Effects of Smoking Environments on Craving and Smoking

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EFFECTS OF SMOKING ENVIRONMENTS ON CRAVING AND SMOKING

Principal Investigator:

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Dr. Joseph McClernon has developed, with Chemsultants, the placebo patches that are being used in the study. If the placebo patches are commercially successful in the future, the developers and Duke University may benefit financially.Co Investigator:

Cynthia Conklin, Ph.D.

PURPOSE

The goal of this study is to evaluate the effects of varenicline versus nicotine replacement versus placebo on personal smoking environment (PSE) cue reactivity. In a lab-based model of smoking lapse/relapse, we will assess craving, latency to first cigarette and smoke intake in response to viewing PSEs. The results of this study will inform whether first-line pharmacotherapies for nicotine dependence (e.g. nicotine patch, varenicline) alter reactivity to environment cues. This study will also provide evidence that the efficacy of these treatments is due, in part, to effects on environment reactivity or will suggest a need for adjunctive therapies that further target environment reactivity.

BACKGROUND

Encountering an environment in which smoking has regularly occurred and/or its effects experienced, triggers strong craving and may promote lapse or relapse in smokers who have quit. Clinicians and recovery programs have long recognized the powerful influence of drug-environment associations and counsel patients to avoid “people, places, and things” associated with prior use. Confirming these intuitions, real-world assessment (i.e. ecological momentary assessment) of smoking suggests that relapse most often occurs in environments previously associated with smoking and that abstaining in contexts associated with smoking decreases the probability of later lapse.

Despite recognition of the influence of environment as a determinant of drug use and relapse, and despite a large and growing preclinical literature, surprisingly little empirical work has specifically addressed questions around drug-environment associations in humans. Laboratory-based studies have demonstrated that environments previously unassociated with smoking, when paired with or made predictive of smoking, can elicit urges to smoke. More recently, preference for a room paired with a low dose of amphetamine has been demonstrated in amphetamine-naïve subjects and has been suggested as a human analog of conditioned place preference (CPP). Collectively, this and other cue-conditioning research in humans provides insight into the formation of drug-environment associations but leave open questions regarding the influence of *real-world environments* on subjective experience, behavior and brain function among individuals with long drug use histories.

DESIGN AND PROCEDURES

We propose to obtain consent from a total of 400 participants in order to identify 120 who meet all inclusion and exclusion criteria and complete all aspects of the study. During a phone screening interview, the study will be described in detail and preliminary participant characteristics (e.g. age, number of cigarettes per day) will be assessed. Participants will be made aware of all exclusion criteria. Those participants who meet criteria for participation will be invited to our offices for an informed consent and screening visit.

Screening session. During screening, all aspects of the study will be described to subjects and informed consent will be acquired. Breath and saliva samples will be collected in order to verify smoking status and blood alcohol level (BAL); and measures including, but not limited to, smoking history, nicotine dependence, and mood will be collected. Vitals such as heart rate, blood pressure and weight/height will also be measured. Urine samples will be obtained in order to screen for illicit drug use. Use of illegal drugs will be exclusion criteria, except for marijuana. A blood sample will be obtained in order to assess pregnancy status and blood chemistry as part of the medical evaluation. The medical evaluation will be conducted by the study physician and will include medical history, physical exam, and electrocardiogram (ECG). Participants will also be interviewed regarding their smoking behavior including an assessment of contexts (places) in which they smoke and abstain from smoking cigarettes. At the end of the screening session, if participants qualify to continue in the study (excluding review of lab work) they will complete 2 computer tasks where they will look at pictures of tobacco retail outlets and cigarette point of sale displays. During the tobacco retail outlet task subjects will indicate whether the retail location being shown is personally familiar to them. During the point of sale task subjects will indicate whether they would purchase an item in the display. During each task we will collect eye tracking data using an eyetracker.

