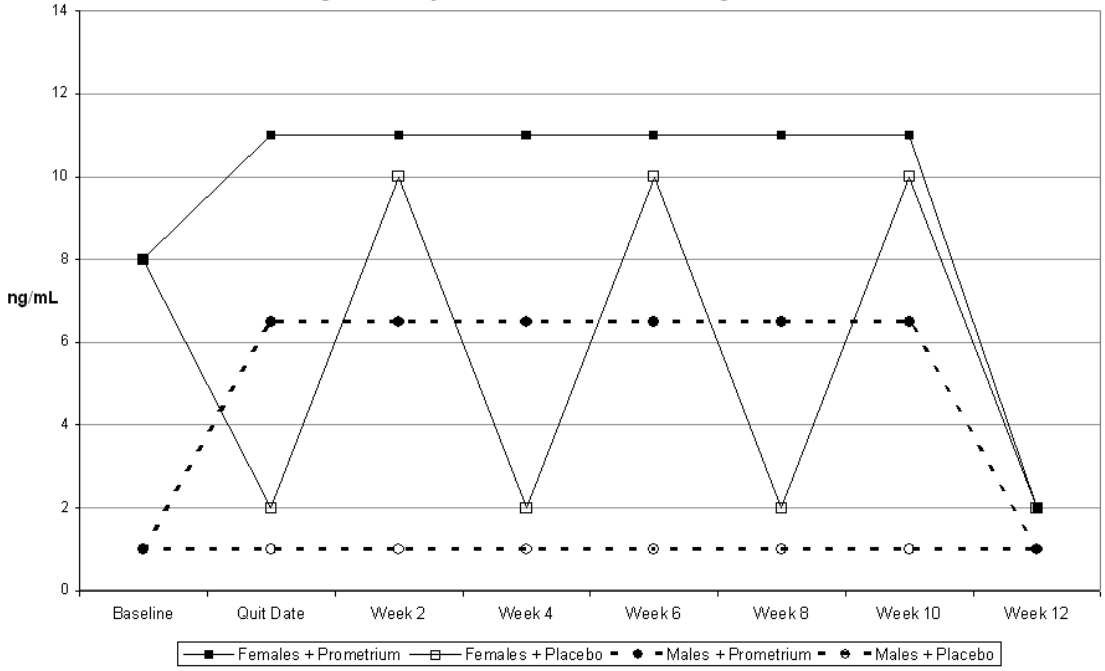
Subjects will receive compensation at each study visit for their time and effort. Subjects will be compensated $25 for Screening Visit 1 and $25 for Screening Visit 2. For each visit thereafter, they will be compensated $10 for their time and completing study procedures plus $10 to cover transportation costs (Total=$20). The subject will also be eligible for study bonuses: $100 for missing fewer than three follow-up clinic visits and a $30 bonus for attending the Week 4, 8 and 12 clinic visits. At Screening Visit 2, Week 4, Week 8, and Week 12 subjects will also be compensated for their performance on the BART computer task. The amount of compensation depends on their performance. It is estimated that subjects will receive between $10 and $50 each time they complete the task (average estimated payment=$35 each time). Therefore, subjects will receive approximately $660 ($25 Screening Visits x 2 visits + $20 follow-up visits x 14 visits + $190 in bonus payments + an average of $140 in BART payments).

B.4.5. Study Medication

Subjects will be stratified by sex and then randomly assigned to PRO or PBO, as described above. All medication (active and placebo) will be prepared by the University of Minnesota Clinical Trials Research Pharmacy, which is a specialized facility that prepares medication clinical trials including our ongoing research. The research pharmacist (D Luke Pharm D) will provide medications. There is oversight and monitoring with regular audits by local regulatory boards including the IRB. This study requires double-blind procedures, therefore progesterone will be over encapsulated and be identical to the placebo capsules. To prevent against the possibility of missed medication in the event of a missed clinic visits, subjects will receive a two week supply (to ensure no medication is missed in the event of an unexpected miss clinic visit due to illness or transportation issues, for example) of study medication from study staff at each clinic visit beginning with the Baseline Visit. Medications will be discontinued at the Week 11 clinic visit.

Progesterone: The progesterone will be given in the form of an active or placebo micronized natural progesterone (generic Prometrium). All subjects will take 200 mg twice daily (approximately 8am and 8pm) for twelve weeks starting seven days prior to the assigned quit date. The dosage was selected to ensure that serum progesterone levels will be consistent with those observed in the natural Luteal phase of the menstrual cycle (6-14 ng/mL) since that phase has been shown to be favorable for smoking cessation (Allen et al 2008). We expect the following serum progesterone levels by group (Figure 5): (1) females + PRO 9-13 ng/mL; (2) males + PRO 6-7 ng/mL; (3) females + PBO, varies by menstrual phase from 1-14 ng/mL; and (4) males + PBO 0-1 ng/mL (Goletiani et al 2007; Reed et al 2010; Yen et al 1999). Delivery of exogenous progesterone has been successfully used in prior research with a shorter duration of use (i.e. < 1 month) and is generally well tolerated (Sofouglu et al 2001; Sofouglu, et al 2004; Goletaini et al 2007; Reed et al 2010). The most common adverse effect in males and females is sedation. Less common effects include breakthrough bleeding (females), nausea (females and males) and breast tenderness (females) (de Lignieres, 1999; Goletaini et al 2007). While it is possible that progestins may contribute to risk for thromboembolism, we will be using natural micronized progesterone instead of synthetic progestins. Natural micronized progesterone is not known to be associated with thromboembolic risk (PDR, 2002; Goletaini et al 2007), and consequently is a safer choice. Micronized progesterone is not a form of birth control. Therefore, all female subjects will be educated on the importance of using a double-barrier method to protect against pregnancy.

Figure 5. Expected Levels of Serum Progesterone



Adverse Effects: If a subject is unable to tolerate these side effects of the study medication, those subjects will have the dosage decreased to 200 mg daily. The blind will not be broken to make this determination. Dr. Allen will assess the adverse event based on subject self-report of symptoms and advise a dose reduction if needed.

B.4.6. Study Measures

Prevalence of Relapse (Primary Outcome) and Days to Relapse (Secondary Outcomes): We will assess smoking status using three methods (one based on self-report and two based on biochemical confirmations). *First*, at each clinic visit the TimeLine FollowBack (TLFB) method will be completed. The TLFB is a validated retrospective data capture technique (Sobell et al 1996). Marijuana users will complete an additional TLFB for marijuana use. *Second*, the first biochemical confirmation is expired air carbon monoxide (CO) measurement. The CO levels will be collected to each visit. Expired air CO sensitivity and specificity is approximately 90% (Jarvis et al 1987). Subjects will exhale into a CO monitoring device (Bedfont Scientific Limited Company), calibrated weekly to verify accuracy. For sample collection, subjects blow into a breathalyzer and analysis occurs immediately. CO levels > 5 ppm are indicative of acute smoking. *Third*, we will measure urinary cotinine, a major metabolite of nicotine and a biological indicator of nicotine exposure. A spot urine sample will be collected at the Week 4 and Week 12 clinic visits. The cotinine test has a sensitivity of 96-97% and a specificity of 90-100% (Jarvis et al 1987). A cotinine level of less than 15 ng/mL is indicative of abstinence (half-life of cotinine is 19-30 hours). Samples will be analyzed in batches at the Minneapolis Medical Research

Foundation Division of Toxicology using gas chromatography (Hewlett-Packard) in Year 5. The use of two different forms of biochemical confirmation of smoking status will eliminate potential false-positives that occur with using only one of these items.

