



**YALE UNIVERSITY  
HUMAN INVESTIGATION COMMITTEE**

**Application to Involve Human Subjects in Biomedical Research  
100 FR1 (2013-1)**

Please refer to the HIC website for application instructions and information required to complete this application. The Instructions are available at <http://www.yale.edu/hrpp/forms-templates/biomedical.html>  
Submit the original application and one (1) copy of all materials including relevant sections of the grant which funds this project (if applicable) to the HIC.

**HIC OFFICE USE ONLY**

**SECTION I: ADMINISTRATIVE INFORMATION**

<b>Title of Research Project:</b> Progesterone Augmentation of Nicotine Replacement Therapy Study			
<b>Principal Investigator:</b> Kimberly Ann Yonkers, MD		<b>Yale Academic Appointment:</b> Professor	
<b>Department:</b> Psychiatry			
<b>Campus Address:</b> 40 Temple Street, Suite 6B, New Haven, CT 06516			
<b>Campus Phone:</b> 203-764-5914	<b>Fax:</b> 203-764-6766	<b>Pager:</b>	<b>E-mail:</b> Kimberly.yonkers@yale.edu
<b>Protocol Correspondent Name &amp; Address (if different than PI):</b>			
<b>Campus Phone:</b>	<b>Fax:</b>	<b>E-mail:</b>	
<b>Yale Cancer Center CTO Protocol Correspondent Name &amp; Address (if applicable):</b>			
<b>Campus Phone:</b>	<b>Fax:</b>	<b>E-mail:</b>	
<b>Business Manager:</b>			
<b>Campus Phone :</b>	<b>Fax :</b>	<b>E-mail</b>	
<b>Faculty Advisor:</b> (required if PI is a student, resident, fellow or other trainee) <input type="checkbox"/> NA		<b>Yale Academic Appointment:</b>	

<b>Campus Address:</b>			
<b>Campus Phone:</b>	<b>Fax:</b>	<b>Pager:</b>	<b>E-mail:</b>

**Investigator Interests:**

Does the principal investigator, or do any research personnel who are responsible for the design, conduct or reporting of this project or any of their family members (spouse or dependent child) have an incentive or interest, financial or otherwise, that may affect the protection of the human subjects involved in this project, the scientific objectivity of the research or its integrity? Note: The Principal Investigator (Project Director), upon consideration of the individual's role and degree of independence in carrying out the work, will determine who is responsible for the design, conduct, or reporting of the research.

See Disclosures and Management of Personal Interests in Human Research

<http://www.yale.edu/hrpp/policies/index.html#COI>

☐ Yes ☒ No

Do you or does anyone on the research team who is determined by you to be responsible for the design, conduct or reporting of this research have any patent (sole right to make, use or sell an invention) or copyright (exclusive rights to an original work) interests related to this research protocol?

☐ Yes ☒ No

If yes to either question above, list names of the investigator or responsible person:

*The Yale University Principal Investigator, all Yale University co-investigators, and all Yale University individuals who are responsible for the design, conduct or reporting of research must have a current financial disclosure form on file with the University's Conflict of Interest Office. Yale New Haven Hospital personnel who are listed as con-investigators on a protocol with a Yale University Principal Investigator must also have a current financial disclosure form on file with the University's Conflict of Interest Office. If this has not been done, the individual(s) should follow this link to the COI Office Website to complete the form:*

<http://www.yale.edu/coi/>

NOTE: The requirement for maintaining a current disclosure form on file with the University's Conflict of Interest Office extends primarily to Yale University and Yale-New Haven Hospital personnel. **Whether or not they are required to maintain a disclosure form with the University's Conflict of Interest Office, all investigators and individuals deemed otherwise responsible by the PI who are listed on the protocol are required to disclose to the PI any interests that are specific to this protocol.**

<b>SECTION II: GENERAL INFORMATION</b>
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1. **Performing Organizations:** Identify the hospital, in-patient or outpatient facility, school or other agency that will serve as the location of the research. Choose all that apply:

**a. Internal Location[s] of the Study:**

- |  |  |
|--|--|
| <input type="checkbox"/> Magnetic Resonance Research Center (MR-TAC)   | <input type="checkbox"/> Yale University PET Center                              |
| <input type="checkbox"/> Yale Cancer Center/Clinical Trials Office (CTO)   | <input type="checkbox"/> YCCI/Church Street Research Unit (CSRU)                 |
| <input type="checkbox"/> Yale Cancer Center/Smilow   | <input type="checkbox"/> YCCI/Hospital Research Unit (HRU)                       |
| <input checked="" type="checkbox"/> Yale-New Haven Hospital  | <input type="checkbox"/> YCCI/Keck Laboratories                                  |
| <input type="checkbox"/> Cancer Data Repository/Tumor Registry   | <input checked="" type="checkbox"/> Yale-New Haven Hospital—Saint Raphael Campus |
| <input checked="" type="checkbox"/> Specify Other Yale Location: 40 Temple Street, Suite 6B<br>1 Long Wharf, New Haven |  |

**b. External Location[s]:**

- |   |  |
|---|--|
| <input type="checkbox"/> APT Foundation, Inc.                       | <input type="checkbox"/> Haskins Laboratories                                  |
| <input type="checkbox"/> Connecticut Mental Health Center           | <input type="checkbox"/> John B. Pierce Laboratory, Inc.                       |
| <input type="checkbox"/> Clinical Neuroscience Research Unit (CNRU) | <input type="checkbox"/> Veterans Affairs Hospital, West Haven                 |
| <input type="checkbox"/> Other Locations, Specify:                  | <input type="checkbox"/> International Research Site<br>(Specify location(s)): |

**c. Additional Required Documents (check all that apply):**

- |  |                              |
|--|------------------------------|
| <input type="checkbox"/> *YCCI-Scientific and Safety Committee (YCCI-SSC)  | <input type="checkbox"/> N/A |
| <input type="checkbox"/> *Pediatric Protocol Review Committee (PPRC)   | Approval Date:               |
| <input type="checkbox"/> *YCC Protocol Review Committee (YRC-PRC)  | Approval Date:               |
| <input type="checkbox"/> *Dept. of Veterans Affairs, West Haven VA HSS   | Approval Date:               |
| <input type="checkbox"/> *Radioactive Drug Research Committee (RDRC)   | Approval Date:               |
| <input type="checkbox"/> YNHH-Radiation Safety Committee (YNHH-RSC)  | Approval Date:               |
| <input type="checkbox"/> Magnetic Resonance Research Center PRC (MRRC-PRC)   | Approval Date:               |
| <input type="checkbox"/> YSM/YNHH Cancer Data Repository (CaDR)  | Approval Date:               |
| <input type="checkbox"/> Dept. of Lab Medicine request for services or specimens form  |                              |
| <input type="checkbox"/> Imaging on YNHH Diagnostic Radiology equipment request form (YDRCTO request) found at <a href="http://radiology.yale.edu/research/ClinTrials.aspx">http://radiology.yale.edu/research/ClinTrials.aspx</a> |                              |

*\*Approval from these committees is required before final HIC approval is granted. See instructions for documents required for initial submission and approval of the protocol. Allow sufficient time for these requests. Check with the oversight body for their time requirements.*

2. **Probable Duration of Project:** State the expected duration of the project, including all follow-up and data analysis activities.

3. **Research Type/Phase: (Check all that apply)**

**a. Study Type**

- ☒ Single Center Study  
☐ Multi-Center Study

Does the Yale PI serve as the PI of the multi-site study? Yes ☐ No ☐

- ☐ Coordinating Center/Data Management

☐ Other:

b. **Study Phase** ☐ N/A

☒ Pilot ☐ Phase I ☐ Phase II ☐ Phase III ☐ Phase IV  
☐ Other (*Specify*)

4. **Area of Research: (Check all that apply)** Note that these are overlapping definitions and more than one category may apply to your research protocol. Definitions for the following can be found in the instructions section 4c:

☒ Clinical Research: Patient-Oriented ☐ Clinical Research: Outcomes and Health Services  
☐ Clinical Research: Epidemiologic and Behavioral ☒ Interdisciplinary Research  
☐ Translational Research #1 ("Bench-to-Bedside") ☐ Community-Based Research  
☐ Translational Research #2 ("Bedside-to-Community")

5. Is this study a clinical trial? Yes ☒ No ☐

*NOTE the current ICMJE (International Committee of Medical Journal Editors) definition of a clinical trial: "any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes." Health-related interventions include any intervention used to modify a biomedical or health-related outcome (for example, drugs, surgical procedures, devices, behavioral treatments, dietary interventions, and process-of-care changes). Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events"*

If yes, where is it registered?

Clinical Trials.gov registry ☐

Upon funding will be registered in clinical trials.

Other (*Specify*)

Registration of clinical trials **at their initiation** is required by the FDA, NIH and by the ICMJE.

*If this study is registered on [clinicaltrials.gov](http://clinicaltrials.gov), there is new language in the consent form and compound authorization that should be used.*

For more information on registering clinical trials, including whether your trial must be registered, see the YCCI webpage, <http://ycci.yale.edu/researchers/ors/registerstudy.aspx> or contact YCCI at 203.785.3482)

6. Does the Clinical Trials Agreement (CTA) require compliance with ICH GCP (E6)?  
 Yes ☒ No ☐

7. Will this study have a billable service? A Billable Service is defined as a service or procedure that will be ordered, performed or result in charging in EPIC for individuals who are enrolled in

a clinical research study, regardless if the charge is intended to be paid by the subject/their insurance or the research study.

Yes ☐ No ☒

If you answered "yes", this study will need to be set up in OnCore Support

<http://medicine.yale.edu/ymg/systems/ppm/index.aspx>

8.. Are there any procedures involved in this protocol that will be performed at YNHH or one of its affiliated entities? Yes \_\_\_ No X *If Yes, please answer questions a through c and note instructions below. If No, proceed to Section III.*

a. Does your YNHH privilege delineation currently include the **specific procedure** that you will perform? N/A

b. Will you be using any new equipment or equipment that you have not used in the past for this procedure? No

c. Will a novel approach using existing equipment be applied? N/A

If you answered "no" to question 7a, or "yes" to question 7b or c, please contact the YNHH Department of Physician Services (688-2615) for prior approval before commencing with your research protocol.

### SECTION III: FUNDING, RESEARCH TEAM AND TRAINING

1. **Funding Source:** Indicate all of the funding source(s) for this study. Check all boxes that apply.

Provide information regarding the external funding source. This information should include identification of the agency/sponsor, the funding mechanism (grant or contract), and whether the award is pending or has been awarded. Provide the M/C# and Agency name (if grant-funded). If the funding source associated with a protocol is "pending" at the time of the protocol submission to the HIC (as is the case for most NIH submissions), the PI should note "Pending" in the appropriate section of the protocol application, provide the M/C# and Agency name (if grant-funded) and further note that University (departmental) funds support the research (until such time that an award is made).