Inclusion criteria:

1) generally healthy [(i.e. ambulatory, not currently sick)]
2) between the ages of 18 and 65
3) smoking of at least 5 cig/day of a brand delivering $\geq$ 0.5 mg nicotine (FTC method) for $\geq$ 1 year
4) an expired CO concentration of at least 10 ppm (to confirm inhalation) or urinary cotinine >1000 ng/mL (NicAlert = 6).
5) interest in quitting smoking within the timeframe of the experiment.
6) ability to identify 4 personal smoking and 4 personal non-smoking places.
7) must have smartphone or daily access to email

Exclusion criteria:

1) immediate or no desire to quit smoking;
2) inability to attend all required experimental sessions;
3) use of other tobacco products or e-cigarettes more than 9 days in the past 30 days;
4) current alcohol or drug abuse;
5) positive toxicology screen for any of the following drugs: cocaine, opiates, methadone, benzodiazepines, barbiturates, amphetamines, methamphetamines, and PCP
    a. marijuana will be tested for but will not be exclusionary;
    b. participants with valid prescriptions for opiates, benzodiazepines, barbiturates, amphetamines or methadone will not be excluded;
    c. participants failing the toxicology screen will be allowed to re-screen once;
6) use of experimental (investigational) drugs;
7) current use of nicotine replacement therapy or other smoking cessation treatment;
8) Hypertension (systolic >140 mm Hg, diastolic >100 mm Hg, coupled with a history of hypertension); subjects with no previous diagnosis of hypertension may have a screening blood pressure up to 160/100. Participants with a history of hypertension may, however, be allowed to participate in the study if the study physician determines that the condition is stable, controlled by medication, and in no way jeopardizes the individual's safety;
9) Hypotension with symptoms (systolic <90 mm Hg, diastolic <60 mm Hg);
10) Coronary heart disease;
11) Lifetime history of heart attack;

12) Cardiac (heart) disorder (including but not limited to valvular heart disease, heart murmur, heart failure, arrhythmia); Abnormal EKG results suggestive of ischemia or undiagnosed cardiovascular disease.
13) Active skin disorder (e.g., psoriasis) within the last year, except minor skin conditions (including but not limited to facial acne, minor localized infections, and superficial minor wounds);
14) Medical condition that may contraindicate participation in the opinion of the investigator and study physician.(for example, EKG results)
15) Current psychiatric disease:
    a. schizophrenia and schizoaffective disorder
    b. with the exception of anxiety disorders, OCD and ADHD;
16) unstable psychiatric conditions (any significant change in psychiatric symptoms during the past 3 months as determined by the study physician)
17) Suicidal ideation (within the past 10 years) or lifetime occurrence of attempted suicide;
18) Current depression - The Prime-MD will be used to screen for current (within 2 weeks) depression. Potential subjects who score >9 (or who score >0 on item #9 ("Thoughts that you would be better off dead, or of hurting yourself in some way") will be excluded from study participation, and, at the discretion of the study physician, referred to appropriate psychiatric treatment;
19) Significant adverse reaction to Chantix/Varenicline in the past;
20) Currently pregnant, breast feeding or likely to become pregnant;
21) History of seizure disorder.
22) A quit attempt within the last 30 days.

Among females, pregnancy at screening as measured by a blood test will be exclusionary. Females of child bearing potential must agree to use appropriate contraception during the course of the study. They must further agree to notify the study staff if they become pregnant during the study. If serum pregnancy test is negative and subject meets all other inclusion criteria, a urine pregnancy test will be conducted prior to randomization. If participants indicate at the Camera Turn-in session that they are not practicing appropriate contraception, another serum pregnancy test will be conducted prior to randomization.

Participants will be asked to indicate in the consent form whether they would like to be contacted about future studies while the present study is ongoing. Participants will be informed there is no obligation to participate and their refusal for future contact will in no way affect their participation in this study.

Training session. Participants will be introduced to the digital camera they will use to capture images of their personal environments. All information regarding the recording of events, the taking of pictures and operation of the camera (e.g. recharging, storage) will be reviewed with the participant. Any questions from participants regarding the use of the camera will be discussed. Participants will also be allowed to take photos with their own personal devices and email them to the study staff. If participants choose to take photos with device(s) other than the camera provided, the device(s) must have a photo resolution of at least 72 dpi. During the training session a breath CO sample will be collected as well as a saliva sample. Participants will also be familiarized with the Cue Reactivity Task.

Participants will receive a Qualtrics survey via email each day where they will record smoking behavior, tobacco purchasing information, and study drug adherence. Participants will be compensated $2 for completing the survey by the end of each day (up to $196).