Days to relapse will be defined using continuous abstinence (CA), prolonged abstinence (PA) and point prevalence (PP) definitions (Hughes et al 2003). CA, a traditional measure, defines a single puff off a cigarette as relapse. The more liberal PA measure reflects sustained abstinence and defines relapse as seven consecutive slips (i.e., a puff or more) without a 24-hour period between any slip. The day of relapse is the first day of a slip. The CA and PA smoking outcomes will ranging from 0 (i.e. smoking on quit date) to 90 (i.e. not smoking at the end of the study). PP is a binary outcome of smoking relapse and is defined as a single puff off a cigarette during the seven days prior to a pre-specified time point of interest – Week 4 and Week 12. Week 4 prevalence of relapse is our primary outcome; week 12 prevalence of relapse is a secondary outcome. Self-report and biochemical measures will be combined to determine CA, PA, and PP.

Impulsivity Measures (Secondary Outcome): This P50 will examine "impulsivity" correlates broadly in rodents and humans across two substance use disorders (nicotine, cocaine-nicotine). Here we operationalize determination of impulsivity with several instruments.

Subjects will complete *three self-report measures* that have been computerized at each clinic visit beginning at Screening Visit 2. These measures will assess the characteristics of impulsivity, inhibition, planfulness, and cognitive impairments, key areas of focus in this grant.

- *Behavioral Inhibition/Activation scales (BIS/BAS):* These short 20 items forms commonly used scales to study externalizing tendencies (Carver and White, 1994). Investigators in Project II have used this instrument with success.
- *Barratt Impulsiveness Scale (BIS)*: This item contains 30 item self-report measure self-control (Patton et al 1995). Doran and colleagues (2004) demonstrated that impulsivity, as measured with this item, was a predictor of smoking relapse.
- *Brief Self Control Scale (BSCS)***:** This item consists of 13 questions rated on a 4-point scale from "very true" to "very false" on items reflecting the ability to control problematic behaviors (Tangney et al 2004).

The *Impulsivity Tasks* represent two forms of impulsivity, 1) impaired cognitive inhibitory mechanisms, and 2) deficits in motor inhibitory mechanisms. "Delay discounting" entails higher-level cognitive inhibitory processes that may characterize the behavior of individuals who are drug dependent (Bickel and Marsch, 2001) tobacco users (Baker et al. 2003), cocaine users (Monterosso et al, 2001), other drug users (e.g. Vuchinich and Simpson, 1998; Kollins, 2003) and pathological gamblers (Dixon et al, 2003). The following items will be completed at Screening Visit 2, Week 4, Week 8 and Week 12:

- *Delay Discounting Task*: Developed by de Wit and colleagues (Richards et al, 1999), delay discounting refers to the reduction in value of a reward over time relative to its immediate worth. One's discount rate, also known as a time preference, is a measurable individual difference and involves a series of choices (e.g. Petry and Casarella, 1999): one option is an immediate payment (e.g. $1); the second option is a larger payment (e.g. $50) after a delay (e.g. 6 hours to 25 years). Titrating the payment amounts at each delay interval allows the identification of points of indifference (the point at which the subject switches from choosing the immediate to the larger reward at a given delay interval). We additionally included a probability discounting condition to measure risk aversion in addition to time preference (Richards et al, 1999).
- *GoStop Task***:** This task measures response inhibition. A series of five-digit numbers are presented on a computer monitor at a rate of 500ms for ever two seconds. Subjects are instructed to click the mouse button when the number they see is identical to the previous number. Half of the numbers change color from black to red at 50, 150, 250 and 350. Subjects are instructed to respond to the matching number only when the displayed number is black. The primary outcome of this task is the percent of inhibition failures for the 150ms delay (Dougherty et al 2008). This item has been successfully used to assess tobacco dependence and smoking behavior (Billieux et al 2010).
- *Balloon Analogue Risk Task (BART):* This task, with 15 replications/session, is a measure of risk-taking. It involves displaying a small balloon on a computer screen. Each "pump" to inflate the balloon accumulates five cents, with each pump potentially breaking the balloon. The average pumps to the

breaking point is 64. To ensure attentive responding, subjects will receive the actual amount of money accrued on this task. The primary outcome on this task was the number of exploded balloons divided by the number of trials (Lejuez et al, 2002).

- *Immediate Memory Task / Delayed Memory Task (IMT/DMT):* This task is a continuous performance task that has two phases. First, the IMT displays a series of five-digit numbers in on a computer monitor for 500 ms followed by a blank screen 500 ms. Subjects click the mouse button whenever an identical number is displayed. Next, the DMT requires the subject to remember a five-digit number and compare it to another that is presented 3.5 seconds later. During the 3.5 interval subjects are presented with a distracter (12345) and told to ignore it. The primary outcome of this task is the IMT/DMT ratio which is defined as the proportion of commission errors to correct detections (Mathias et al 2002). This item is included as it we have used it in prior studies to identify menstrual phase differences in impulsivity and attention (see Preliminary Studies B.2.1.), and therefore is expected to be sensitive to the group differences in sex and progesterone.

Our recently completed P20 studies indicate greater impulsivity as measured by delay discounting in cocaine subjects as compared to age and sex matched controls. Here comparisons will be made across the smoking only subjects in Project I, the cocaine+smoking subjects in Project II, and results of the animal models (Project III). The composite measures of impulsivity will include: 1) Self-report measures (BIS, BSCS), 2) Inability to delay gratification (delay discounting), 3) Inability to inhibit a prepotent motor response (GoStop task), 4) Inability to make choice to stop when reward becomes unlikely (BART), and 5) Immediate memory/delayed memory assessing cognitive processes (IMT/DMT).

Independent Measures (sex, randomization and serum progesterone): Sex will be collected via self-report on the Demographics form completed at Screening Visit 1. Randomization, assignment (PRO vs. PBO) will be known as of the Baseline Visit to the SAC and Clinical Trials Research Pharmacy, but not will be unblended to other staff or participants until after completion of all measurements. Participants will be informed on their randomization assignment in a letter mailed within six months of the study's completion; this letter will also briefly summarize the study's findings. Measurement of serum progesterone will be measured by collecting a blood sample at clinic visits 0-4, 8 and 12. Blood (20 cc) will be drawn then centrifuged. The serum stored at -20°C in sealed storage tubes to prevent evaporation. Approximately two mL of serum will be analyzed by the HealthEast Medical Laboratories for progesterone sample using chemiluminescence. The remaining serum (approximately two to four mL) will be used for estradiol measurement (described below) and/or stored as back-up to be used in the event that problems occur during analyses.

Other Covariates: Information on potential covariates is collected at the clinic visits, including:

- *Smoking Behavior*: Specifically, number of cigarettes smoked per day during ad libitum smoking, self-reported number of past quit attempts, past longest quit attempt, motivation to quit smoking, and social influences such as partner smoking. This item will be completed at Screening Visit 1 only.
- *Fagerström Test for Nicotine Dependence* (FTND; Heatherton et al 1991): This item will be administered during the first screening session to assess level of nicotine dependence. The FTND is a 6-item self-report measure derived from the Fagerström Tolerance Questionnaire. This item will be completed at Screening Visit 1 only.
- *Minnesota Nicotine Withdrawal Scale* (MNWS; Hughes & Hatsukami, 1998): This item includes measurement of: irritability, anger, anxiety, difficulty concentrating, restlessness, depressed or sad mood, and hunger. MNWS scores are calculated without the item of craving. We have changed the wording of the craving item to 'desire to smoke,' and its mean scores are analyzed separately in light of evidence suggesting distinct patterns of craving from other withdrawal symptoms (Hughes & Hatsukami 1998). This item will only be completed once during the screening process. This item will be completed at Screening Visit 1. This item will be completed at each clinic visit thereafter.
- *Questionnaire for Smoking Urges* (QSU-brief; Cox et al. 2001): This item is the shortened version of the QSU (Tiffany & Drobes, 1991) and will assess smoking urges. It includes 10 items clustered into two factors similar to those assessed by the longer version of QSU. Factor 1 includes items that indicate a strong desire and intention to smoke. Factor 2 includes items indicating expectation of a relief from negative affect with an urgent desire to smoke (Cox et al, 2001). This item will only be completed once during the screening process. This item will be completed at Screening Visit 1. This item will be

completed at each clinic visit thereafter.