PI	Title of Grant	Name of Funding Source	Funding	Funding Mechanism
Kimberly Yonkers, MD	Progesterone Augmentation for Smoking Cessation in Women	National Cancer Institute R21CA198187	<input checked="" type="checkbox"/> Federal <input type="checkbox"/> State <input type="checkbox"/> Non Profit <input type="checkbox"/> Industry <input type="checkbox"/> Other For Profit <input type="checkbox"/> Other	<input checked="" type="checkbox"/> Grant-M# 160200 <input type="checkbox"/> Contract# <input type="checkbox"/> Contract Pending <input type="checkbox"/> Investigator/Department Initiated <input type="checkbox"/> Sponsor Initiated <input type="checkbox"/> Other, Specify:

			<input type="checkbox"/> Federal <input type="checkbox"/> State <input type="checkbox"/> Non Profit <input type="checkbox"/> Industry <input type="checkbox"/> Other For Profit <input type="checkbox"/> Other	<input type="checkbox"/> Grant-M# <input type="checkbox"/> Contract# <input type="checkbox"/> Contract Pending <input type="checkbox"/> Investigator/Department Initiated <input type="checkbox"/> Sponsor Initiated <input type="checkbox"/> Other, Specify:
			<input type="checkbox"/> Federal <input type="checkbox"/> State <input type="checkbox"/> Non Profit <input type="checkbox"/> Industry <input type="checkbox"/> Other For Profit <input type="checkbox"/> Other	<input type="checkbox"/> Grant-M# <input type="checkbox"/> Contract# <input type="checkbox"/> Contract Pending <input type="checkbox"/> Investigator/Department Initiated <input type="checkbox"/> Sponsor Initiated <input type="checkbox"/> Other, Specify:

IRB Review fees are charged for projects funded by Industry or Other For-Profit Sponsors. Provide the Name and Address of the Sponsor Representative to whom the invoice should be sent. **Note: the PI's home department will be billed if this information is not provided.**

**Send IRB Review Fee Invoice To:**

Name:

Company:

Address:

2. **Research Team:** List all members of the research team. Indicate under the affiliation column whether the investigators or study personnel are part of the Yale faculty or staff, or part of the faculty or staff from a collaborating institution, or are not formally affiliated with any institution. **ALL members of the research team MUST complete Human Subject Protection Training (HSPT) and Health Insurance Portability and Accountability Act (HIPAA) Training before they may be listed on the protocol. See NOTE below.**

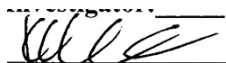
	Name	Affiliation: Yale/Other Institution (Identify)	NetID
<b>Principal Investigator</b>	Kimberly Yonkers, MD	Yale	
<b>Role: Co-Investigator</b>	Mehmet Sofuoglu, MD	Yale	
<b>Role: Co-Investigator</b>	Aileen Garipey, MD	Yale	
<b>Role: Co-Investigator</b>	Haiqun Lin, MD	Yale	
<b>Role: Co-Investigator</b>	Ariadna Forray, MD	Yale	
<b>Role: Biostatistician</b>	Kathryn Gilstad-Hayden	Yale	

**NOTE: The HIC will remove from the protocol any personnel who have not completed required training. A personnel protocol amendment will need to be submitted when training is completed.**

**SECTION IV:  
PRINCIPAL INVESTIGATOR/FACULTY ADVISOR/ DEPARTMENT CHAIR  
AGREEMENT**

As the **principal investigator** of this research project, I certify that:

- The information provided in this application is complete and accurate.
- I assume full responsibility for the protection of human subjects and the proper conduct of the research.
- Subject safety will be of paramount concern, and every effort will be made to protect subjects' rights and welfare.
- The research will be performed according to ethical principles and in compliance with all federal, state and local laws, as well as institutional regulations and policies regarding the protection of human subjects.
- All members of the research team will be kept apprised of research goals.
- I will obtain approval for this research study and any subsequent revisions prior to my initiating the study or any change and I will obtain continuing approval of this study prior to the expiration date of any approval period.
- I will report to the HIC any serious injuries and/or other unanticipated problems involving risk to participants.
- I am in compliance with the requirements set by the University and qualify to serve as the principal investigator of this project or have acquired the appropriate approval from the Dean's Office or Office of the Provost, or the Human Subject Protection Administrator at Yale-New Haven Hospital, or have a faculty advisor.
- I will identify a qualified successor should I cease my role as principal investigator and facilitate a smooth transfer of investigator responsibilities.



\_\_\_\_\_  
PI Name (PRINT) and Signature

9/11/2015

\_\_\_\_\_  
Date

**Department Chair's Assurance Statement**

Do you know of any real or apparent institutional conflict of interest (e.g., Yale ownership of a sponsoring company, patents, licensure) associated with this research project?

☐ Yes (provide a description of that interest in a separate letter addressed to the HIC.)

☐ No

As Chair, do you have any real or apparent protocol-specific conflict of interest between yourself and the sponsor of the research project, or its competitor or any interest in any intervention and/or method tested in the project that might compromise this research project?

☐ Yes (provide a description of that interest in a separate letter addressed to the HIC)

☐ No

I assure the HIC that the principal investigator and all members of the research team are qualified by education, training, licensure and/or experience to assume participation in the conduct of this research trial. I also assure that the principal investigator has departmental support and sufficient resources to conduct this trial appropriately.

\_\_\_\_\_  
Chair Name (PRINT) and Signature

\_\_\_\_\_  
Date

\_\_\_\_\_  
Department

### YNHH Human Subjects Protection Administrator Assurance Statement

*Required when the study is conducted solely at YNHH by YNHH health care providers.*

As Human Subject Protection Administrator (HSPA) for YNHH, I certify that:

- I have read a copy of the protocol and approve it being conducted at YNHH.
- I agree to notify the IRB if I am aware of any real or apparent institutional conflict of interest.
- The principal investigator of this study is qualified to serve as P.I. and has the support of the hospital for this research project.

\_\_\_\_\_  
YNHH HSPA Name (PRINT) and Signature

\_\_\_\_\_  
Date

### For HIC Use Only

\_\_\_\_\_  
Date Approved

\_\_\_\_\_  
Human Investigation Committee Signature

This protocol is valid through \_\_\_\_\_



## SECTION V: RESEARCH PLAN

**1. Statement of Purpose:** State the scientific aim(s) of the study, or the hypotheses to be tested.

This pilot randomized clinical trial will test whether modifying the hormonal milieu during the menstrual cycle through administration of exogenous progesterone will augment the effectiveness of NRT for smoking cessation in regularly cycling women. Our study hypothesis regarding progesterone's augmentation effects are supported by systematic studies conducted by our group and others. Findings from this study may lead to novel treatment approaches tailored specifically to female smokers

This study seeks to determine if modifying the hormonal milieu of the menstrual cycle, through administration of exogenous progesterone, will improve the effectiveness of treatments for smoking cessation in women. Progesterone, a gonadal hormone, is used clinically for treatment of endometrial hyperplasia, amenorrhea, dysfunctional uterine bleeding, and for assisted reproduction in women. Progesterone also shows promise for the treatment of multiple central nervous system disorders including cocaine addiction, seizure disorder, and traumatic brain injury (1, 2). The utility of progesterone for smoking cessation is suggested by a number of previous studies. In a clinical trial, progesterone dominance during the luteal phase of the menstrual cycle, as compared to estrogen dominance in the follicular phase, significantly enhanced smoking abstinence in women attempting to quit smoking (3). Our group conducted pioneering human studies to determine the safety and potential efficacy of progesterone for the treatment of nicotine addiction. In these studies, progesterone, compared to placebo, attenuated the pleasurable effects of cigarette smoking or intravenously administered nicotine in abstinent smokers (4, 5). Progesterone also reduced craving for cigarettes and improved response inhibitory function in abstinent female smokers (6). These findings are promising because attenuating nicotine reward, and improving withdrawal symptoms and response inhibition are potential treatment targets for nicotine addiction (7, 8). As the next step, we seek to determine if progesterone augments standard smoking cessation treatments (e.g., NRT) in regularly cycling women. We hypothesize that co-treatment with progesterone, compared to placebo, will enhance the effectiveness NRT for smoking cessation. To test this hypothesis, we propose an 8-week, double-blind, placebo-controlled clinical trial, which will randomize 50 smokers using a 1:1 assignment ratio to 400 mg/day progesterone or placebo. Consistent with the Clinical Practice Guidelines (9), all participants will also receive transdermal nicotine patch (TNP) plus brief counseling for smoking cessation during the study participation. The dose of TNP will be 21mg/24 hours for 4 weeks, 14mg for weeks 5 and 6 and 7 mg for weeks 7 and 8 for women who smoked at least 10 cigarettes per week. We will start a 14 mg/day dose of TNP for women who smoke less than 10 cigarettes per week.

Specific Aim #1: To determine if progesterone + TNP is superior to placebo + TNP for prolonged and 7-day point prevalence of smoking abstinence rates at the end of 8 weeks of treatment and at 1 and 3 month follow-up time points. We will also evaluate the safety and tolerability of progesterone treatment, compared to placebo. Our co-primary outcome measures will be 7-day point prevalence of smoking abstinence and breath CO at the end of treatment and 1- and 3-months after the end of the trial.

Specific Aim #2: To determine if progesterone + TNP treatment, compared to placebo + TNP, improves response inhibitory function, as assessed by the Stroop, The Go/No Go task, and the Digit Symbol Task.

Specific Aim # 3: To determine if progesterone + TNP treatment, compared to placebo + TNP, leads to a greater reduction in cigarette craving and nicotine withdrawal symptoms, as assessed

by the Questionnaire on Smoking Urges-Brief (QSU-B) and the Minnesota Nicotine Withdrawal Scale (MNWS), respectively.

Specific Aim #4: To evaluate with affective changes, as shown on the Positive and Negative Affect Schedule, mediates the effects of progesterone on smoking abstinence.

Exploratory Aim: We will evaluate the degree to which serum estradiol and progesterone levels achieved during the trial are associated with a) greater smoking abstinence, b) improved response inhibition, and c) less craving and withdrawal symptoms.

2. **Background:** Describe the background information that led to the plan for this project. Provide references to support the expectation of obtaining useful scientific data.

Nicotine addiction continues to be the main preventable cause of death in developed countries, with an estimated 435,000 premature deaths in the U.S and 5 million deaths worldwide (11). About 18% of women and 22% of men in the US smoke (11). Some evidence suggests that women respond less favorably to NRTs, even though they maintain their nicotine addiction with lower levels of nicotine intake than men (12-15). Women, compared to men, may be more vulnerable to the complications of smoking, most notably lung cancer (16, 17). In the US, lung cancer kills more women than the breast and colon cancer combined. These findings support the need to develop more effective treatments tailored for female smokers.

*Current pharmacological treatments for smoking cessation:* Current first line treatments for smoking cessation include NRT (including nicotine gum, lozenge, inhaler and spray), bupropion, and varenicline (10, 18). With some minor differences, these treatments increase the odds of quitting smoking by 2 to 3 fold (19, 20). Still, this only translates to smoking abstinence at one year for 10%-30% of smokers who attempt to quit. Combination treatments may be more effective than a single agent for smoking cessation suggesting that there is room for improved efficacy among smoking cessation treatments(21). Unfortunately, concerns about the neuropsychiatric adverse effects of varenicline and bupropion, especially suicidal ideation and behavioral changes, limit their use alone or in combination with other medications (22). Among NRTs, there are no significant differences between different products in their efficacy for smoking cessation (23). Transdermal nicotine patch (TNP) has advantages over other NRTs for its consistent delivery of nicotine for 24 hours, ease of use and favorable adverse effect profile.

*Role of sex hormones in addictive behaviors:* Both estradiol and progesterone have well-documented actions on multiple neurotransmitters affecting the brain reward pathway (24). While estradiol activates the reward pathway, progesterone has the opposite effects (25). For example, in the mid-follicular phase of the human menstrual cycle (when progesterone is low and estrogen is high), as compared to the progesterone dominant luteal phase, the reward circuitry (midbrain, striatum, and left fronto-polar cortex) is more highly activated (26). As summarized below, the therapeutic potential of sex hormones, especially progesterone, suggest that progesterone may have a role in treatment of nicotine addiction in female smokers (27).