Camera Turn-in session. Once participants have collected at least 32 photographs of personal neutral and smoking environments, participants will return to the lab with the camera. The images from the

camera will be uploaded, examined, and reviewed with each participant to ensure enough useable pictures were taken. Participants will be instructed to review and remove any pictures of other people from the camera prior to uploading. After uploading the pictures, if the study staff discover any pictures of other people those images will be permanently deleted. Pictures taken by participants will become property of the Duke Health Behavior Neuroscience Research Program for research purposes. A participant's pictures of any private location, such as a home, will not be shown to any other research participants in this or any other study. Any pictures of public places (bus stop, restaurant, etc.) may be used and shown to participants in future studies.

Randomization and Medication. Smokers will be randomized (stratified according to gender and smoking frequency) to one of three study drug combinations : placebo patch and capsule (PLAC; n=40), transdermal nicotine patch/placebo capsule (NRT; n=40) or varenicline/placebo patch (VAR; n=40) in a double blind, double-dummy design. The ratio of participants assigned to each group will be 1:1:1. Once participants have been randomized they will receive an 8 day supply of study drugs and instructions for use. Participants will undergo a 7 day induction phase where those in the VAR group and NRT group will be titrated up to a full dose of study drug (see description below) and then all participants will continue on their study drug for 7 more days while they complete two cue reactivity sessions. Following completion of the cue reactivity sessions, all participants will make a quit attempt. Participants in the VAR and NRT groups will continue to receive study drug as usual for the remaining 10 weeks of the study. Participants in the PLAC group will switch to wearing a nicotine patch (21mg if ≥10 cigarettes/day, 14mg if <10 cigarettes/day) the morning of their quit day in order to provide them with the minimum standard of care. Figure 1 describes the study drug schedule for dispensing patches and capsules. Participants will be given an extra 3 day supply of capsules and patches at each visit.

Figure 1. Medication Schedule*

NRT

Week	0	1	2	3		Quit Day	4	5	6	14
Visit	Screen	Train	Cam Return	CE 1	CE2		PQ1 (1wk)	PQ2 (3wk)	PQ3 (6wks)	PQ4 (10wks)
.5 mg PboVAR	0	0	11	0	0		0	0	0	0
1 mg PboVAR	0	0	2	6	20		28	42	56	0
7 mg NicPatch	0	0	0	0	0		0	0	14	0
14 mg NicPatch	0	0	0	0	0		0	0	14	0
21 mg NicPatch	0	0	8	3	10		14	21	0	0

VAR

Week	0	1	2	3		Quit Day	4	5	6	14
Visit	Screen	Train	Cam Return	CE 1	CE2		PQ1 (1wk)	PQ2 (3wks)	PQ3 (6wks)	PQ5 (10wks)
.5 mg VAR	0	0	11	0	0		0	0	0	0
1 mg VAR	0	0	2	6	20		28	42	56	0
7 mg PboPatch	0	0	0	0	0		0	0	14	0
14 mg PboPatch	0	0	0	0	0		0	0	14	0
21 mg PboPatch	0	0	8	3	10		14	21	0	0

PLAC

Week	0	1	2	3		Quit Day	4	5	6	14
Visit	Screen	Train	Cam Return	CE 1	CE2		PQ1 (1wk)	PQ2 (3wk)	PQ3 (6wks)	PQ4 (10wks)
.5 mg PboVAR	0	0	11	0	0		0	0	0	0
1 mg PboVAR	0	0	2	6	20		28	42	56	0
7 mg PboPatch	0	0	0	0	0		0	0	0	0
14 mg PboPatch	0	0	0	0	0		0	0	0	0
21 mg PboPatch	0	0	8	3	2		0	0	0	0
7 mg NicPatch	0	0	0	0	0		0	0	14	0
14 mg NicPatch	0	0	0	0	0		0	0	14	0
21 mg NicPatch	0	0	0	0	8		14	21	0	0

* Schedule is for participants that smoke >=10 cigarettes per day. If <10 cigs/day participants will start on 14mg/day patche