- *Profile of Mood States* (POMS; McNair et al, 1971): On this 72-item form subjects use a 5-point Likert-type scale, to indicate 10 subscales (Evans et al 1998) including positive mood, arousal, vigor, elation, friendly, fatigue, tension-anxiety, depression-dejection, confusion, and anger-hostility. This item will only be completed once during the screening process. This item will be completed at Screening Visit 1. This item will be completed at each clinic visit thereafter.
- *Beck Depression Inventory-II* (BDI-II, Beck et al, 1996): This is the most commonly used screening measure for adults and will be used to assess depressive symptoms. This item will only be completed once during the screening process. This item will be completed at Screening Visit 1. This item will be completed at each clinic visit thereafter.
- *Perceived Stress Scale* (PSS; Roberti et al, 2006): This ten item questionnaire will measure perceived stress. The items are rated on a 5-point scale, ranging from 0 (never) to 4 (very often), and they focus on events during the last week. The scale has adequate reliability and validity. This item will only be completed once during the screening process. This item will be completed at Screening Visit 1. This item will be completed at each clinic visit thereafter.
- *Life Event Occurrence* Survey (LEOS; McKee et al, 2005): This item will assess and account for the presence of current or recent significant life events. This measure includes 38 yes/no questions assessing various events that may have happened in the last six months including aspects of work, social life, family and finances. The measure includes instructions on how to rate the level of disruption the event caused in the subjects life from none too severe disruption. This measure will be administered at screening visit 1 and the final visit W12.
- *Columbia-Suicide Severity Rating Scale:* This questionnaire (C-SSRS; Posner et al, 2009) will be completed at each clinic visit to assess suicidal ideation, given this is listed as an SAE on the Prometrium label. If any item of suicidality is endorsed referrals to the appropriate mental health care will be made.
- *Sociodemographic Variables*: At the first screening visit we will collect information on age, race/ethnicity, education, income and other related variables. This item will be completed at Screening Visit 1 only.
- *Serum Estradiol*: At Screening Visit 1 and clinic visits 0-4, 8 and 12, blood samples will be collected to allow for the measurement of serum estradiol. Following identical procedures described above for serum progesterone, approximately two mL of serum will be analyzed by HealthEast Medical Laboratories using chemiluminescence.
- *Leisure Time Exercise Questionnaire* (LTEQ): This questionnaire has four-items to assess strenuous, moderate and mild exercise completed during leisure time and has high reliability (r=0.83, 0.85; Gordin & Shepard, 1985).
- *Caffeine Use:* Caffeine use will be collected via self-report at each clinic visit using the TimeLine FollowBack methods in which participants will report the total number of ounces of caffeinated beverages drank per day for each day.
- *Marijuana Use:* Marijuana use will be collected via self-report at each clinic visit using the TimeLine FollowBack methods in which participants will report number of days marijuana was used since the last clinic visit.
- *Adverse Childhood Experience (ACE):* Participants will complete this form at the SC2 visit.
- *Debriefing Questionnaire:* At end of study participation or Week 12, whichever is later, participants will complete a questionnaire to indicate which study medication (active or placebo) they thought they were on.
- *Pittsburgh Sleep Quality Index:* This survey is a part of the SCOR Core Battery and will be used to facilitate collaboration across SCORs in the future. To be completed at SC2 visit
- *Quick Inventory of Depressive Symptoms:* To be completed at SC2 visit
- *Anxiety:* This survey is a part of the SCOR Core Battery and will be used to facilitate collaboration across SCORs in the future. To be completed at SC2 visit

- *Quality of Life*: This survey is a part of the SCOR Core Battery and will be used to facilitate collaboration across SCORs in the future. To be completed at SC2 visit
- *Body Map:* This survey is a part of the SCOR Core Battery and will be used to facilitate collaboration across SCORs in the future. To be completed at SC2 visit

B.4.7. Sample Size & Power Analysis

We expect an approximate drop-out rate of 25% based on our current, more burdensome protocol within a sample of 18-40 year-old females. Therefore, we will enroll a total of 125 female and 125 male participants to ensure we have 100 per sex group to complete the 4 week follow-up for the primary outcome. Participants will be randomized 1:1 to PRO or placebo, separately by sex group, as described above. In our earlier work (Allen et al, 2008), the luteal quit group had a prevalence of 66% relapse at 30 days; this estimates the placebo group relapse rate for our proposed study. Based on a two-tailed Pearson chi-square test with alpha=0.025 for each sex group, a sample size of 100 completers per sex group will have 80% power to detect an odds ratio of 3.5 or higher for comparing smoking relapse prevalence in the placebo group to smoking relapse prevalence in the PRO group. We observed an odds ratio of 3.2 for follicular quit group relapse compared to luteal quit group relapse (Allen et al, 2008). Since our PRO group will receive substantially more progesterone than the typical natural female cycle, it is reasonable to expect a slightly larger odds ratio for PRO compared to placebo. Since the difference in progesterone levels between the male PRO group and the male PBO group will be larger than the difference between the female PRO group and the female PBO group (see Figure 5), we expect a larger odds ratio (hence higher power) for the male treatment comparison.

B.4.8. Statistical Analysis

Randomization scheme: Our power calculation for the primary outcome specifies 100 males and 100 females. Since we expect approximately 25% drop-out before determination of the primary endpoint, we will over-enroll, approximately 125 of each sex. Thus we will build randomization tables for up to 150 male and 150 female potential enrollees. Each sex group will be randomized 1:1 to PRO vs. PBO. Since enrollment and randomization will occur over several years, we will employ a randomly permuted blocks allocation, rather than a simple random allocation, stratified by sex. This will reduce the possibility of a chance imbalance in treatment assignments, ensuring that we have treatment balance maintained within sex group consistently across the enrollment period. Block sizes of 4 and 6 will be used in a 1:1 ratio.

Primary outcome analyses: This addresses Hypothesis 1. Our primary outcome is the binary indicator of relapsed yes/no at the week 4 visit. An unadjusted assessment of the treatment effect will come from a logistic regression of this binary outcome on randomized treatment assignment, separately by sex. The sex-specific treatment effect will be considered statistically significant if the p-value is <0.025. All persons randomized and with a measured primary outcome at the week 4 visit will be included in this analysis, regardless of whether or not they ever took any of their assigned treatment (intent-to-treat analysis); persons with missed visits are discussed below. While we expect baseline covariates to be balanced across treatment groups due to the randomization, an adjusted assessment of the treatment effect will then be carried out by a logistic regression including the randomized treatment assignment and pre-specified adjusting covariates such as age, baseline progesterone, estradiol, baseline impulsivity measures, etc. This pre-specified list will be determined by the study team during the finalization of the protocol, prior to the first study enrollment. We expect these analyses to be somewhat conservative, since they do not explicitly account for the randomized permuted blocking (Matts and Lachin, 1988). An analysis that accounts for the blocking (such as a stratified Mantel-Haenzel test) cannot be generalized to include the adjustment for impulsivity measures, for example, which are a focus of this proposal.