*Progesterone as a neurosteroid:* Progesterone is a hormone produced by male and female gonads, adrenal glands and in the brain by oligodendrocytes and neurons (hence the moniker "neurosteroid") (28). In premenopausal women, progesterone levels are low in the follicular phase of the menstrual cycle, and are comparable to those in men, < 1 ng/ml (29). Women have higher progesterone levels than men during the luteal phase of the menstrual cycle (2-28

ng/ml), and during pregnancy (9 to 200 ng/ml) (30). Progesterone and its metabolites interact with multiple neurotransmitter receptors including GABAA, glycine, sigma1, kainate, serotonin3, and nicotinic receptors (31). Among these actions, the best studied are the effects of progesterone on the GABA receptors. Progesterone's active metabolites, pregnanolone and allopregnanolone, have positive modulatory effects on GABAA receptors, and enhance GABA transmission (31). This may lead to reduced nicotine reward given the inhibitory actions of GABA on dopamine release in nucleus accumbens, a key step in mediating reward (32).

*Endogenous progesterone modulates nicotine addiction:* Many preclinical studies demonstrate that progesterone administration reduces the rewarding effects of cocaine (33, 34). Although the actions of exogenous progesterone on nicotine reward have not been assessed (27), Lynch (35) showed that in adolescent rats that are trained to self-administer nicotine, levels of responding under a progressive-ratio schedule are negatively associated with plasma progesterone levels. These results support an inhibitory influence of progesterone on nicotine self-administration.

In a human laboratory study using an ad lib smoking paradigm in female smokers, a lower progesterone to estrogen ratio was associated with greater number of puffs and increased puff intensity (36). Similarly, in a clinical trial, Allen et al. (4) randomized 200 women to quit in follicular or luteal phase of the menstrual cycle. Women who quit in the follicular phase relapsed faster to smoking than those who quit during the progesterone dominant luteal phase ((OR) = 2.87, 95% CI= 1.47– 5.59). The effect was robust; at 30 days the odds of remaining abstinent for the luteal phase group was 3.18 (95% CI= 1.59–6.34) higher than the follicular phase group. This same group showed that abstinence during the luteal phase of the cycle was accompanied by increases in allopregnanolone.(37) Mazure et al. (38) produced similar findings using bupropion. However, there are divergent findings (39, 40) that may be a result of differing study methods. Our proposed study will help clarify the literature by providing exogenous progesterone rather than relying on timing of the menstrual cycle to infer hormone levels.

*Progesterone as a treatment for nicotine addiction.* Our group has conducted a series of pioneering studies demonstrating the safety and potential effectiveness of progesterone for the treatment of nicotine addiction in women. In our initial study (5), we found that oral progesterone, compared to placebo, attenuated the craving for and pleasurable or hedonic effects from smoking in 12 female smokers. In our next study, we confirmed these findings using our intravenous nicotine administration paradigm (6). We observed that progesterone attenuated the pleasurable effects of intravenous nicotine in abstinent 12 male and female smokers.

We have also evaluated underlying mechanisms of the potential therapeutic effects of progesterone (7). We found that 400 mg of progesterone treatment, administered for four days, reduced urges to smoke in female abstinent smokers. Further, progesterone treatment improved performance in the Stroop and the Digit Symbol Substitution Test (DSST) but the effect on the Stroop performance was sex specific in that only women (n=30) showed improvement. Given that the Stroop test is a measure of ability to inhibit pre-potent responses, our findings suggest that progesterone improves response inhibition in abstinent female smokers (7). Our findings are consistent with preclinical and clinical suggesting that progesterone improves response inhibition or impulsive behavior which may contribute to its proposed efficacy for smoking cessation (41, 42).

*Safety of Progesterone:* Progesterone is used treat a variety of gynecological and obstetrical disorders. Although extensive first pass effects limited oral use, oral micronized progesterone formulations are now FDA approved. The safety and tolerability of micronized progesterone is

well established (43, 44). The most common adverse effect of progesterone is mild sedation. Other less common adverse effects include menstrual irregularity, spotting or breakthrough bleeding, dizziness, cramps, nausea, fatigue, headache, and breast tenderness (44, 45). In our previous studies, micronized progesterone has been well tolerated without any serious adverse events (2, 5-7, 46-49).

Progesterone is commonly confused with progestins, a group of synthetic progesterone analogs that include medroxyprogesterone and norethindrone, are included in most oral contraceptives and some hormone replacement therapies. Progestins differ from natural progesterone in their pharmacological properties and side effect profiles. Most progestins, but not progesterone, have well-characterized androgenic, glucocorticoid, and anabolic effects and have been associated with unfavorable side effects including fluid retention, alterations in lipid profile, and increase risk for breast cancer and cardiovascular events. These side effects are not associated with natural progesterone treatment (50-52). An additional key difference between progesterone and most progestins is that the former, but not the latter, are metabolized to pregnanolone and allopregnanolone, which, as noted above, have significant GABAergic and other CNS effects. Consistent with these distinctions, progestins and progesterone differ in their influence on many CNS functions including learning, memory, and reward functions (53). Finally, progesterone (but not progestins) is also under investigation for the treatment of cocaine addiction, seizure disorder, and traumatic brain injury (54, 55).

*Summary of the rationale:* Progesterone's capacity to attenuate smoking urges, to diminish the positive subjective effects of smoking, and to improve cognitive performance all point to its potential therapeutic value for smoking cessation. Because smoking urges predict relapse to smoking, progesterone-related attenuation supports its potential efficacy for smoking cessation (56). Greater positive subjective effects from smoking before a quit attempt or during a lapse also predict relapse to smoking (57, 58). Similarly, improvement of cognitive function in association with progesterone use, especially with regard to response inhibition is a potential mechanism for the proposed efficacy of progesterone for smoking cessation (59).

#### b) Innovation

A number of current researchers are exploring combined treatment for smoking cessation. Targeting the hormonal milieu to develop novel treatments for female smokers is a novel new direction. Although previous studies compared the different phases of menstrual cycle for smoking cessation outcomes, no previous study has directly modified the hormonal milieu. Second, the use of progesterone as an adjunct to NRT for smoking cessation is innovative. This study will translate findings from pre-clinical and human laboratory studies into treatment development by testing the efficacy of progesterone for smoking cessation in a clinical trial. Third, we also propose to evaluate response inhibition as the cognitive mediator of progesterone's therapeutic effects on nicotine addiction. Data on response inhibition will shed light on how, as well as if, progesterone is effective in this population. Lastly, we will assay hormone levels to provide a direct assessment of the role of gonadal steroids (estrogen and progesterone) on likelihood of smoking abstinence.

#### Previous research

As summarized above, our human laboratory and outpatient studies have demonstrated the safety and potential efficacy of micronized progesterone for smoking cessation in regularly cycling women.

We have extensive experience in recruiting and conducting clinical trials with pre-menopausal cigarette smokers. Dr. Sofuoglu is an expert in medications development and laboratory studies

for medications development; Dr. Yonkers is an expert in treatment of women with mental health and addiction problems (see attached biosketches). She has conducted numerous menstrual cycle studies as well as studies on women and addiction. As an example of our successful collaboration, we have completed the first study examining progesterone's safety and effectiveness in postpartum women with cocaine used disorder (2).

We have successfully recruited and retained women in prior studies. In a study of progesterone for treatment of postpartum cocaine users (R21 DA029914), we recruited the targeted 50 women and retained 82% in a 12- week clinical trial. In an ongoing study, R01 DA034243 we have recruited 423 women, including more than 250 reproductive aged women who smoke, to a randomized clinical trial of screening, motivational interviewing and referral to substance abuse treatment. Retention at 1, 3 and 6 months has been 86%, 83% and 83%, respectively.

3. **Research Plan:** Summarize the study design and research procedures using non-technical language that can be readily understood by someone outside the discipline. Be sure to distinguish between standard of care vs. research procedures when applicable, and include any flowcharts of visits specifying their individual times and lengths. Describe the setting in which the research will take place.

#### *Overview of the study design*

This will be a double-blind, placebo-controlled, pilot, randomized clinical trial. A total of 50 women who have regular menstrual cycles will be randomized to either progesterone (200 mgs BID) + Transdermal Nicotine Patch (TNP; 21 or 14 mg/day) or placebo + TNP (21 mg or 14mg/day) for 8 weeks. TNP will be tapered after 4-6 weeks as recommended by the Clinical Practice Guidelines for treating tobacco dependence (9). Participants who smoke more than 10 cigarettes per day will receive the following dose of TNP: 21mg/24 hours for 4 weeks, 14mg for weeks 5 and 6 and 7 mg for weeks 7 and 8. Participants who smoke between 5-10 cigarettes per day will receive the following dose of TNP: 14mg/24 hours for 6 weeks, 7mg for weeks 7 and 8.

Study medications will be discontinued at the end of Week 8. All participants will also be provided behavioral treatment for smoking cessation. Participants will be inducted onto progesterone (or placebo) + TNP over a one-week period (Week 1) during the mid luteal phase, within a week before menses and the target quit date will be set for the 5 (+/-2) days after onset of menses. Participants will have post-trial follow-up visits at 1 and 3 months following the end of the trial. The main study outcomes will be self- report of smoking abstinence, biochemically verified smoking abstinence, measures of cigarette craving and nicotine withdrawal, and measures of response inhibition.

#### *Human subjects*

Recruitment: Recruitment will take place over 1.5 years, requiring enrollment of approximately 2-3 subjects per month. In our previous studies, we have been able to recruit on average 4 female smokers per month. Recruitment is further explained in Humans Subjects but will be accomplished by direct screening in our reproductive health centers (20% of women seen for services in these centers are smokers), direct mail invitations, posters and flyers placed in local obstetrician-gynecologist offices. We have successfully used these techniques to recruit substance users, smokers and women with premenstrual dysphoric disorder in prior clinical trials. Dr. Yonkers has a secondary appointment in Obstetrics & Gynecology and has conducted numerous studies that entailed screening women in the reproductive health settings of Yale New Haven Hospital and their faculty (see Biosketch).

Update June 2017: All participants had blood levels of progesterone drawn. We were blind to assignment of participants but at the end of the study found that those who were randomized to active progesterone had low progesterone levels. This could be due to the progesterone preparation or the fact that smokers metabolize it very quickly. In any case, the low progesterone levels in the active treatment group obviates our ability to test our hypothesis that progesterone augmentation assists abstinence for smokers. Given the lack of funds, we cannot repeat the project. Rather, we are recruiting a second cohort and are using a commercially available oral micronized progesterone rather than the previous medication that was compounded for the study. We plan to enroll a minimum of 12 people with an imbalanced ratio of 6 active to 1 placebo. We will continue to obtain plasma levels of progesterone. This will enhance our ability to test our hypothesis. If need be in a final analysis, and give that this is a pilot project, we may be able to use the participants randomized to placebo in the first cohort and second cohort and the participants randomized to active in the second cohort.

Update September 2017: We request an additional blood draw (timeline is around Visit #6 or #7) to confirm progesterone plasma levels and compliance with pill taking. The second blood draw will be the same as the first one, completed at a professional lab on the first floor of the research site building. Approximately 6 ccs of blood will be drawn for each.

Urn Randomization: To increase the likelihood that the two groups are balanced for age and the amount of smoking, participants will be assigned to the two study conditions through “urn” randomization (Stout *et al*, 1994). A categorical variable will be created based on the number of cigarettes/day in the month before randomization: 1= $\leq 15$ ; and 2= $\geq 15$  or more cigarettes on average, per day, to distribute severity of smoking evenly over the two groups.

Update June 2017: We plan to enroll a minimum of 12 people with an imbalanced ratio of 6 active to 1 placebo.

We will post the study on the research team’s website [www.ResearchForHer.com](http://www.ResearchForHer.com), YCCI’s Help Us Discover database, and on Yale’s Department of Psychiatry Website as well as other websites. We will also include the study in some of Yale’s online newsletters.