Varenicline and placebo varenicline capsules will be obtained from Central Compounding Center where it will be randomized and blinded. Central Compounding will provide a kit for each participant and it will be picked up by a member of the study team. Each kit will contain capsules (prepared in vials) and patches (repackaged in material for light sensitive products) for all visits for one participant. The medication for each visit will be separated and labeled by visit and group. Varenicline (VAR) will be administered by titrating to steady state levels over a 7 day induction period (.5 mg once daily in Days 1-3; .5 mg twice daily on Days 4-7 and 1 mg twice daily on Days 8-14). Participants will continue on 1mg twice daily until the end of treatment (days 15-84). The main side effects accompanying use of varenicline ("Chantix") are nausea, vomiting, gas, insomnia, and vivid dreams. If troublesome symptoms occur, the dose may be reduced to 1 mg daily (discontinuing the second dose) or discontinued altogether. Rarely, more serious side effects can occur including changes in behavior, hostility, agitation, depressed mood, suicidal thoughts and behavior, and attempted suicide. Participants will be asked about these symptoms at each visit and the study physician will be called in to evaluate the participant if any are endorsed. At randomization, participants will be given the "Medication Guide" that accompanies prescription Chantix. This information will be reviewed with the participant by study staff and participants will be encouraged to contact study staff upon experiencing any changes in behavior. As is standard in our protocols, all participants will have access to the PI's cell phone number and the study physician's pager number.

Nicotine patches (Nicoderm CQ®) will also be obtained from Central Compounding Center. Participants will wear 21mg/day patches for days 1-14. After day 14, participants will continue to wear the 21mg/d patches for 6 weeks, then step down to 14mg/d patches for 2 weeks and finally step down 7mg/d for the last 2 weeks of study protocol. If the participant smokes less than 10 cigarettes/day, we will start them on 14mg/day patches for days 1-14. After day 14 they will continue on 14mg/day patches for 6 weeks before stepping down to 7mg/day patches for the final 4 weeks of treatment. Insomnia and abnormal dreams are common and expected side effects associated with 24 hour nicotine patches. If a subject complains of disturbed sleep, he or she will be instructed to remove the patch at bedtime and apply a new one the next day at the usual time. Skin irritation may occur, although this will be minimized by changing the site of patch application daily. Using 1% hydrocortisone cream on the affected area will be recommended to help reduce skin irritation. If a subject develops itching or a rash at the patch site, he or she will be advised to use 1% hydrocortisone cream on the affected area. Symptoms associated with nicotine toxicity include lightheadedness, dizziness, nausea, fainting and vomiting. Symptoms considered moderate to severe in nature will be evaluated by the study medical staff by telephone or in person, depending upon the level of severity. Upon evaluation, the subject will then be given the choice of continuing in the study while discontinuing patch use. Placebo nicotine patches will be obtained from Chemsultants International. Participants assigned to the placebo patch condition will also be instructed to wear one patch each day, applying new patches in the morning. Placebo patches will be shipped directly to Central Compounding Center where all patches will be repackaged before being given to participants so that all patch materials are identical.

Cue-Reactivity sessions. In the week following the study drug induction phase there will be 2 cue-reactivity sessions, which will be at least 24 hours apart but less than 72 hours apart. The first cue-reactivity session will take place 8 days (+ 2 day window) after the randomization visit. Both 1 hour cue-reactivity sessions will begin following 6 hours smoking abstinence. Participants will provide breath and saliva samples. To verify smoking abstinence, the breath CO level must be less than 60% of the highest CO measurement obtained from either the screening session or training session. Subjective and behavioral responses will be assessed in two separate laboratory sessions—one involving reactivity to personal smoking environment cues; the other reactivity to personal nonsmoking environment cues (order randomly assigned and counterbalanced). Following CO assessment, participants will be seated in front of a computer monitor. Participants will be video recorded using a handheld recorder during the session to gather data about their smoking behavior. They will be instructed that throughout the session pictures of places will appear on the screen and they are to focus intently on the environment they see in front of them. The cue-reactivity (CR) sessions will be computer automated: participants will 1) complete on-screen assessments of craving and mood 2) view personal smoking or nonsmoking environment cues, and 3) complete assessments a 2nd time. Following completion of the 2nd assessment, participants will be instructed to watch the slides and concentrate on their content, followed immediately by a screen stating that “At any time from this point on, you may smoke as much as you like until the end of the session. You do not have to smoke if you choose not to.” The environment cues will then be presented for the next 12 minutes. During this ad lib smoking period, choice to smoke, latency to first puff and other smoking topography will be collected while the participant focuses on the picture cues. Following the ad lib period, a prompt to complete assessments will again appear. During the task, heart rate and respiration will be measured using a BIOPAC system.