Safety analyses: Adverse events will be quantified separately by sex and treatment groups and compared across treatment groups with Fisher's exact test (for binary events) or with chi-square test (for counts of events or event rates).

Secondary outcome analyses: These address Hypothesis 2. Our secondary outcomes include the binary indicator of relapsed yes/no at the week 12 visit, and days to relapse, as described above. The binary outcome will be analyzed as described for the primary outcome. Days to relapse will be analyzed using Kaplan-Meier

curves with a log-rank test comparing treatments (unadjusted) and Cox proportional hazards analysis (adjusted for other characteristics), both of which allow for loss-to-follow up via right censoring (Therneau and Grambsch, 2000), separately for the CA and PA definitions. Adjusting variables will be selected as described for the primary outcome. The proportional hazards assumption on the treatment effect will be examined and tested (Lin, Wei, and Ying, 1993; Grambsch and Therneau, 1994).

Other analyses: To address Hypothesis 3, we will pool the male and female data and test for an interaction between sex and treatment assignment in an adjusted Cox regression for the days to relapse outcomes. To address Hypothesis 4, we will test a baseline impulsivity by sex interaction in the logistic regressions for the binary outcomes and in the Cox regressions for the days to relapse outcomes. To address Hypothesis 5, we will test a baseline impulsivity by baseline serum progesterone interaction in the logistic regressions for the binary outcomes and in the Cox regressions for the days to relapse outcomes. While this study was designed to be powered for Hypothesis 1, rather than for these comparisons, these will be used to generate preliminary data and hypotheses for future research on sex differences in addiction treatment and impulsivity.

Handling missing outcomes: For persons who do not attend a week 4 visit, assessment of the primary outcome is not directly possible. During their week 5, study staff will attempt to contact them in order to collect by phone and/or email a self-reported recall of smoking status as of week 4; outcomes collected in this way will be denoted separately in the study database. The primary outcome analysis will be carried out once excluding these persons, once including those for whom we were able to obtain a self-reported recall outcome, and once where we conservatively assume all these persons relapsed as of their week 4 visit. Since 'missing at random' is a strong statistical assumption to make in the primary outcome analysis, we will also carry out descriptive analyses to see whether persons missing their week 4 visit differed in their baseline characteristics or treatment assignment from persons not missing their week 4 visit.

B.4.9. Existing Challenges & Barriers

To test our study hypothesis in females, it is critical to produce and maintain serum progesterone levels consistent with those observed in the Luteal phase (6-14 ng/mL; Yee et al, 1999). To do this, we considered many different options for the delivery of exogenous hormones. First, we decided not to use combined synthetic progestin-estradiol hormonal contraceptive pills because this option would further complicate the study design by introducing another variable (exogenous estradiol; Goletiani et al 2007). Second, we also considered using synthetic progestin-only hormonal contraceptive pills. However, as we have observed in our current study, they also do not result in levels of serum progesterone consistent with the Luteal phase. Further, synthetic progestin has more risks associated it with it than natural progesterone (Goletiani et al 2007). Next, delivery of progesterone via intravaginal or rectal suppository, or intramuscular injection was eliminated because the serum progesterone levels would still be substantially lower than those typical of Luteal phase. Therefore, using natural micronized progesterone (generic Prometrium) is the best way to ensure serum progesterone levels remain consistent with levels observed during the Luteal phase. Since the half-life of natural progesterone is short, twice daily dosing is necessary. While there may be a question of subject compliance with taking two oral doses per day, we will confirm compliance via the assessment of serum progesterone levels at all study visits postpartum. Natural progesterone is also the easiest way to administer supplemental progesterone for male participants and has been successfully done in other studies (Goletaini et al 2007). On a related note, a second challenge is estrogen. Estrogen fluctuates naturally during the menstrual cycle (Yee et al 1999), and has also been shown to be associated with the facilitation of drug abuse behaviors (Carroll & Anker, 2010). While it is impossible to remove estrogen from our sample population, we will measure it (via blood samples to measures serum estradiol levels) and consider it in our analyses.

B.4.10. Timeline

The study timeline is displayed in Table 2.

Table 2. Timeline of Study Events

	Year 1				Year 2				Year 3				Year 4				Year 5			
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Training Staff and Study Preparation	X	X																		
Subject Recruitment		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Subject Follow-up			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Data Entry and Cleaning			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Analysis and Report Writing															X	X	X	X	X	X

B.4.11. Future Directions

The expected outcomes of this project will be a better understanding of the relationship between sex, sex hormones, impulsivity and smoking behavior. Upon completing this project, we intend to continue our exploration into the role of sex hormones on smoking behavior. Specifically, if our expectations are confirmed, we plan to conduct a similar study in a time associated with increased risk for smoking relapse for both men and women – the postpartum period.

C. Inclusion of Children.

Children (under 18 years old) are not included since young age is associated with menstrual cycle irregularities (e.g., anovulation). Further, since this study requires the continuous (or a recent history) of regular use of cigarettes, it is unlikely adolescents will meet this criterion. Young men and women (e.g., aged 18-20 years) will be recruited for participation in our study. The trial site is at the University of Minnesota, which has a large undergraduate population. Campus media will be also used to recruit young men and women. We will also target venues and institutions frequented by young non-college men and women (bars, festivals, coffee shops, and community events) to ensure the sociodemographic diversity of the youngest component of our participant sample.

D. Inclusion of Women and Minorities

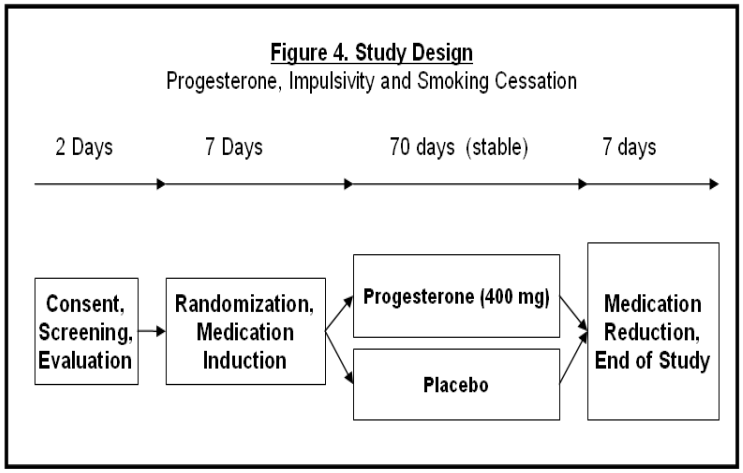
This study will be recruiting both men and women because the research question addressed is designed to assess sex differences. We are looking specifically at the effects of a female sex hormone (progesterone) on smoking cessation in men and women who are motivated to quit smoking. The study will use participants recruited from the greater metropolitan area of Minneapolis and St. Paul, via mass media advertisements. The Twin Cities metropolitan area has a sufficiently large female smoking population to ensure an adequate sample. We have been successful in recruiting similar numbers of women in similar periods of time in previous studies. Estimates indicate that as of 2009 the Minneapolis and St. Paul, Minnesota Twin Cities metro area included approximately 50.5% female and 20.2% of the population in the racial minority groups (Black= 11.0%, Asian = 5.8%, American Indian = 1.2%, other = 4.0%) and the Hispanic population is 6.4%. If minority women do not respond to the advertisements, we will make special efforts to solicit their participation by advertising in local neighborhood newspapers with high minority readership (such as the Southside Pride, Phillips/ Powderhorn, and Riverside Editions); by posting flyers in free clinics in the metro area who service minorities (e.g., Community University Healthcare Center, Pilot City); and by identifying contacts in churches, health centers, and community centers with high minority participation and disseminating information regarding the study opportunity; and once we have garnered initial contact with participants we receive multiples word of mouth referrals. Our current study has been successful in recruiting a diverse sample in that of the 163 participants enrolled to date 49% are White, 33% are Black, 8% are more than one race and 10% are other.