### *Study Procedures*

Recruitment: Women will be recruited by word of mouth, flyer, advertisement, direct screening and online postings. Women will be contacted by telephone or seen face to face if the screening is direct. We will obtain verbal consent from the potential participant to conduct a brief, preliminary screen. Women will be asked if they smoke at least 5 cigarettes, are receiving any medical treatment for smoking cessation, use hormonal contraceptives, use illicit substances, have regular menstrual cycles. No PHI will be collected for women who are ineligible at this point, although we will keep a list of women who were screened and ineligible so that they will not be screened again. We will also keep a de-identified (not linked) list of reasons for non-participation. Women who are provisionally not eligible or interested will be provide referrals if desired. Women who are provisionally eligible will be undergo the consenting procedure and they will be offered a face to face appointment to complete screening

and baseline assessments. If they are screened face-to-face we will obtain consent at this point and set a face-to-face assessment visit.

Determination of Eligibility and Baseline Visit: This interview will occur between estimated days 18-24 of the typical menstrual cycle. This will be a 120 minute visit. It will be broken down into two parts: 1) we will determine eligibility for the randomized clinical trial (RCT) and 2) we will obtain baseline measures for those who are eligible. The first procedure will be obtaining informed consent (please see consent procedures below). In the process of consent, we will explain to the provisionally eligible participant that part of the visit will be to determine eligibility for the RCT. For determination of eligibility, women will complete the NIDA Quickscreen (10); DSM 5 psychosis screener and DSM 5 screener for major depressive disorder, panic disorder or post-traumatic stress disorder (PTSD; current). Any positive responses on these measures will trigger an evaluation, including the SCID and assessment by a study clinician (a physician for medical issues; a psychologist, physician or social worker if the issues is an exclusionary psychiatric diagnosis) that will indicate whether or not the participant is eligible; 2) a medical history will be gathered to obtain information on allergies, especially progesterone, use of medication, pregnancy planning, history of breast cancer, deep vein thrombosis, coagulation problems, liver failure, cervical intraepithelial neoplasm, allergy to nuts, etc; and 3) nicotine intake history including use of all nicotine products, number of cigarettes smoked and use of other nicotine products in the previous month, prior treatment for smoking cessation; prior intolerance or allergy to transdermal nicotine patch; 4) laboratory tests that include urine for pregnancy, cotinine and drugs of abuse and expired breath CO.

The RA will complete a checklist that indicates eligibility criteria. The checklist will be reviewed by study clinician who will confirm that this information has been gathered and that the participant meets criteria for participation. For women who continue to be eligible, the RA and/or study clinician will ask baseline measures that include: 1) a menstrual history form including module for diagnosis of premenstrual dysphoric disorder and menstrual cycle dating, the Fagerstrom Test for Nicotine Dependence (FTND) (11); the Minnesotal Nicotine Withdrawal Scale (MNWS) (12), the Questionnaire on Smoking Urges-Brief (QSU-B) (13) and the Positive and Negative Affect Schedule(14) . They will also complete the following neurocognitive tasks: 1) the Stroop, (15) 2) Go/No Go, 3) Digit Symbol SubstitutionTest (part of the WAIS III), 4) The Shipley Institute of Living Scale (SILS) is a paper-and-pencil, self-administered scale that consists of a 40-item vocabulary and a 20-item pattern recognition section (16).

Randomization/Visit 1: After eligibility is confirmed and the baseline assessments are completed, women will be randomized. Women will then begin smoking cessation counseling and will receive two weeks supply of their study medication, TNP + either oral micronized progesterone or placebo. They will be instructed to apply one nicotine patch /day and to take one pill twice daily after the visit. They will be instructed to set a quit date for the 5 (+/-2) days after the onset of menses, ideally around the 3-4<sup>th</sup> day when perimenstrual symptoms have abated and before estrogen peaks. We will call them at the estimated time of menses onset to confirm dates and quit date plans. We used similar strategies in smoking studies and menstrual cycle studies (6).

Treatment Phase (Visit 2 to 8): Women will be seen for follow up around days 7-11 of their menstrual cycle, shortly after their quit date. This visit will confirm that treatment with TNP + progesterone or placebo was initiated and maintained for the estimated 2 weeks since Visit 1. Medication compliance will be assessed by pill count. Support and counseling will be

provided for the quit attempt. Assessments will be repeated although the neurocognitive battery will only be done a second time at this first follow up visit. A blood draw will be completed twice throughout the study, the first around Visit #2 and the other around Visit #6 or Visit #7 at a professional lab on the first floor of the research site building. Approximately 6 ccs of blood will be drawn for each.

Other assessments will be conducted weekly for the additional weeks of the study. Assessments will include a weekly calendar of cigarettes smoked, if any, breath CO. We will collect urine for cotinine if the breath test is negative and there are concerns about compliance with TNP. If there is a possibility that a participant is pregnant (i.e. she is not menstruating or in the week following menstruation) we will also test urine for positive pregnancy. Additionally, subjects will have brief behavioral treatment sessions for smoking abstinence.

End of study (Visit 8), Termination and follow-up: At the end of the 8-week treatment period, participants will complete their weekly ratings, collect breath CO. Participants and study staff will be asked to guess their treatment condition (progesterone or placebo) and will discontinue study capsules and TNP. All participants will be encouraged to remain abstinent from smoking (9). Follow-up visits will be scheduled at 1 and 3 months after the end of the study. At follow up, assessments of smoking and the PANAS will be repeated. We will not repeat the neurocognitive measures.

Strategies to minimize attrition and enhance follow up: We will: 1) rapidly assign study treatments after application confirmation of eligibility, 2) thoroughly explain study treatments and requirements, and 3) specify uniform procedures across treatment conditions regarding study staff's handling of participants who miss or come late to sessions. Study investigators will monitor participants who drop out and explore with the staff reasons for the dropouts. We will follow the full randomized sample, regardless of their retention in treatment, by including: 1) a thorough explanation at the consent interview of the importance of follow-ups, 2) collecting at least three verified locators who are likely to have knowledge of a subject's whereabouts, 3) paying participants to cover transportation and parking for follow-up visits.

#### *Treatment Conditions*

Transdermal Nicotine Patch (TNP): TNP has been studied extensively as a smoking cessation treatment. Meta-analyses find that there is little difference among the types of NRTs although the patch provides a constant and slow delivery of nicotine. (17) The 24-hour delivery system is available in 7-, 14-, or 21-mg doses. Smokers who smoke more than 10 cigarettes/day begin with a 21-mg/d nicotine patch for the first 4 weeks and switch to 14 mg/d on weeks 5 and 6, and to 7 mg/d on weeks 7 and 8. Smokers who smoke between 5-10 cigarettes/day begin with a 14-mg/d nicotine patch for the first 6 weeks and switch to 7 mg/d on weeks 7 and 8. TNP is generally well-tolerated and has few side effects (skin irritation, nausea, vomiting, sweating, mood and sleep disturbances). In addition, once-daily dosing may lead to better compliance. Neither longer term (> 8 weeks) nor a higher dose (> 21 mg/d) of nicotine patch improves efficacy over the standard treatment (17).

Progesterone: The recommended dose of progesterone for hormone replacement treatment is 200 to 400 mg/day. We chose the 200 mgs BID because at this dose progesterone improved cognitive performance (6) but was associated with lower craving scores. After oral administration, micronized progesterone reaches its peak plasma levels in two to three hours and has an elimination half-life of three to four hours (18). Because of the short half-life of micronized progesterone, progesterone will be given twice daily to maintain stable plasma level of progesterone.



Strategies to protect the blind: 1) Randomization will be done by computer and will be maintained by the statistician. Study staff will only have access in cases of medical emergencies or after the study. 2) Placebo and progesterone will be packaged in similar appearing capsules. 3) Hormone levels will be sent from the lab directly to the study statistician. 4) Participants will meet weekly with the study team for medication dispensing and for monitoring of adverse events. Any gynecological adverse events will be followed up immediately and independently by a gynecological consultant (Dr. Gariepy) and reviewed at regular staff meetings. Dr. Gariepy will not share the gynecological adverse events with the rest of the team except if the blind needs to be broken for safety reasons. 5) At the end of each patient's treatment, we will also ask the study team members (as well as the participants) to guess whether patients were on progesterone or placebo.

Behavioral Platform: All study participants will receive standard behavioral treatment consistent with current clinical practice guidelines for smoking cessation (9). Participants will be provided a booklet, "Clearing the Air" (19) at the beginning of the trial and will be asked to bring it to their weekly sessions. Behavioral treatment sessions will prepare participants for quit day and provide skills to prevent relapse to smoking. These sessions will be brief, 10 to 15 minutes, and cover the topics that are outlined in the booklet. The topics include: 1) reasons to quit smoking, 2) preparing to quit smoking, 3) alternatives to smoking, 4) preventing relapse, 5) focus on new healthier lifestyle, 6) preventing weight gain, 7) long term benefits of quitting smoking and focus on the future. Participants who relapse will be encouraged to set a new quit date and attempt to quit smoking.

Training of Research Personnel: The research associate will have at least a Bachelor's level education and previous experience in clinical rating and interviewing. All staff will receive one month of training on the substance use calendar, expired CO and collection of other scales under the supervision of an experienced clinician. Training includes observation of interviews and ratings, co-rating, and interviews with supervisors (project director and Dr. Yonkers). Behavioral treatment will be audiotaped (with informed consent of the subject) for therapist supervision and adherence ratings. Dr. Yonkers will provide supervision and feedback.

#### **4. Genetic Testing** N/A ☒

##### **A. Describe**

- i. the types of future research to be conducted using the materials, specifying if immortalization of cell lines, whole exome or genome sequencing, genome wide association studies, or animal studies are planned
- ii. the plan for the collection of material or the conditions under which material will be received
- iii. the types of information about the donor/individual contributors that will be entered into a database
- iv. the methods to uphold confidentiality

B. What are the conditions or procedures for sharing of materials and/or distributing for future research projects?

C. Is widespread sharing of materials planned?

D. When and under what conditions will materials be stripped of all identifiers?

E. Can donor-subjects withdraw their materials at any time, and/or withdraw the identifiers that connect them to their materials?

- i. How will requests to withdraw materials be handled (e.g., material no longer identified: that is, anonymized) or material destroyed)?

F. Describe the provisions for protection of participant privacy

G. Describe the methods for the security of storage and sharing of materials

5. **Subject Population:** Provide a detailed description of the types of human subjects who will be recruited into this study.

Please see detailed inclusion/exclusion criteria noted below. In general, otherwise healthy, regularly-menstruating female smokers that do not have a history of major medical or psychiatric illnesses will be recruited for this study.

6. **Subject classification:** Check off all classifications of subjects that will be specifically recruited for enrollment in the research project. Will subjects who may require additional safeguards or other considerations be enrolled in the study? If so, identify the population of subjects requiring special safeguards and provide a justification for their involvement.

- |  |   |  |
|--|---|--|
| <input type="checkbox"/> Children              | <input type="checkbox"/> Healthy                                      | <input type="checkbox"/> Fetal material, placenta, or dead fetus |
| <input type="checkbox"/> Non-English Speaking  | <input type="checkbox"/> Prisoners                                    | <input type="checkbox"/> Economically disadvantaged persons      |
| <input type="checkbox"/> Decisionally Impaired | <input type="checkbox"/> Employees                                    | <input type="checkbox"/> Pregnant women and/or fetuses           |
| <input type="checkbox"/> Yale Students         | <input checked="" type="checkbox"/> Females of childbearing potential |  |

NOTE: Is this research proposal designed to enroll children who are wards of the state as potential subjects? ☐ Yes ☒ No (If yes, see Instructions section VII #4 for further requirements)

7. **Inclusion/Exclusion Criteria:** What are the criteria used to determine subject inclusion or exclusion?