Metria IH1- Participants will have the option of wearing a physiological sensor for one week following the cue-reactivity 2 session. Metria IH1 is a disposable, wearable device that is applied directly to the skin of the left upper arm and enables the collection of up to seven days of physiological data. The Metria IH1 has 4 sensors: 1) 3-axis accelerometer 2) Skin Temperature 3) Near Body Temperature and 4) Galvanic Skin Response. The device will be applied to the participant by a member of the study staff in order to ensure proper placement and use. Participants can shower and exercise with the device but cannot submerse the device in water. After seven days of continuous use, data will then be uploaded to

a computer in the lab via a mini-USB port. Participants will receive $10 for wearing the device for one week.

At the end of the second cue-reactivity session, participants will complete a short computer task about time spent in each personal smoking and non-smoking location. Participants will complete the same task once again at end of their 1 week post-quit lab visit.

Breath alcohol levels will be assessed prior to each cue-reactivity session and participants must record a BAL of 0.0. Participants who test positive for alcohol will be excluded from participation that day and asked to reschedule. Participants testing positive for alcohol on more than one occasion will be excluded from the study.

Lab Visits: Four lab visits will be conducted during the 10 weeks following the quit day. The visits will take place 1 week, 3 weeks, 6 weeks and 10 weeks post quit day. These visits will be largely identical except that instructions and reminders to participants about upcoming events will vary from session to session. At each lab visit the following will be collected: vitals (heart rate, blood pressure and weight); breath CO and saliva samples for characterizing smoking/nicotine consumption; and measures of smoking withdrawal and mood. Depending on group and session, participants will also be provided with patches and medications and instructions for using them. Advice on quitting and minimal support will be provided as requested at these visits. Each lab visit will require 20-30 minutes of participant time.

6 month Follow-Up phone call. Participants will be contacted by phone 6 months after completing the study to complete a brief interview about current smoking status and nicotine dependence.

DATA ANALYSIS

Reactivity variables (craving, latency to smoke, and smoke intake) will be entered into 3 (Study drug: NRT, VAR, PLAC) x 2 (Environment: smoking, nonsmoking) x 2(Time) repeated measures ANOVAs with random-effects. We hypothesize that personal smoking, as compared to nonsmoking environments, will be associated with greater reactivity (i.e. increased craving and smoke intake; decreased latency to smoke). A Medication x Environment X Time interaction will be characterized by decreased reactivity to smoking as compared to nonsmoking environments in the VAR and NRT groups as compared to the PLAC group.

RISK/BENEFIT ASSESSMENT

Blood drawing: Momentary discomfort and/or bruising can occur; infection, excess bleeding, clotting or fainting are possible although unlikely.

Needle stick: There will be mild, momentary pain associated with the needle stick for the needle placement. There is a minimal risk of bruising, bleeding and mild discomfort associated with the needle stick. A small risk of infection at the site of the needle stick can also occur. The use of clean techniques should keep this risk low.

Concomitant smoking and NRT. The currently approved package insert for Nicoderm CQ no longer warns against concurrent use of the patches and cigarette smoking. Thus, we do not believe there are additional health risks associated with the concurrent use of these products above smoking cigarettes alone.

Nicotine Patch. Insomnia and abnormal dreams are common and expected side effects associated with

24 hour nicotine patches. If a subject complains of disturbed sleep, he or she will be instructed to remove the patch at bedtime and apply a new one the next day at the usual time. Skin irritation may occur, although this will be minimized by changing the site of patch application daily. Using 1% hydrocortisone cream on the affected area will be recommended to help reduce skin irritation. If a subject develops itching or a rash at the patch site, he or she will be advised to use 1% hydrocortisone cream on the affected area. Symptoms associated with nicotine toxicity include, lightheadedness, dizziness, nausea, fainting and vomiting. Symptoms considered moderate to severe in nature will be evaluated by the study medical staff by telephone or in person, depending upon the level of severity. Upon evaluation, the subject will then be given the choice of continuing in the study while discontinuing patch use.

Varenicline. The main side effects accompanying use of varenicline (Chantix®) are nausea, vomiting, gas, insomnia, and vivid dreams. If troublesome symptoms occur, the dose may be reduced to 1 mg daily (discontinuing the second dose) or discontinued altogether. Rarely, more serious side effects can occur including changes in behavior, hostility, agitation, depressed mood, suicidal thoughts and behavior, and attempted suicide. Participants will be asked about these symptoms at each visit and the study physician will be called in to evaluate the participant if any are endorsed. Until patients know how Chantix affects their ability to tolerate alcohol, they should decrease the amount of alcohol they drink. Patients who have a seizure while taking Chantix should stop the medicine and seek medical attention immediately. At randomization, participants will be given the "Medication Guide" that accompanies prescription Chantix. This information will be reviewed with the participant by study staff and participants will be encouraged to contact study staff upon experiencing any changes in behavior. As is standard in our protocols, all participants will have access to the PI's cell phone number and the study physician's pager number.