Data Safety and Monitoring Plan (DSMP): 1 P50 DA033942-01
PROJECT 1 – Sex Differences and Progesterone:
Association with impulsivity and smoking cessation

Summary
This is one of two clinical trials for the SCOR *entitled: Sex Differences and Progesterone Effects on Impulsivity, Smoking, & Cocaine Abuse.* The DSMP is described below. Organization and implementation of the Data Safety and Monitoring Board functions will be administered by the Service Core (B) of the P50 (Grabowski, Director). This will be undertaken in close coordination with the Principal Investigators of the two clinical Projects (Drs. Allen and Specker) and the overall SCOR Director (Dr. Carroll), co-Director (Dr. Allen) and study staff members.

A1. Study Design and Implementation

This is a 12-week, two arm (progesterone-PRO- versus placebo-PBO), prospective, parallel groups, randomized placebo-controlled trial examining effects of PRO, compared to placebo (PBO), as well as sex differences on impulsivity and smoking cessation outcomes in females and males who are motivated to quit smoking.



Outcome Measures

The primary focus and outcome measure will be prevalence of smoking relapse at Week 4 using point prevalence definition of abstinence. This will be measured via self-report, carbon monoxide breathalyzer, and urinary cotinine. Secondary outcome measures include days to relapse (also measured by self-report, carbon monoxide breathalyzer, and urinary cotinine using continuous abstinence and prolonged abstinence definitions) and impulsivity measures (self-report questionnaires including Behavioral Inhibition / Activity Scales, Barratt Impulsiveness Scale, and Brief Self Control Scale; and computer tasks including Delay Discounting, GoStop Task, Balloon Analogue Risk Task, and Immediate/Delayed Memory Task).

Setting, Recruitment, Subjects

Setting**:** This project will be conducted at the Delaware Clinical Research Unit (DCRU). The DCRU has both inpatient and outpatient resources for the spectrum of biomedical research including special capabilities that were developed for study of substance use disorders. The Clinical and Translational Sciences Institute (CTSI), runs the DCRU and functions parallel and support the activities of the NIH funded CTSA, which predated it. The DCRU includes: reception area, examination rooms, meeting rooms, clinical interview rooms, testing rooms for computer based performance tasks, a wet lab for handling bloods and other specimens, freezers (to -80°C), all essential staff offices, each with multiple telephone and computer lines through the University of Minnesota servers, a locked limited access protocol, equipment and medication rooms, as well as secure cabinets for study files and essential supply and support areas and services.

Recruitment**:** To meet recruitment goals, we will enroll a total of 250 subjects (~6 subjects/month) to ensure a final sample size of 100 females and 100 males. Our primary recruitment method will be advertising in the mainstream media. While this type of recruitment can be challenging, our team has been successful with this form of recruitment. For example, our current study recruiting females between the ages of 18-40 has had success with Facebook advertising. Specifically, over the past seven months we have advertised on Facebook resulting in 6,483 clicks to our website, an estimated 180 phone calls to our clinic and an enrollment of 29 subjects (~4 subjects/month). We regularly use television, radio, mailings, and other internet sources to identify study subjects with similar success. Using all of these methods, we have successfully enrolled ~8 subjects/month over the past year in our two ongoing tobacco use research studies. Additional advertising and the unique character of this study will further assure an ample sample.

Subjects and Eligibility Criteria

Two hundred and fifty subjects, 50% female, will be consented to achieve the final sample of 200 subjects (50% female). The inclusion and exclusion criteria are:

Inclusion Criteria

1. Males between 18 and 60or females between 18 and 50 years of age;
2. Self-reporting smoking ≥ 5 cigarettes/day for at least the past year;
3. Motivated to quit smoking (self-report ≥ 7 on 10-point Likert-type scale);
4. Stable physical/mental health;
5. Self report of regular menstrual cycles (female only);
6. Willing to use a double-barrier contraception method if sexually active and not surgically sterilized;
7. English fluency;
8. Understanding the study procedures and able to provide informed consent;
9. Ability to participate fully in research elements for the duration of the trial.

Exclusion Criteria

1) Current use of other types of tobacco, nicotine replacement therapy, or smoking cessation medications;
2) Current or recent (< 3 months) breastfeeding (females only),
3) Current or planned pregnancy within the next three months (females only);
4) DSM-IV diagnoses for, bipolar disorder, ADHD, or major depressive disorder within the last 3 month.
5) Substance dependence within the last 3 month with the exception of nicotine dependence and non-daily use of marijuana.
6) Use of psychotropic medications;
7) Current use of exogenous hormones, finasteroid (propecia), efavirenz, red clover, ketoconazole and other drugs that are CYP3A4 inhibitors
8) Conditions contraindicated to progesterone treatment (including, but not limited to, thrombophlebitis, deep vein thrombosis, pulmonary embolus, clotting or bleeding disorders, heart disease, diabetes, history of stroke, allergy to peanuts, hypersensitive to progesterone and liver dysfunction).

Screening and Visit Procedures

The first clinic visit (i.e. Screening Visit 1) will occur within seven days of the onset of menses in females and within two weeks of the telephone interview for males. A brief description of the study will be provided to determine if the subject wishes to proceed with the informed consent process. If agreeable, the informed consent process will be initiated with the candidate subject. Responses will be provided to all candidate subject queries. If the subject agrees to participate, she or he will sign the consent, be provided with a copy of the signed document, and screening will be initiated. Screening will determine final eligibility as determined by meeting inclusion criteria without any exclusionary conditions. Screening will include a general medical examination including history, measurements of height, weight, blood pressure, heart rate, and expired carbon monoxide will be obtained. Female subjects will provide a urine sample that will be used for a pregnancy test. A blood sample will be obtained to assess serum hormone levels and and a psychiatric interview will be completed by trained study staff. Subjects will complete forms to measure smoking-related symptomatology, mood, and potential confounders (i.e. age, education, partner smoking, motivation to quit smoking, level of nicotine dependence). At the end of this visit subjects will schedule their next visit and receive compensation for their time.

The second visit (i.e. Screening Visit 2), completed within three days of Screening Visit 1, will include a series of computer tasks to measure impulsivity, followed by training on study procedures and compensation for their time.

A Baseline Visit will occur seven days prior to the subjects assigned quit date. Females will have their assigned quit date set seven to nine days after ovulation. Ovulation will be determined through the use of urine ovulation tests that female subjects will use daily for ten days in a row. Males will have their assigned quit date matched to a female subject for a similar delay and procedure completion. At this visit subjects' weight, blood pressure, heart rate, and carbon monoxide level will be measured. They will also provide urine and blood samples (20cc) for later measurement of nicotine exposure (specifically nicotine and cotinine) and hormone levels (specifically progesterone and estradiol), respectively. At this visit subjects will receive their study medication and be provided regimen/administration instructions. They will also receive brief smoking cessation behavioral counseling, be compensated for their time, and receive a schedule of all follow-up visits.