Inclusion criteria: a) Aged 18 - 45; b) smoking at least 5 cigarettes/ day for at least one year; c) regular menstrual cycles every 24–36 days for the previous 6 months; d) motivated to quit smoking (i.e., a rating of at least “7” on a 10-point scale where 1 is not at all motivated and 10 is extremely motivated); e) in good health; and f) using an acceptable, non-hormonal birth control.

Exclusion criteria: a) a history of major medical illnesses including liver diseases, heart disease, diabetes, malignancy including history of breast cancer, deep vein thrombosis, blood coagulation problems including a history or family history of thrombophilia, use of an antithrombotic agent, liver failure, cervical intra-epithelial lesions III or greater that are untreated, allergy to peanuts or other nuts, or other medical conditions that the physician investigators deems will make study participation unsafe for the subject; b) current or past history bipolar disorder or schizophrenia or current diagnosis of major depression, panic disorder or post-traumatic stress disorder; c) use of all non-nicotine drug substances are excluded at the mild DSM-V diagnosis; alcohol use is excluded at the moderate DSM-V level diagnosis (caffeine use is not evaluated or excluded); d) currently undergoing treatment with another pharmacological agent for smoking cessation; e) daily use of sedating medications including sleeping aids and others; f) use of nicotine from cigars, pipes, chewing tobacco, e-cigarettes; g) pregnant, breast-feeding or intending to become pregnant within 6 months

and; h) allergy to nicotine patch or progesterone.

8. How will **eligibility** be determined, and by whom?

Women who are provisionally eligible after screening will be seen for a confidential, in office assessment. We will have a checklist that study staff complete at the baseline assessment visit that lists eligibility/ineligibility criteria. The PI or PI-s designee must check the participant's document, verify the checklist and confirm eligibility according to inclusion and exclusion criteria.

9. **Risks:** Describe the reasonably foreseeable risks, including risks to subject privacy, discomforts, or inconveniences associated with subjects participating in the research.

Progesterone, a natural hormone, is safe and well-tolerated by women. The safety, tolerability and efficacy of micronized progesterone is well established and it is FDA approved for hormone replacement therapy (HRT), absence of menstrual periods (amenorrhea), endometriosis, infertility treatment and preterm delivery. The recommended dose of progesterone for hormone replacement treatment is 200 to 400 mg/day, given as a single evening dose. After oral administration, micronized progesterone reaches its peak plasma levels in two to three hours and has an elimination half-life of three to four hours (18). Because of its short half-life progesterone will be given twice daily to maintain stable plasma levels. Progesterone doses higher than 400 mg/day will not be used since they are more likely to cause sedation. The safety and tolerability of micronized progesterone are well established. We have used micronized progesterone in several previous studies with female smokers (4-6). Progesterone was well-tolerated and we did not encounter any serious adverse events. The most common adverse effect is mild sedation. Other less common adverse effects include menstrual irregularity, spotting or breakthrough bleeding, dizziness, cramps, nausea, fatigue, headache and breast tenderness. Other side effects attributed to synthetic progestins, including depression, fluid retention, pruritus, jaundice, rash and thrombotic disorders, have not been observed with natural progesterone. Women will be warned to use caution when driving a motor vehicle or operating machinery while undergoing study treatment.

There is black-box warning for progesterone regarding the risk for cardiovascular disorders and breast cancer. The black box warning mentions the Women's Health Initiative (WHI) study in which treatment of postmenopausal women (50 to 79 years of age) with daily oral conjugated estrogens combined with medroxyprogesterone acetate (MPA), relative to placebo, reported increased risks of deep vein thrombosis, pulmonary embolism, stroke, and myocardial infarction (20). The pharmacological effects of MPA, a progestin, differ substantially from those of progesterone. MPA, but not progesterone, has well-characterized androgenic, glucocorticoid and anabolic effects and have been associated with unfavorable side effects including fluid retention, androgenic effects, alterations in lipid profile, increase risk for breast cancer (21, 22), and cardiovascular events (23). In contrast to MPA, progesterone is not known to cause these adverse events (24).

**10. Minimizing Risks:** Describe the manner in which the above-mentioned risks will be minimized.

As a safety measure for these serious adverse events, we will exclude subjects with history of nut allergy, thrombophlebitis, deep vein thrombosis, pulmonary embolus, clotting or bleeding disorders, heart disease, diabetes or history of stroke, breast cancer or other cancers. Subjects will be warned about these side effects and the physician will be alert to the earliest manifestations of thrombotic disorders including thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis. If any of these occur or be suspected, the study medication will be discontinued immediately.

We will also monitor women for less severe side effects such as cramps, breast tenderness, and breakthrough bleeding.

Our research team includes a gynecologist, Dr. Aileen Gariepy, who has been involved in designing the current study and will provide expertise in progesterone treatment including monitoring adverse events.

All potential risks and benefits of the study medication will be reviewed as part of the consent process, and will be assessed for at every check-in visit and when reminder phone calls by a research nurse or physician are made for appointments via study provided cell phones. Study staff will query about possible side effects in an open-ended fashion that will allow us to elicit the most problematic side effects. We will specifically ask about symptoms that would be indicative of thromboembolic events (swelling of the legs, shortness of breath, etc. and other known side effects (drowsiness)). All participants will receive standard TNP and some may find additional benefit from progesterone.

Medical Monitoring: Potential participants will be carefully screened to rule out medical conditions that may increase the possibility of adverse events. Study participants will be carefully monitored by the study RA and a physician on the research team during each weekly visit.

Participants will be withdrawn from the treatment arm of the study if they show severe psychological or symptomatic deterioration, unacceptable levels of adverse events as determined by the study physician, or if clinically necessary for ethical or safety purposes. Participants dropped from a study for these reasons or because they wish to withdraw from a study will be offered treatment as usual at the clinic or be referred to a higher level of care when appropriate. Private referral and/or hospitalization may also be offered according to the participants' needs and wishes.

Confidentiality will be protected by having records identified by code number only with the master list including names kept in a sealed envelope in a locked file in the Principal Investigator's office and by the pharmacy. Subjects will be given telephone numbers to call in case of emergency, 24 hours a day.

**11. Data and Safety Monitoring Plan:** Include an appropriate Data and Safety Monitoring Plan (DSMP) based on the investigator's risk assessment stated below. (Note: the HIC will make the final determination of the risk to subjects.) For more information, see the Instructions, page 24.

- a. What is the investigator's assessment of the overall risk level for subjects participating in this study?

The risk associated with participating in this study is moderate, because progesterone treatment may be associated with mild side effects. Serious side effects associated with this treatment are not expected.

- b. If children are involved, what is the investigator's assessment of the overall risk level for the children participating in this study?
- c. Copy, paste, and then tailor an appropriate Data and Safety Monitoring Plan from <http://www.yale.edu/hrpp/forms-templates/biomedical.html> for
  - i. Minimal risk
  - ii. Greater than minimal/moderate risk
  - iii. High risk

## **Moderate Risk DSMP**

### **1. Personnel responsible for the safety review and its frequency:**

The principal investigator will be responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews at the specified frequency, which must be conducted at a minimum of every 6 months (including when re-approval of the protocol is sought). During the review process, the principal investigator (monitor) will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment. Either the principal investigator, the IRB or NCI have the authority to stop or suspend the study or require modifications.

### **2. The risks associated with the current study are deemed greater than minimal for the following reasons: (choose those that apply)**

We do not view the risks associated with the micronized progesterone as minimal risks.

Although we have assessed the proposed study as one of greater than minimal risk, the potential exists for anticipated and/or unanticipated adverse events, serious or otherwise, to occur since it is not possible to predict with certainty the absolute risk in any given individual or in advance of first-hand experience with the proposed study methods. Therefore, we provide a plan for monitoring the data and safety of the proposed study as follows:

Data and safety of patients will be monitored on a daily basis. Dr. Yonkers will have the primary responsibility for monitoring data and adverse events. Subjects will be seen by a study clinician at each visit. The Project Director will review subjects' safety daily and will present subjects' clinical status and adverse experiences at the weekly Study Personnel meeting. Entrance criteria of all subjects are reviewed at this meeting including results of self-report and other data collection measures. Dr. Yonkers will oversee appropriate assessment and make a determination with regard to study discontinuation. She will refer subjects who have had significant deterioration for further treatment but will follow them until they are connected with treatment. Dr. Yonkers will ensure that information on subjects' adverse effects are systematically collected and evaluated.

All serious AND unanticipated adverse effects which are deemed possibly, probably or definitely related will be reported to the Yale Human Research Protection Program, Internal Review Board (IRB) in compliance with University and Medical School research review boards' protocols. In

addition, the external Data and Safety Monitoring Board (see below) will be informed about any serious adverse effect, and their recommendation will be communicated to the IRB and NCI. We will report recruitment, follow-up and adverse events to this panel on a twice-yearly schedule. Prior to study initiation, critical parameters for collection of side effects and for study discontinuation will be recommended to the DSMB who may use these or other measures to monitor safety of the ongoing trial.

**Data and Safety Monitoring Board (DSMB):** This project will be monitored by a Data and Safety Monitoring Board (DSMB), because the study involves double-blind treatment of smokers with nicotine. This board is composed of persons not otherwise affiliated with the clinical study who are experienced in various aspects of the conduct of clinical trials for the treatment of addictive disorders. We propose three investigators located here in Connecticut who are not directly involved in this trial – Heather Lipkind, MD, Steve Bernstein, MD, and Hochang B. Lee, MD as the membership of the DSMB. These three clinicians have appropriate expertise in smoking cessation. None of these three are directly involved with this proposed trial and consequently should not pose a conflict of interest.

We will report recruitment, follow-up, and adverse events to this panel on a quarterly fashion. Prior to study initiation, critical parameters for collection of side effects and for study discontinuation will be recommended to the DSMB who may use these or other measures to monitor safety of the ongoing trial. The DSMB will be available to convene outside of scheduled meetings, if necessary, due to concerns regarding a particular subject or due to any troublesome developments in subjects' experiences during the study. The DSMB will make appropriate recommendations for changes in the study protocol, if needed.

This monitoring will be consistent with NIH policy regarding the protection of human subjects in research, and FDA guidance on practices for clinical trials (ICH E9) and good clinical practices (ICH E6). In general, the data to be reviewed will include screening data, baseline data, efficacy data, and safety data.

In order for the DSMB to fulfill its mission of assuring the safety of human subjects and the scientific integrity of the studies conducted, the Board will have access to accumulating study outcome data in a manner that will protect its confidentiality and preserve its statistical integrity. The Board will examine accumulating data to assure that the risks and benefits of participation remain acceptable and that the results of the trial will be considered scientifically reliable. The conditions under which the Board will examine this data are described below. This monitoring will be consistent with NIH policy regarding the protection of human subjects in research, and FDA guidance on statistical practices for clinical trials (ICH E9) and good clinical practices (ICH E6). In general, the data to be reviewed will include screening data, baseline data, efficacy data, safety data, quality assurance data, accrual status including projections, total number of case report forms that are in-house, total number of case report forms that have been quality assured, times to milestones, FDA reports including annual IND reports, safety data from other sources for each clinical trial reviewed, and any other data that will help in the assessment of the effectiveness of the clinical trial.

The study will be monitored for safety in an ongoing way as well as twice each year formally by the DSMB. The principal investigator will attend an initial part of this meeting to present the study's adverse events and ongoing subject accrual, as well as any potential study design changes under consideration. The remainder of the meeting will not include any direct study personnel until the end of the meeting, when the DSMB will convey directly to the principal investigator any safety or study conduct concerns, as well as requests for potential interim analyses.