Women of childbearing potential: Pregnant or nursing women will be excluded from the study. Female participants will undergo a serum pregnancy test at screening. Subjects must also agree to use appropriate contraception during the course of the trial. They will be encouraged in the consent form to notify study staff if they believe a change in their pregnancy status has occurred during the trial.

Management of side effects: Reports of side effects will be obtained by study staff and communicated to the principle investigator and study physician, who will determine the most appropriate course of action, which may include options for termination of study participation. Participants will be reminded of their option to withdraw from the study at any time. If a participant decides to withdraw from the study, we will ask them to return for a final visit to return all study materials. Because all subjects will receive either placebo patches or placebo tablets/capsules, in the event of significant side effects it will be necessary to reduce both patch and oral dosing concomitantly in order to preserve the double blind while ensuring a dose reduction in the active treatment. In response to complaints of insomnia, instructions will be given to remove skin patches at bedtime and discontinue the second daily dose of oral medication. In the event of other intolerable side effects, both patch and oral medications will be discontinued completely

PARTICIPANT RECRUITMENT AND COMPENSATION

We will advertise in local newspapers, the radio, flyers on bulletin boards and on the internet (including but not limited to trianglesmokingstudies.com and craigslist). When we receive calls from potential subjects we will return their call and ask information including name, address, age, and smoking history. Potential subjects may also complete an on-line Qualtrics screening survey accessed from our website. They will be given a brief description of our studies and will be asked questions to determine interest and eligibility. If they do qualify we will schedule a screening session where we will follow all IRB protocols of informed consent.

Participants will receive $10 at the screening session if they pass the drug test, breath alcohol test and CO test. Individuals who do not pass these tests will be dismissed from the screening visit without payment, except in the event they can produce a current, valid prescription for the medication that caused them to fail the drug test. Participants will also receive $25 for completing the training session, $25 for the camera return/randomization visit plus $25 in cash if they returned complete and useable photos within one week of the training session, $50 for each cue-reactivitysession ($100 total), $30 for each post-quit lab visit ($120 total) and a $100 at the end of the study if they complete all sessions (up to $405 total). Participants may also earn $2 each day they complete the Qualtrics surveys on time (up to $196) and $10 for completing a 6 month post quit date follow-up phone call. Participants will also earn up to $10 for wearing the Metria device if they choose to participate in this part of the study. Participants that decide to withdraw from the study before fulfilling all of the requested tasks will be given compensation for each session completed.

DATA AND SAFETY MONITORING

The Principal Investigator will report all serious adverse events and unanticipated findings and problems relating to the study in an expedited manner to the Duke University Health System (DUHS) Institutional Review Board (IRB) office and all applicable regulatory authorities in accordance with standard operating procedures.

COSTS TO PARTICIPANTS

There are no costs to participants for taking part in this study. All the study costs, including any procedures related directly to the study, will be paid for by the study.

DATA STORAGE AND CONFIDENTIALITY

Participants will be informed, in their consent forms, of the data storage and confidentiality safeguards, which are practiced according to current HIPAA regulations.

Except when required by law, the participant will not be identified by name, social security number, address, telephone number or any other direct personal identifiers in the study records.

All photographic images acquired by participants will be reviewable by participants prior to upload to the secure server. Data from the server can only be accessed by authorized study staff with a username and password. All photographs of private locations taken by participants will be destroyed by the PI or CRC upon completion of the study. Photographs that include persons not known to subject will be deleted. The participant will be assigned a unique code number and the key to the code will be kept in a locked room accessible to the study coordinator.

Blood samples coded with participant number, initials and birth year will be sent to LabCorp, 1447 York Ct., Burlington, N.C. 27215 for blood chemistry and serum pregnancy testing. LabCorp work order #37 outlines the agreement for this protocol.

Dr. Cynthia Conklin at UPMC will be a collaborator for the study. She is listed as outside key personnel and will not have access to any study PHI or identifiable information.