At the follow-up visits (weekly visits, Week 0 - Week 12) all subjects will have their weight, blood pressure, heart rate and expired carbon monoxide measured. The subjects will provide urine (nicotine, cotinine) at all visits and blood (progesterone, estradiol) samples at visits 0-4, 8 and 12 and complete several forms to measure smoking-related symptomatology, mood, and related items. The study nurse will assess their adverse events. At the end of each visit subjects will receive additional behavioral counseling, additional study medication and be compensated for their time.

Subjects could earn up to $480 for their study participation ($25 for screening visit x 2 screening visits + $20 for baseline visit + $20 for follow-up clinic visits x 13 visits + $75 bonus for missing less than three visits + $75 for completing the study).

Power Analysis and Sample Size

We expect an approximate drop-out rate of 25% based on our current more burdensome protocol within a sample of 18-40 year-old females. Therefore, we will enroll a total of 125 female and 125 male participants to ensure we have 100 per sex group to complete the 4 week follow-up for the primary outcome. Participants will be randomized 1:1 to PRO or placebo, separately by sex group, as described above. In our earlier work (Allen et al, 2008), the luteal quit group had a prevalence of 66% relapse at 30 days; this estimates the placebo group relapse rate for our proposed study. Based on a two-tailed Pearson chi-square test with alpha=0.025 for each sex group, a sample size of 100 completers per sex group will have 80% power to detect an odds ratio of 3.5 or higher for comparing smoking relapse prevalence in the placebo group to smoking relapse prevalence in the PRO group. We observed an odds ratio of 3.2 for follicular quit group relapse compared to luteal quit group relapse (Allen et al, 2008). Since our PRO group will receive substantially more progesterone than during the typical natural female cycle, it is reasonable to expect a slightly larger odds ratio for PRO compared to placebo. Since the difference in progesterone levels between the male PRO group and the male PBO group will be larger than the difference between the female PRO group and the female PBO group, we expect a larger odds ratio (hence higher power) for the male treatment comparison.

B. TRIAL MANAGEMENT

Enrolling Clinics and Data Collection Centers. All study subject enrollment and data collection will be done at the Delaware Clinical Research Unit at the University of Minnesota.

Projected Timetable. The projected timetable is displayed in Table 1.

Table 1. Project Timeline

	Year 1				Year 2				Year 3				Year 4				Year 5			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Training Staff and Study Preparation	X	X																		
Participant Recruitment		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Participant Follow-up			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Data Entry and Cleaning			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Analysis and Report Writing															X	X	X	X	X	X

Target Population Distribution. This study will be recruiting both men (n=100) and women (n=100) because the research question addressed is designed to assess sex differences. Specifically, the effects of a female sex hormone (progesterone) on smoking cessation in men and women who are motivated to quit smoking will be examined. Study participants will be recruited from the greater metropolitan area of Minneapolis and St. Paul, via mass media advertisements. Estimates indicate that as of 2009 the Minneapolis and St. Paul, Minnesota Twin Cities metro area included approximately 50.5% female and 20.2% of the population in the racial minority groups (Black= 11.0%, Asian = 5.8%, American Indian = 1.2%, other = 4.0%) and the Hispanic population is 6.4%. In the absence of minority population response to advertisements, additional targeted strategies will be implemented to solicit their participation. These efforts are effective; for example, our current study has been successful in recruiting a diverse sample: 49% are White, 33% are Black, 8% are more than one race and 10% are other.

Enrollment Table

Study Title: Progesterone, Impulsivity and Smoking Cessation

Total Planned Enrollment: 250

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	4	4	8
Not Hispanic or Latino	121	121	242
Ethnic Category: Total of All Subjects *	125	125	250
Racial Categories			
American Indian/Alaska Native	4	4	8
Asian	4	4	8
Native Hawaiian or Other Pacific Islander	1	1	2
Black or African American	15	15	30
White	101	101	202
Racial Categories: Total of All Subjects *	125	125	250

* The "Ethnic Category: Total of All Subjects" must be equal to the "Racial Categories: Total of All Subjects."

C. DATA MANAGEMENT AND ANALYSIS

Data Acquisition and Transmission. Data collection at study visits will take the form of subjective measures (forms), blood and urine samples, and will be identified with a three-digit identification number. Samples will be collected and stored with the subject ID code only. The coordinator will keep the code that links the subject ID with the identity of the subject in a database protected by two-levels of security stored it separately from the data.

Data Entry Methods. All self-report data collection items throughout the study will be self-administered per direction of study staff via a computer program (REDCap; http://project-redcap.org/) to improve the quality of data (by avoiding missing data, illegible data, etc) and limit the time spent on data entry and cleaning. Any data not entered directly into a computer system (i.e. height, weight, blood pressure) will be double entered on our password protected server by trained data entry personnel at the Tobacco Research Programs using the Access data entry programs. The study coordinator will be available to monitor the data and correct any discrepancies based on source documents.

Data Analysis Plan. Addressing Hypothesis 1: Our primary outcome is the binary indicator of relapsed yes/no at the week 4 visit. An unadjusted assessment of the treatment effect will come from a logistic regression of this binary outcome on randomized treatment assignment, separately by sex. The sex-specific treatment effect will be considered statistically significant if the p-value is <0.025. All persons randomized and with a measured primary outcome at the week 4 visit will be included in this analysis, regardless of whether or not they ever took any of their assigned treatment (intent-to-treat analysis); persons with missed visits are discussed below. While we expect baseline covariates to be balanced across treatment groups due to the randomization, an adjusted assessment of the treatment effect will then be carried out by a logistic regression including the randomized treatment assignment and pre-specified adjusting covariates such as age, baseline progesterone, estradiol, baseline impulsivity measures, etc. This pre-specified list will be determined by the study team during the finalization of the protocol, prior to the first study enrollment. We expect these analyses to be somewhat conservative, since they do not explicitly account for the randomized permuted blocking (Matts and Lachin, 1988). An analysis that accounts for the blocking (such as a stratified Mantel-Haenzel test) cannot be generalized to include the adjustment for impulsivity measures, for example, which are a focus of this proposal.

Hypotheses:

Hypothesis 1: For both males and females, a lower proportion of subjects randomized to PRO will relapse by 4 weeks after quit date compared to those randomized to PBO.

Hypothesis 2: For both males and females, subjects randomized to PRO will have more days to relapse compared to those randomized to PBO.

Hypothesis 3: There will be a sex difference in smoking relapse such that females, regardless of randomization assignment, will have fewer days to relapse compared to males.

Hypothesis 4: Impulsivity will be a stronger relapse predictor in females than males.

Hypothesis 5: Among those with higher levels of serum PRO the influence of impulsivity on smoking relapse will be dampened.

Addressing Hypothesis 2: Our secondary outcomes include the binary indicator of relapsed yes/no at the week 12 visit, and days to relapse, as described above. The binary outcome will be analyzed as described for the primary outcome. Days to relapse will be analyzed using Kaplan-Meier survival curves with a log-rank test comparing treatments (unadjusted) and Cox proportional hazards analysis (adjusted for other characteristics), both of which allow for loss-to-follow up via right censoring (Therneau and Grambsch, 2000), separately for the CA and PA definitions. Adjusting variables will be selected as described for the primary outcome. The proportional hazards assumption on the treatment effect will be examined and tested (Lin, Wei, and Ying, 1993; Grambsch and Therneau, 1994).