Following each DSMB meeting written minutes will be prepared and distributed summarizing any recommendations. These written reports will insure timely communication with the study principal investigator with preparation of any protocol amendments necessary. After each DSMB meeting, this written report will describe all recommendations including additional safety steps. The FDA adverse drug experience reporting timelines will be utilized as timelines to disseminate feedback from the DSMB to the principal investigator and sub investigators. That is, three days for acute circumstances and ten days for non-acute circumstances. The recommendation of the DSMB will be communicated to the NCI Program Official.

### **3. Attribution of Adverse Events:**

Adverse events will be monitored for each subject participating in the study and attributed to the study procedures / design by the principal investigator, Kimberly Yonkers, MD, according to the following categories:

- a.) Definite: Adverse event is clearly related to investigational procedures(s)/agent(s).
- b.) Probable: Adverse event is likely related to investigational procedures(s)/agent(s).
- c.) Possible: Adverse event may be related to investigational procedures(s)/agent(s).
- d.) Unlikely: Adverse event is likely not to be related to the investigational procedures(s)/agent(s).
- e.) Unrelated: Adverse event is clearly not related to investigational procedures(s)/agent(s).

### **4. Plan for Grading Adverse Events:**

The following scale will be used in grading the severity of adverse events noted during the study:

- 1. Mild adverse event
- 2. Moderate adverse event
- 3. Severe

### **5. Plan for Determining Seriousness of Adverse Events:**

#### **Serious Adverse Events:**

In addition to grading the adverse event, the PI will determine whether the adverse event meets the criteria for a Serious Adverse Event (SAE). An adverse event is considered serious if it results in any of the following outcomes:

- 1. Death;
- 2. A life-threatening experience in-patient hospitalization or prolongation of existing hospitalization;
- 3. A persistent or significant disability or incapacity;
- 4. A congenital anomaly or birth defect; OR
- 5. Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

An adverse event may be graded as severe but still not meet the criteria for a Serious Adverse Event. Similarly, an adverse event may be graded as moderate but still meet the criteria for an

SAE. It is important for the PI to consider the grade of the event as well as its “seriousness” when determining whether reporting to the IRB is necessary.

## 6. Plan for reporting UPIRSOs (including Adverse Events) to the IRB

The principal investigator will report the following types of events to the IRB:

Any incident, experience or outcome that meets ALL 3 of the following criteria:

1. Is unexpected (in terms of nature, specificity, severity, or frequency) given (a) the research procedures described in the protocol-related documents, such as the IRB-approved protocol and informed consent document and (b) the characteristics of the subject population being studied; AND
2. Is related or possibly related to participation in the research (*possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); AND
3. Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, legal, or social harm) than was previously known or recognized.

Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) may be medical or non-medical in nature, and include – but are not limited to – *serious, unexpected, and related adverse events* and *unanticipated adverse device effects*. **Please note** that adverse events are reportable to the IRB as UPIRSOs **only** if they meet all 3 criteria listed above.

These UPIRSOs/SAEs will be reported to the IRB in accordance with IRB Policy 710, using the appropriate forms found on the website. All related events involving risk but not meeting the *prompt* reporting requirements described in IRB Policy 710 should be reported to the IRB in summary form at the time of continuing review. If appropriate, such summary may be a simple brief statement that events have occurred at the expected frequency and level of severity as previously documented. In lieu of a summary of external events, a current DSMB report can be submitted for research studies that are subject to oversight by a DSMB (or other monitoring entity that is monitoring the study on behalf of an industry sponsor).

## 7. Plan for reporting adverse events to co-investigators on the study, as appropriate the protocol’s research monitor(s), e.g., industrial sponsor, Yale Cancer Center Data and Safety Monitoring Committee (DSMC), Protocol Review Committee (PRC), DSMBs, study sponsors, funding and regulatory agencies, and regulatory and decision-making bodies.

For the current study, the following individuals, funding, and/or regulatory agencies will be notified (choose those that apply):

- ☒ All Co-Investigators listed on the protocol.
- ☐ Yale Cancer Center Data and Safety Monitoring Committee (DSMC)
- ☒ National Institutes of Health



- ☐ Food and Drug Administration (Physician-Sponsored IND # \_\_\_\_\_)
- ☐ Medical Research Foundation (Grant \_\_\_\_\_)
- ☐ Study Sponsor
- ☐ Other Data Safety Monitoring Board (DSMB) or Committee (DSMC)

The principal investigator Kimberly Ann Yonkers MD, will conduct a review of all adverse events upon completion of every study subject. The principal investigator will evaluate the frequency and severity of the adverse events and determine if modifications to the protocol or consent form are required.

- d. For multi-site studies for which the Yale PI serves as the lead investigator: **N/A**
- i. How will adverse events and unanticipated problems involving risks to subjects or others be reported, reviewed and managed?
  - ii. What provisions are in place for management of interim results?
  - iii. What will the multi-site process be for protocol modifications?

**12. Statistical Considerations:** Describe the statistical analyses that support the study design.

Main outcomes are prolonged smoking abstinence (Y/N at each point) and rates of 7-day point prevalence of abstinence (Y/N at each point). Following the recommendations of the Society for Research on Nicotine and Tobacco workgroup, the 7-day point prevalence is defined by self-reported smoking abstinence for the last 7 days, and expired carbon monoxide <10 ppm. Prolonged smoking abstinence is self-reported smoking abstinence starting with a 2-week grace period after the quit day (i.e., last 5 weeks of the treatment phase) without relapse to: the end of the trial, 1 month and 3 months post trial. Relapse is defined by a) smoked for 7 consecutive days or b) smoked at least once each week for 2 consecutive weeks, or c) missed 2 consecutive weekly appointments or 2) failed breath test at any previous outcome assessment. Additional outcomes include measures of withdrawal (MNWS and QSU-B), and response inhibition (Stroop and SST).

Data Analysis: We will follow CONSORT guidelines for the conduct and reporting of the trial. Descriptive statistics will be used to summarize the data on all randomized subjects, although, as per CONSORT, these parameters will not be included in the statistical model for primary analyses. Aim #1: To determine whether progesterone with TNP is superior to placebo and TNP we will use generalized estimating equations (GEE), an autoregressive correlation structure a binomial distribution and either identity or log link. A time-by-treatment interaction will be included in the GEE model. The 8-week period will include a continuous version for the time variable and the follow up periods will treat time as categorical. A GEE model such as this can evaluate whether there is an overall difference between the progesterone and the placebo groups and whether the rate of change in smoking abstinence is different between the two groups. For data that are missing, we will perform inverse weighting to determine if data are missing at random (25). The weight will be the inverse of the probability not dropping out. If there are concerns of informative dropout and/or informative intermittent missing data, which is typical of clinical trial data, we will use

pattern mixture models (26) and perform sensitivity analyses. In sensitivity analyses, participants who miss visits will be coded as smoking. Exploratory analysis will include plasma estradiol and progesterone levels as covariates in order to determine if they contribute to treatment response and PANAS scores as mediators of response to progesterone or placebo. Secondary analyses (the MNWS QSU-B) will be modelled similarly. The main outcome measures for the Stroop test are throughput and interference score. For the SST, the main outcomes are stop signal reaction time (msec) and go reaction time (msec). We will use hierarchical linear models with each cognitive measure as separate longitudinal outcomes and treatment group assignment as regressors.

**Power:** The sample size of 25 per condition was selected to provide an adequate assessment of feasibility and estimate effect sizes. Nonetheless, we determined what level of power we would have based upon a significance level of  $p < 0.05$ , 2 sided test for 7-day or prolonged abstinence. If rates of abstinence are 0.2 in the TNP only group and 0.4 in the progesterone and TNP group then the power would be 88%. If the rate of abstinence in the treated group is 0.38, power is reduced to 80%. In prior studies with the Stroop and SST, we found effect sizes  $> 0.5$  of progesterone vs placebo. Our sample size would have adequate power ( $> 80\%$ ) to detect a 2-fold difference in response. Clearly, these are large differences between groups but would provide a stable effect size estimate for a larger trial if findings are suggestive of a therapeutic effect of the combination treatment.

**Timeline:** We will use the first 3 months for study set up that will include final human subjects' approval, hiring and training of staff, database set up, computerization of the interview and assessment measures. Recruitment will begin immediately afterward. We will conduct ongoing data cleaning and will prepare reports for the human subjects' board, the DSMB and NCI at regular intervals. The final analysis and study report will occur in the last 3 months of the work period.

<b>SECTION VI: RESEARCH INVOLVING DRUGS, BIOLOGICS, RADIOTRACERS, PLACEBOS AND DEVICES</b>
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*If this section (or one of its parts, A or B) is not applicable, state N/A and delete the rest of the section.*

#### **A. DRUGS, BIOLOGICS and RADIOTRACERS**

1. **Identification of Drug, Biologic or Radiotracer:** What is (are) the **name(s)** of the drug(s) biologic(s) or radiotracer(s) being used? Identify whether FDA approval has been granted and for what indication(s).

All protocols which utilize a drug, biologic or radiotracer **not** approved by, but regulated by, the FDA, or a radiotracer regulated by the RDRC, must provide the following information:

- a. What is the Investigational New Drug (IND) **number** assigned by the FDA? We will not be applying for an IND.
- b. Who holds the IND? Multiple companies since the compound is generic.
- c. All protocols which utilize a radiotracer not approved by, but regulated by the FDA must provide the IND number: \_\_\_\_\_

Alternatively, use of the investigational radiotracer may be under RDRC/RSC oversight: (check if appropriate) \_\_\_\_\_

For all investigational radiotracers, attach a copy of the RDRC/RSC application (for radioisotopes used in the PET Center, PET Center personnel may complete this step) Go to <http://rsc.med.yale.edu/login.asp?url=myApps.asp>. When you have logged in, complete the application and attach a copy to this submission.

Alternatively, an **exemption from IND filing requirements** may be sought for a clinical investigation of a drug product that is lawfully marketed in the United States. If there is no IND and an exemption is being sought, review the following categories and complete the category that applies (*and delete the inapplicable categories*):

### **Exempt Category 1**

The clinical investigation of a drug product that is lawfully marketed in the United States can be exempt from IND regulations if all of the following are yes:

- i. The intention of the investigation is NOT to report to the FDA as a well-controlled study in support of a new indication for use or to be used to support any other significant change in the labeling for the drug. X Yes ☐ No
- ii. The drug that is undergoing investigation is lawfully marketed as a prescription drug product, and the intention of the investigation is NOT to support a significant change in the advertising for the product. X Yes ☐ No
- iii. The investigation does NOT involve a route of administration or dosage level or use in populations or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product. X Yes ☐ No
- iv. The investigation will be conducted in compliance with the requirements for institutional (HIC) review and with the requirements for informed consent of the FDA regulations (21 CFR Part 50 and 21 CFR Part 56). X Yes ☐ No
- v. The investigation will be conducted in compliance with the requirements regarding promotion and charging for investigational drugs. X Yes ☐ No

2. **Background Information:** Provide a description of previous human use, known risks, and data addressing dosage(s), interval(s), route(s) of administration, and any other factors that might influence risks. If this is the first time this drug is being administered to humans, include relevant data on animal models.

1) Progesterone: Progesterone, a natural hormone, is safe and well-tolerated by women. The safety, tolerability and efficacy of micronized progesterone is well established and it is FDA approved for hormone replacement therapy (HRT), absence of menstrual periods (amenorrhea), endometriosis, infertility treatment and preterm delivery. The recommended dose of progesterone for hormone replacement treatment is 200 to 400 mg/day, given as a single evening dose. After oral administration, micronized progesterone reaches its peak plasma levels in two to three hours and has an elimination half-life of three to four hours (18). Because of its short half-life progesterone will be given twice daily to maintain stable plasma levels. Progesterone doses higher than 400 mg/day will not be used since they are more likely to cause sedation. The safety and tolerability of micronized progesterone are well established.