To address Hypothesis 3, we will pool the male and female data and test for an interaction between sex and treatment assignment in an adjusted Cox regression for the days to relapse outcomes. To address Hypothesis 4, we will test a baseline impulsivity by sex interaction in the logistic regressions for the binary outcomes and in the Cox regressions for the days to relapse outcomes. To address Hypothesis 5, we will test a baseline impulsivity by baseline serum progesterone interaction in the logistic regressions for the binary outcomes and in the Cox regressions for the days to relapse outcomes. While this study was designed to be powered for Hypothesis 1, rather than for these comparisons, these will be used to generate preliminary data and hypotheses for future research on sex differences in addiction treatment and impulsivity.

D. QUALITY ASSURANCE

Data collected via computer programs (EMAs and REDCap) will be monitored by the study coordinator by random inspection of completed forms, and any problems detected will be discussed with the PI. The Statistics Core (Eberly, Director) will analyze the data using the SAS program. In addition, the Statistics Core will provide support in developing data entry programs. Data analyses will be completed at the end of the study. For missing data: Persons who do not attend a week 4 visit, assessment of the primary outcome is not directly possible. During their week 5, study staff will attempt to contact them in order to collect by phone and/or email a self-reported recall of smoking status as of week 4; outcomes collected in this way will be denoted separately in the study database. The primary outcome analysis will be carried out after excluding these subjects, including those for whom we were able to obtain a self-reported recall outcome, where we conservatively assumed all these individuals relapsed as of their week 4 visit. Since 'missing at random' is a strong statistical assumption to make in the primary outcome analysis, we will also carry out descriptive analyses to see whether persons missing their week 4 visit differed in their baseline characteristics or treatment assignment from persons not missing their week 4 visit.

E, Regulatory Issues: Adverse Events, Serious Adverse Events, Collection and Reporting

Adverse Events: An adverse event is any unwanted experience or event occurring during the course of a clinical trial. At each visit, either a research nurse or physician will query the participant and log side effects and other treatment emergent events since the past visit, recording their severity (mild, moderate, severe, life-threatening), what action was taken, and whether the symptoms are continuing or resolved. The study investigators will follow all AEs to the point of a satisfactory resolution. A study subject may be withdrawn from the study if the PI determines it is the best decision for protection of the safety of the subject. All AEs will be assessed to determine if they meet criteria for an SAE. AEs will be quantified separately by sex and treatment groups and compared across treatment groups with Fisher's exact test (for binary events) or with chi-square test (for counts of events or event rates). The event will be documented as to whether there is 1) no relationship between the study drug and the adverse event, 2) the adverse event is unlikely related to administration of the study drug, 3) the adverse event is possibly related to study drug administration, or 4) the adverse event is probably related to the administration of the study drug.

Serious Adverse Events (SAE): A serious adverse event is defined as an outcome that is 1) fatal or life-threatening, 2) significantly or permanently disabling or incapacitating, 3) requires or prolongs inpatient hospitalization, or 4) results in

a congenital anomaly. *SAE's,* whether or not related to study medication, will be reported to the IRB and NIDA. All drug related adverse events of a non-serious nature are reported to the University of Minnesota's IRB on a quarterly basis. Serious adverse events will be reported by telephone to the IRB, and to NIDA and the FDA within the three days of our receipt of information regarding the event and written reports will be submitted within ten days. If a subject either withdraws from the study or the investigator decides to discontinue a subject due to SAE, the subject will have appropriate follow-up medical monitoring. Monitoring will continue until the problem requiring hospitalization was resolved or stabilized with no further change expected, is clearly unrelated to study medication, or results in death. Outcome of SAEs will be periodically reported to NIDA. A summary of the SAEs that occurred during the previous year will be included in the annual progress report to NIDA. Finally, the PI's will ensure that serious adverse events reported to NIDA via the serious adverse event tracking and reporting system at https://saetrs.nida.nih.gov/.

The Principal Investigator will then take appropriate action (including study modification) as agreed upon by these monitoring groups including the DSMB when needed. The Principal Investigator will determine whether the seriousness of the event warrants removal of the participant from the study. Appropriate diagnostic and therapeutic interventions will be initiated and the participant will be medically followed and kept under observation as long as medically indicated. After the review of the data, the DSMB report will make recommendations about whether the trial should continue with or without modifications, or be terminated. Any potential conflict of interest in the Data and Safety Monitoring Board will be disclosed.

F. Trial Safety

*Potential Risks and Benefits for Participants***.** The potential risks for study subjects are minimal to moderate. Medical histories for all subjects will be reviewed prior to entry into the study and all subjects will be under medical supervision while in the study. Urine and breath samples will be obtained and should not present risk to the subjects. Blood samples will be obtained by trained phlebotomists. A minimal amount of blood will be collected (20cc) per collection. Blood drawing may result in slight discomfort, bruising, or there may be some soreness at the puncture site. In some cases there may be dizziness or fainting.

Generic Prometrium, a natural progesterone, is generally well tolerated. The most common adverse effect is sedation. Other less common adverse effects include menstrual irregularity, spotting or breakthrough bleeding, dizziness, cramps, nausea, fatigue, headache and breast tenderness (de Lignieres, 1999; Simon, 1995, Sofuglu, 2009). Other side effects attributed to synthetic progesterone, including depression, fluid retention, pruritus, jaundice, rash and thrombotic disorders, are unlikely to occur. Recently there have been reports of increased risk of stroke, coronary artery disease, venous thromboembolism and breast cancer in postmenopausal females who have been on long-term hormone replacement treatment with estradiol and progestin (medroxyprogesterone) combination (Anonymous, 2002; Grady et al., 2002; Hulley et al., 2002; Nelson et al., 2002). While some of these adverse events develop after years of treatment, venous thromboembolism is seen within the first year of treatment (Anonymous, 2002). It is possible that progestins may contribute to thromboembolism seen during estradiol and progestin treatment and thromboembolism is listed in the PDR as one of the adverse events for medroxyprogesterone treatment (PDR, 2002). In contrast to synthetic progestins, natural progesterone is not known to cause thromboembolism (PDR, 2002). However, as a safety measure for these serious adverse events, we will exclude subjects with history of thrombophlebitis, deep vein thrombosis, pulmonary embolus, clotting or bleeding disorders, heart disease, diabetes or history of stroke. Possible adverse events from generic Prometrium will be assessed weekly by the research nurse (Schulz, NP) in consultation with the study physicians (Allen MD, Specker MD). If the side effects cannot be tolerated the medication dosage will be decreased to 200 mg daily.

Although uncomfortable, withdrawal symptoms do not pose significant health risks. Subjects who participate in this study will be asked to quit smoking on an assigned quit date. The smoking abstinence may result in increased irritability, anxiety, tension, depression, increased hunger or drowsiness.

a. Recruitment and Informed Consent. Subjects will be recruited via metro mass media advertisements (television, radio, print, email, and internet). Those who see the mass media advertisements will contact Tobacco Research Programs in response to advertisements. Each subject interested in participating will be screened by telephone interview for eligibility. If eligible, subjects will be asked to attend a screening visit. At this visit subjects are provided with a detailed explanation of the study purpose and procedures (including risk involved), any questions a subject may have will be answered, subjects will be asked questions to assess their understanding of the study, and informed consent will be obtained before any study procedures are completed.

b. Protection against Risk. Subjects will be told the potential risks involved in this study. Although risks to subjects in

the proposed study are minimal, the following actions will be taken to minimize these risks. We will exclude subjects with health conditions that may be exacerbated by their participation. Subjects will be monitored regularly by medical personnel employed by the study. Dr. Sharon Allen (PI) will be available for emergency phone calls 24 hours/day and for office visits in case of problems. Blood will be collected by trained phlebotomists to reduce the risks involved with blood draws.

During generic Prometrium administration, the first dose of the study medication will be taken at 8 PM to minimize possible sedation from initiation of progesterone treatment. Subjects will be warned about using caution when driving a motor vehicle or operating machinery. Subjects will also be warned about the side effects associated with generic Prometrium. Further, although unlikely, the study physician (Dr. Allen, PI) will be alert to the earliest manifestations of thrombotic disorders including thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis (PDR, 2002). If any of these occur or are suspected, the study medication will be discontinued immediately and medical treatment will be sought.

There may be risk to confidentiality and privacy of study data. To minimize this risk, subjects will be assigned unique three-digit identification numbers. The questionnaires and study samples will retain only the unique study number. These numbers will be linked to the subject's identifier information in a database separate from assay results or other data collected. The database requires at least 2 levels of security (i.e., passwords), which will allow only authorized research team members to access the information.

Potential Benefits of the Proposed Research to the Subjects and Others

Whereas no assurance can be made to an individual subject that he/she will personally benefit from such research, the experience should be beneficial. Subjects will have the opportunity to learn about their smoking behavior and receiving smoking cessation behavioral counseling. Society may benefit from a better understanding of the role of sex and sex hormones on smoking behavior and impulsivity. A better understanding of this relationship will help improve treatment strategies for nicotine dependence. The risks in relation to the potential benefits are minimal to the individual research subject and virtually nonexistent to society in general.

G. Trial Efficacy

No interim analyses of efficacy are planned for the proposed study.

H. Data Safety and Monitoring Plan, Board, and Administration.

The Service Core (Grabowski, Director) of the P50 will implement the plans and organize review by the Data Safety and Monitoring Board (DSMB). The Service Core (B) will administratively oversee the DSM Plan, Board and complying with reporting requirements. This provides additional separate attention to, monitoring and focus on safety. The DSMB will meet annually and will, post meeting, provide a summary of discussion, which will be conveyed to NIDA. This repor will include subject demographics, expected versus actual recruitment rates, summary of any quality assurance or regulatory issues, summary of adverse events (AEs) or serious adverse events (SAEs) which may have occurred, and any changes in the protocol as a result of these issues. The DSMB will receive current data and blinded data unless a specific request or cause to view unblinded data is evident. The final report will be complete and inclusive with the unblended data set.

The Service Core Project Manager (A. Allen) will meet with the Study Coordinator (D. Babb) and PI (S. Allen) on a weekly basis to review the study's progress. Additionally, the Service Core Director (J. Grabowski) will also be available to identify and solve problems in the study's implementation, as well as advise on any adverse events experienced by subjects during the study. Drs. Grabowski, Allen (PI Project 1) and Specker (PI Project 2) will meet regularly and as needed regarding data and project safety. Additionally, all key personnel will meet regularly regarding overall progress, specific problems and problem resolution. The daily monitoring of subjects will be the coordinator's responsibility. The coordinator will also report to the Project Manager and PI as needed.

Participants will be closely monitored throughout the trial. A summary of all data, with the exception of information that entails breaking the blind, will be provided to the DSMB at annual meetings. SAE's will be reported to the head of the DSMB when they have been identified and characterized. The chair of the DSMB may request a special meeting of the panel as needed. The Board will consist of Drs. Frances Levin, Dr. Scott Crow and Dr. Sofuoglu. These individuals will serve to monitor SCOR projects involving human subjects.

The group will meet on an annual basis and review data including recruitment, progress, safety, adverse events, and serious adverse events associated with the study. The DSMB meeting will include open, closed and executive

sessions. The Principal Investigator, co-investigators, and statisticians will attend the open session and present during the meeting. The purpose of the open session is to provide relevant information to the Board about general aspects of the trial. The open session will focus on the background of the study, the protocol, status of the study, problems with accrual and follow-up, baseline demographic data, compliance issues, frequency of adverse events, documentation of endpoints, data quality issues, flow of forms, data based protocol modification issues, and any other issue regarding the studies under review that can be discussed without reference to interim comparative results.

Following the open session, a closed session will be held. During the closed session, the chairperson (Frances R Levin MD) will conduct the review of all issues and puts each issue to a vote. This session will be attended by the DSMB members and if necessary the statistician, principal investigator. During the closed session, the discussions will focus on the treatment safety, requesting and reviewing additional information if needed and updating the Board on actions taken related to their actions and recommendations of the previous meeting.

Following the closed session, an executive meeting may be held. The executive meeting will be restricted to DSMB members. During these sessions, the Board may discuss any sensitive issues surrounding the clinical trials under review.

The Board Chairperson will prepare a draft report of the meeting along with minutes for inclusion in the final DSMB report. The report will outline and summarize discussion during the open and closed sessions of the meeting. Recommendations and action items will be clearly marked within the body of the report. If the DSMB conducts an executive session, a statement will be included in the Minutes of the Meeting stating that an executive session was conducted, but content of the discussion will be retained by the chair and not included in the report. The draft report shall be reviewed and edited by all Board members prior to issuance of the final report.

If deemed necessary, the DSMB can request to know whether or not the participant received active medication or placebo. If they believe that termination of the trial is warranted, the blind of all study participants will be broken. DSMB recommendations will be communicated to the NIDA Project Officer soon after the DSMB meetings.

Affiliation and contact information for the DSMB members are listed below:

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Reference:

The data safety and monitoring plan is based on the investigators experience, expertise and the template developed by Dr. Ivan Montoya, NIDA/NIH.

http://www.drugabuse.gov/funding/clinical-research/guidelines-developing-data-safety-monitoring-plan

SCOR P1 and MJ

Rules/Changes — Last Updated: 9/8/16

- In order to be eligible at BL, subject must be averaging 4.5 CPD for the past 2 weeks. If a subject is smoking less than 4.5 CPD, they will be dropped from the study and filed as "SCREEN FAIL" (1/1/15).

- Week 0 clinic visit must be completed on the subject's quit date. If this is not possible, it may be completed AFTER the quit date but a protocol deviation must be made. Week 0 cannot be completed BEFORE quit date (1/3/15).

- Subjects are allowed to miss 2 clinic visits over the entire study to eligible for the $75 bonus at Week 12 – unless a cancelation was made by study staff (instead of the subject). That absence would NOT count against the bonus (1/29/15).

- ALT/AST levels must not be higher than double the normal range to be enrolled at SC. If levels are higher than double the normal range, the subject will be notified of the results, referred to PCP for follow-up and invited back in 4 weeks to re-test. If levels are high but within double the normal range, the subject may be enrolled per Dr. Allen's approval. He/she will be tested again at Week 1 and as long as levels have not gone up, they will be allowed to continue in the study (1/29/15).

- The last available time to start a follow-up appointment will be 5:00pm (Week 4, 8, 12 – 4:30pm)

- We will only collect 2 urine samples at each visit (00 & 01) (4/7/15).

- Samples to be sent for analysis:

Hormones	BL	W4	W12	(Blood)
Cotinine		W4	W12	(Blood)

- BDI scores will be monitored weekly by study staff. If a subject scores ≥20 or endorsed suicidal thoughts (Question #9), staff will start an AE and continue to monitor scores. If score decreases and is <14 after three weeks with no suicidal thoughts, the AE may be closed.