Update June 2017: All participants had blood levels of progesterone drawn. We were blind to assignment of participants but at the end of the study found that those who were randomized to active progesterone had low progesterone levels. This could be due to the progesterone preparation or the fact that smokers metabolize it very quickly. In any case, the low progesterone levels in the active treatment group obviates our ability to test our hypothesis that progesterone augmentation assists abstinence for smokers. Given the lack of funds, we cannot repeat the project. Rather, we are recruiting a second cohort and are using a commercially available oral micronized progesterone rather than the previous medication that was compounded for the study. We plan to enroll a minimum of 12 people with an imbalanced ratio of 6 active to 1 placebo.

We will continue to obtain plasma levels of progesterone. This will enhance our ability to test our hypothesis. If need be in a final analysis, and give that this is a pilot project, we may be able to use the participants randomized to placebo in the first cohort and second cohort and the participants randomized to active in the second cohort.

**2) Transdermal Nicotine Patch (TNP):** TNP is currently available as an over the counter medication as an aid for smoking cessation. Consistent with the clinical guideline, participants who smoke more than 10 cigarettes per day will receive the following dose of TNP: 21mg/24 hours for 4 weeks, 14mg for weeks 5 and 6 and 7 mg for weeks 7 and 8. Participants who smoke between 5-10 cigarettes per day will receive the following dose of TNP: 14mg/24 hours for 6 weeks, 7mg for weeks 7 and 8. Neither longer term (> 8 weeks) nor a higher dose (> 21 mg/d) of nicotine patch improves efficacy over the standard treatment. Adverse effects of TNP include skin irritation, nausea, vomiting, sweating, mood and sleep disturbances. To avoid skin irritation, participants will be instructed to place a new patch on a relatively hairless location, typically between the neck and waist at the start of each day and to rotate the site of application. Smokers who experience sleep disturbances will be instructed to remove the patch before bedtime.

3. **Source:** a) Identify the source of the drug or biologic to be used.

Banner Pharmacaps.

b) Is the drug provided free of charge to subjects? ☒ Yes ☐ No

If yes, by whom? The medication is provided free of charge to the subjects, but is paid for by the grant supporting this research.

4. **Storage, Preparation and Use:** Describe the method of storage, preparation, stability information, and for parenteral products, method of sterilization and method of testing sterility and pyrogenicity.

Check applicable Investigational Drug Service utilized:

☐ **YNHH IDS**

☐ **CMHC Pharmacy**

☐ **PET Center**

☐ **Other:**

☐ **Yale Cancer Center**

☐ **West Haven VA**

☐ **None**

*Note: If the YNHH IDS (or comparable service at CMHC or WHVA) will not be utilized, explain in detail how the PI will oversee these aspects of drug accountability, storage, and preparation.*

As we have done with our previous studies, the oral micronized progesterone and placebo will be stored at room temperature in the locked medication cabinet at the PMS and Perinatal Research Program clinic.

5. **Use of Placebo:** ☐ **Not applicable to this research project**

If use of a placebo is planned, provide a justification which addresses the following:

- a. Describe the safety and efficacy of other available therapies. If there are no other available therapies, state this.  
All participants are receiving behavioral counseling and support as a first line treatment for relapse prevention.
- b. State the maximum total length of time a participant may receive placebo while on the study.  
8 weeks
- c. Address the greatest potential harm that may come to a participant as a result of receiving placebo.  
It is possible that subjects will relapse to smoking. However, it is not known in receipt of the active medication could prevent such a risk.
- d. Describe the procedures that are in place to safeguard participants receiving placebo.  
Safety procedures are identical for all study subjects. Most notably, all subjects are also receiving high-quality supportive counseling to teach relapse prevention skills. Participants are seen for weekly visits with study physician and research nurse, and are at every visit evaluated for symptoms of depression, use of alcohol/cigarettes and illicit substances, safety risk towards themselves and others, and other comprehensive health checks.

6. **Use of Controlled Substances:**

Will this research project involve the use of controlled substances in human subjects?

☐ Yes ☒ No *See HIC Application Instructions to view controlled substance listings.*

If yes, is the use of the controlled substance considered:

☐ Therapeutic: The use of the controlled substance, within the context of the research, has the potential to benefit the research participant.

☐ Non-Therapeutic: *Note, the use of a controlled substance in a non-therapeutic research study involving human subjects may require that the investigator obtain a Laboratory Research License. Examples include controlled substances used for basic imaging, observation or biochemical studies or other non-therapeutic purposes. See Instructions for further information.*

7. **Continuation of Drug Therapy After Study Closure** ☐ **Not applicable to this project**

Are subjects provided the opportunity to continue to receive the study drug(s) after the study has ended?

☐ Yes If yes, describe the conditions under which continued access to study drug(s) may apply as well as conditions for termination of such access.

☒ No If no, explain why this is acceptable.

We will not provide study drug after the study has ended because we do not know if it is helpful.

**B. DEVICES**

1. Are there any investigational devices used or investigational procedures performed at YNHH, e.g., YNHH Operating Room or YNHH Heart and Vascular Center? Yes ☐ No ☒

**SECTION VII: RECRUITMENT/CONSENT AND ASSENT PROCEDURES****1. Targeted Enrollment: Give the number of subjects:**

- a. targeted for enrollment at Yale for this protocol 50
- b. If this is a multi-site study, give the total number of subjects targeted across all sites N/A

**2. Indicate recruitment methods below.** Attach copies of any recruitment materials that will be used.

- |   |  |   |
|---|--|---|
| <input checked="" type="checkbox"/> Flyers                          | <input type="checkbox"/> Internet/Web Postings   | <input type="checkbox"/> Radio                |
| <input checked="" type="checkbox"/> Posters                         | <input type="checkbox"/> Mass E-mail Solicitation  | <input type="checkbox"/> Telephone            |
| <input checked="" type="checkbox"/> Letter                          | <input type="checkbox"/> Departmental/Center Website   | <input type="checkbox"/> Television           |
| <input type="checkbox"/> Medical Record Review                      | <input type="checkbox"/> Departmental/Center Research Boards                                   | <input checked="" type="checkbox"/> Newspaper |
| <input checked="" type="checkbox"/> Departmental/Center Newsletters | <input checked="" type="checkbox"/> Web-Based Clinical Trial Registries                        |   |
| <input checked="" type="checkbox"/> YCCI Recruitment database       | <input checked="" type="checkbox"/> Clinicaltrials.gov Registry (do not send materials to HIC) |   |
| <input type="checkbox"/> Other (describe):                          |  |   |

**3. Recruitment Procedures:**

- a. Describe how potential subjects will be identified.

We will recruit by direct screening from women attending regular care at the Women's Center at the Yale New Haven Hospital York Street site, the Reproductive Health Clinic at Yale New Haven Hospital's St. Raphael's site and 1 Long Wharf, New Haven. Women will be approached and we will ask them screening questions (if they smoke and how much, Fagerstrom scale, if they are interested in stopping smoking). Women who meet the above smoking criteria and state that they would like to participate in a smoking cessation trial will be eligible for additional screening.

We may also screen by media advertisement if above methods are inadequate.

- b. Describe how potential subjects are contacted.

In clinic, potential subjects (i.e. patients arriving for regularly-scheduled care in the participating clinic) will be approached by trained research assistant personnel (yet to be hired). If need be, we will also conduct mailings from commercially available mailing lists. This will include a letter describing our study and providing a phone number and return envelope for people who are interested in participating. We will contact women by phone and follow similar procedures. A third method is by posters and brochures that will be placed in Obstetrician-Gynecologists offices. This information will include our phone number for interested participants. Flyers and brochures will be placed around the community and hospital websites for clinical trials. This will also include call-back information. Finally, we may place advertisements in print and electronic media. People will be given call in information and we will return their phone calls.

- c. Who is recruiting potential subjects?

Research Assistant, Virginia Otero-Santos has been hired and highly trained for this task.

#### 4. Screening Procedures

- a. Will a form be used to screen potential subjects for eligibility prior to the potential subject coming to the research office? ☒ Yes ☐ No
- b. If yes, identify below all health information to be collected as part of screening and check off any of the following HIPAA identifiers to be collected and retained by the research team during this screening process.

Women who are screened face-to-face, will be read a consent for screening script and those consenting will be asked if they smoke <5 cigarettes, are undergoing treatment for smoking, use illicit substances, are planning on moving out of the area within 6 months or have irregular menstrual cycles. Any yes response will indicate that they are not eligible and we will not retain any PHI. Participants who are potentially eligible will undergo written consent and will be scheduled for an appointment that will include a full evaluation.

Possible participants who call in will be asked these questions and if they are not eligible will be thanked for their time. No PHI will be retained.

Possible participants who call in and are potentially eligible will be read a consent for screening script about the study, will be asked eligibility questions and if potentially eligible and interested will undergo phone consent and offered an appointment. The consent will be reviewed and signed during the subsequent face to face appointment. Any PHI (name, phone number and address) from possible participants who did not attend the appointment or were not provisionally eligible will be destroyed. No additional information will be collected over the phone

#### HEALTH INFORMATION TO BE COLLECTED:

##### HIPAA identifiers:

- ☒ Names (only for possible participants with a positive screen)
- ☒ All geographic subdivisions smaller than a State, including: street address, city, county, precinct, zip codes and their equivalent geocodes, except for the initial three digits of a zip code if, according to the current publicly-available data from the Bureau of the Census: (1) the geographic unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people, and (2) the initial three digits of a zip code for all such geographic units containing 20,000 or fewer people is changed to 000. (only for possible participants with a positive screen)
- ☒ Telephone numbers (only for possible participants with a positive screen)
- ☐ Fax numbers
- ☒ E-mail addresses (only for possible participants with a positive screen)
- ☐ Social Security numbers
- ☐ Medical record numbers
- ☐ Health plan beneficiary numbers
- ☐ Account numbers
- ☐ All elements of dates (except year) for dates related to an individual, including: birth date, admission date, discharge date, date of death, all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older
- ☐ Certificate/license numbers
- ☐ Vehicle identifiers and serial numbers, including license plate numbers
- ☐ Device identifiers and serial numbers
- ☐ Web Universal Resource Locators (URLs)
- ☐ Internet Protocol (IP) address numbers
- ☐ Biometric identifiers, including finger and voice prints
- ☐ Full face photographic images and any comparable images
- ☐ Any other unique identifying numbers, characteristics, or codes

**5. Assessment of Current Health Provider Relationship for HIPAA Consideration:**

Does the Investigator or any member of the research team have a direct existing clinical relationship with any potential subject?

☐ Yes, all subjects

☒ Yes, some of the subjects

The YNHH Women's Center and related St Raphael Chapel St site Women's Clinic serve a large volume of patients from the greater New Haven area. Patients in these clinics are quite loyal to the clinic and receive their healthcare there throughout the lifespan, from initial gynecological checkups, through pregnancy, and into menopause. There is the possibility that some patients may know or be known to the Principal or Co-Investigator, although patients known to study providers will in no way be specifically recruited for this trial.

☐ No

If yes, describe the nature of this relationship.

**6. Request for waiver of HIPAA authorization:** (When requesting a waiver of HIPAA Authorization for either the entire study, or for recruitment purposes only. Note: if you are collecting PHI as part of a phone or email screen, you must request a HIPAA waiver for recruitment purposes.) **N/A**

**Choose one:** For entire study: \_\_\_\_\_ For recruitment purposes only: X \_\_\_\_\_

- i. Describe why it would be impracticable to obtain the subject's authorization for use/disclosure of this data;

The brief pre-screening questions are minimal and PHI is collected only on participants for whom an appointment is scheduled. For these individuals, the consent will be signed if screened in person or will be read to them over the phone. We do not request subject's authorization to use/disclose data if they are clearly not eligible in the brief pre-screening process because we will not collect or retain PHI.

- ii. If requesting a waiver of **signed** authorization, describe why it would be impracticable to obtain the subject's signed authorization for use/disclosure of this data;

The brief phone screen (smoked < 5 cigarettes, undergoing smoking treatment, irregular menstrual cycle) may be administered over the phone and it is not possible to obtain written signatures. However, we will read the consent to possible participants who are scheduled for a complete screening visit.

**By signing this protocol application, the investigator assures that the protected health information for which a Waiver of Authorization has been requested will not be reused or disclosed to any person or entity other than those listed in this application, except as required by law, for authorized oversight of this research study, or as specifically approved for use in another study by an IRB.**



*Researchers are reminded that unauthorized disclosures of PHI to individuals outside of the Yale HIPAA-Covered entity must be accounted for in the “accounting for disclosures log”, by subject name, purpose, date, recipients, and a description of information provided. Logs are to be forwarded to the Deputy HIPAA Privacy Officer.*

- 7. Required HIPAA Authorization:** If the research involves the creation, use or disclosure of protected health information (PHI), separate subject authorization is required under the HIPAA Privacy Rule. Indicate which of the following forms are being provided:

- ☒ Compound Consent and Authorization form  
☐ HIPAA Research Authorization Form

- 8. Consent Personnel:** List the names of all members of the research team who will be obtaining consent/assent.

Kimberly Ann Yonkers, MD  
Ariadna Forray, MD  
Marla Genova, MA  
Heather Howell, MSW  
Virginia Otero-Santos

- 9. Process of Consent/Assent:** Describe the setting and conditions under which consent/assent will be obtained, including parental permission or surrogate permission and the steps taken to ensure subjects' independent decision-making.

Recruitment and Informed consent: The procedure for obtaining informed consent entails a face-to-face discussion between the potential subject and a trained member of the research staff (research assistant, or study-related physician). The entire protocol and all of its procedures and requirements, risks and potential benefits, are explained at length. To ensure that the respondent has the capacity to provide consent, the study personnel will ask women to summarize their understanding of the study. Additionally, women are encouraged to ask questions about any confusing points, and to consider carefully their choice to participate in this, or any, research protocol. Subjects are informed that they may withdraw from the project at any time, without prejudice, and without any effect on their medical care.

Circumstances of consent: All subjects will be asked to provide consent at the study inception (any one who is preliminarily eligible on the brief pre-screen). All study data will be kept in a research chart or computer. Computerized data are all encrypted. Additionally, a number identifier rather than subject name is used for computerized data. Further, tables are separated from programs so there will be no way for people to associate data with responses of individuals. All subjects will be told through the informed consent process that if she develops suicidal or homicidal intent, this would incur assessment for voluntary or involuntary hospitalization, or a loss of some confidentiality. All subjects will be informed about the limits of confidentiality concerning suicidal intent or homicidal intent. Women who decline participation in the study will be given information on smoking cessation, informed of assets available from the CT Quitline, and referred for further treatment according to their clinic's referral protocol.

Of note: women may also be offered participation in other studies run by the same PI, based upon eligibility, at the time of screening. The research staff would request permission from the subject

to contact her for other studies. Women who decline this offer will be given information about the other study, and provided with a telephone number to call if she is interested.

- 10. Evaluation of Subject(s) Capacity to Provide Informed Consent/Assent:** Indicate how the personnel obtaining consent will assess the potential subject's ability and capacity to consent to the research being proposed.

To ensure that the respondent has the capacity to provide consent, the study personnel will ask women to summarize their understanding of the study. Additionally, women are encouraged to ask questions about any confusing points, and to consider carefully their choice to participate in this, or any, research protocol. Subjects are informed that they may withdraw from the project at any time, without prejudice, and without any effect on their medical care.

- 11. Documentation of Consent/Assent:** Specify the documents that will be used during the consent/assent process. Copies of all documents should be appended to the protocol, in the same format that they will be given to subjects.

Compound authorization is attached for your review.

- 12. Non-English Speaking Subjects:** Explain provisions in place to ensure comprehension for research involving non-English speaking subjects. Translated copies of all consent materials must be submitted for approval prior to use.

All study procedures are available to English-speaking study subjects only.

- 13. Consent Waiver: In certain circumstances, the HIC may grant a waiver of signed consent, or a full waiver of consent, depending on the study.** If you will request either a waiver of consent, or a waiver of signed consent for this study, complete the appropriate section below.

- ☒ **Not Requesting a consent waiver**  
☐ **Requesting a waiver of signed consent**  
☐ **Requesting a full waiver of consent**

**A. Waiver of signed consent:** (Verbal consent from subjects will be obtained. **If PHI is collected, information in this section must match Section VII, Question 6)**

- ☒ **Requesting a waiver of signed consent for Recruitment/Screening only**

If requesting a waiver of signed consent, please address the following:

a. Would the signed consent form be the only record linking the subject and the research?

☒ Yes ☐ No

b. Does a breach of confidentiality constitute the principal risk to subjects?

☐ Yes ☒ No

**OR**

c. Does the research activity pose greater than minimal risk?

☐ Yes ***If you answered yes, stop. A waiver cannot be granted.*** Please note:  
 Recruitment/screening is generally a minimal risk research activity

☒ No

**AND**

d. Does the research include any activities that would require signed consent in a non-research context? ☐ Yes ☒ No

☐ **Requesting a waiver of signed consent for the Entire Study** (Note that an information sheet may be required.)

If requesting a waiver of signed consent, please address the following:

a. Would the signed consent form be the only record linking the subject and the research?

☐ Yes ☐ No

b. Does a breach of confidentiality constitute the principal risk to subjects?

☐ Yes ☐ No

**OR**

c. Does the research pose greater than minimal risk? ☐ Yes *If you answered yes, stop. A waiver cannot be granted.* ☐ No

**AND**

d. Does the research include any activities that would require signed consent in a non-research context? ☐ Yes ☐ No

**B. Full waiver of consent:** (No consent from subjects will be obtained for the activity.)

☐ **Requesting a waiver of consent for Recruitment/Screening only**

a. Does the research activity pose greater than minimal risk to subjects?

☐ Yes *If you answered yes, stop. A waiver cannot be granted.* Please note:

Recruitment/screening is generally a minimal risk research activity

☐ No

b. Will the waiver adversely affect subjects' rights and welfare? ☐ Yes ☐ No

c. Why would the research be impracticable to conduct without the waiver?

d. Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date?

☐ **Requesting a full waiver of consent for the Entire Study** (Note: If PHI is collected, information here must match Section VII, question 6.)

If requesting a full waiver of consent, please address the following:

a. Does the research pose greater than minimal risk to subjects?

☐ Yes *If you answered yes, stop. A waiver cannot be granted.*

☐ No

b. Will the waiver adversely affect subjects' rights and welfare? ☐ Yes ☐ No

c. Why would the research be impracticable to conduct without the waiver?

d. Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date?

**SECTION VIII: PROTECTION OF RESEARCH SUBJECTS****Confidentiality & Security of Data:**

- a. What protected health information (medical information along with the HIPAA identifiers) about subjects will be collected and used for the research?

Name, date of birth, address, telephone number, pap smear results, mental health and addictions questionnaires, general overview of medical history (including indicators related to inclusion/exclusion medical criteria) and measurements collected in the physical exam with the PI (ie weight, blood pressure, etc), results of urine laboratory tests (pregnancy "hcg" levels, presence of cotinine and/or drugs of abuse in the body, Serum Progesterone Level) and detailed information about use of cigarettes.

- b. How will the research data be collected, recorded and stored?

Data will be collected on paper questionnaires and via computer interview. Both documents are coded.

- c. How will the digital data be stored? ☐ CD ☐ DVD ☐ Flash Drive ☐ Portable Hard Drive ☒ Secured Server ☐ Laptop Computer ☐ Desktop Computer ☐ Other
- d. What methods and procedures will be used to safeguard the confidentiality and security of the identifiable study data and the storage media indicated above during and after the subject's participation in the study?

Patient identifying information is kept in a separate location from her data. The two are linked by her study id number. The key to this id code is kept in a separate location, accessible by study PI and Project Director. Access to the code is limited to the PI and study Project Director and will be maintained until the study is completed and data analysis team determine that all data collection is complete and the dataset can be stripped of identifiers. At such time, the code linking subject data to her name etc will be destroyed.

Do all portable devices contain encryption software? ☒ Yes ☐ No

*If no, see <http://hipaa.yale.edu/guidance/policy.html>*

- e. What will be done with the data when the research is completed? Are there plans to destroy the identifiable data? If yes, describe how, by whom and when identifiers will be destroyed. If no, describe how the data and/or identifiers will be secured.

All HSPT and HIPAA guidelines are followed. Once a subject completes her study participation and data has been cleaned, her case-file is stripped of identifying information. De-identified data is kept onsite for 7 years while analysis and manuscripts are being prepared.

- f. Who will have access to the protected health information (such as the research sponsor, the investigator, the research staff, all research monitors, FDA, Yale Cancer Center Data and Safety Monitoring Committee (DSMC), SSC, etc.)? (please distinguish between PHI and de-identified data)

PI and research staff have access to PHI, for the purposes of conducting study-related procedures only. NCI has the right to view study records.

g. If appropriate, has a [Certificate of Confidentiality](#) been obtained?

Yes, it has been obtained by NCI on January 6, 2016. It expires on November 30, 2017.

h. Are any of the study procedures likely to yield information subject to mandatory reporting requirements? (e.g. HIV testing – reporting of communicable diseases; parent interview -incidents of child abuse, elderly abuse, etc.). Please verify to whom such instances will need to be reported.

In the unlikely event that study personnel have reason to believe a child is in danger of neglect or abuse, the study consent form indicates that we will report this to DCF

#### SECTION IX: POTENTIAL BENEFITS

**Potential Benefits:** Identify any benefits that may be reasonably expected to result from the research, either to the subject(s) or to society at large. (Payment of subjects is not considered a benefit in this context of the risk benefit assessment.)

Participation in this study may be helpful to women to quit smoking. Every participant will receive evidence-based behavioral treatments for smoking cessation. The results of this study may lead to new treatments for smoking cessation in women. Progesterone hormone has the potential to be such a treatment as it is safe and well-tolerated by women. Thus, if proven to be effective, the use of progesterone for smoking cessation in women is feasible.

#### SECTION X: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

1. **Alternatives:** What other alternatives are available to the study subjects outside of the research?

There are a myriad of evidenced-based treatment for nicotine cessation, and patients will be provided with such medical and community resources should they be eligible, but wish not to participate in our trial.

2. **Payments for Participation (Economic Considerations):** Describe any payments that will be made to subjects, the amount and schedule of payments, and the conditions for receiving this compensation.

There will be no cost to subjects for participating in this research protocol.

Study medication and testing is provided free of charge.

3. **Costs for Participation (Economic Considerations):** Clearly describe the subject's costs associated with participation in the research, and the interventions or procedures of the study that will be provided at no cost to subjects.

None

4. **In Case of Injury:** This section is required for any research involving more than minimal risk.

Although injury is not expected, in the event that it occurs, treatment will be provided and the subject's insurance will be responsible for payment. Subjects do not give up any legal rights by signing the study consent form.

- a. Will medical treatment be available if research-related injury occurs? Participants may be referred for treatment
- b. Where and from whom may treatment be obtained? They may seek treatment through their insurance or their current providers
- c. Are there any limits to the treatment being provided? They may receive any treatment their providers deem necessary.
- d. Who will pay for this treatment? They may use their personal insurance or personal funds
- e. How will the medical treatment be accessed by subjects? We will assist them in finding providers if they do not have providers

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