PENNSTATE

HRP-592 - Protocol for Human Subject Research with Use of Test Article(s)

Protocol Title:
Pharmacokinetics of Nicotine Film in Smokers

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Version Date:
1/26/17

Clinicaltrials.gov Registration #:
NCT02239770

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1.0 Objectives

1.1 Study Objectives

The objective of this study is to test the effect of a range of doses of a novel nicotine film on plasma nicotine levels and, via a questionnaire, subjective ratings of the film and side effects. We predict that delivery of nicotine via the film will produce plasma nicotine levels akin to other methods of nicotine replacement therapy (NRT) and that it will be easy to use, safe, and well tolerated. The nicotine film is not part of standard of care and is not available in a non-investigational setting in the United States.

1.2 Primary Study Endpoints

The primary endpoint is plasma nicotine.

1.3 Secondary Study Endpoints

The secondary endpoint is subjective ratings of the film and side effects in order to determine whether blood levels are of significant magnitude for the participant to detect drug effects.

2.0 Background

2.1 Scientific Background and Gaps

According to the CDC, cigarette smoking is associated with profound morbidity and mortality. In the United States alone, cigarette smoking is responsible for about 443,000 deaths per year and it costs the nation nearly $200 billion annually. About 20% of all adults smoke in the United States and by 12th grade, 42% of students report having smoked. Starting, however, is one problem and stopping is another. Cigarette smoking is a disease of chronic relapse. Indeed, once having started, smokers will make as many as 20 quit attempts before they are successful [1] and abstinence rates can be as low as 7%, even following NRT with the patch, gum, or nasal spray [2]. As with other addictions, cue-induced craving contributes to relapse following a quit attempt [3]. Along with cue-induced craving and relapse, addicts also suffer from drug-induced devaluation of natural rewards, as evidenced by less responding for a sweet in anticipation of the availability of drug in rats [4] and weaker responses to monetary rewards in striatum (a key brain reward region) in humans waiting to smoke [5, 6]. Importantly, those subjects (rats and humans) found least responsive to the natural reward are, in turn, most responsive to drug [4, 7].

From a global perspective, it would seem that there are three options for the treatment of cigarette smoking: no support (unaided cessation), behavioral support of one manner or another, and/or pharmacological intervention. With nearly 70% of smokers reporting that they would like to quit, yet most failing, we must assume that will, alone, is not sufficient. Certainly, the ability to quit any addiction can be bolstered by behavioral and/or pharmacological support. Contingency management is a behavioral intervention where abstinence is reinforced with tangible incentives such as money. However, and as alluded to, addicts may be insensitive to the very reward upon which their behavior is contingent. NRT is a long-standing and widely used smoking cessation tool. Yet, as discussed, NRT too is only modestly effective. We propose that the limited effectiveness of NRT is due, at least in part, to a failure to prevent cue-induced craving and relapse and to a failure to attenuate drug-induced devaluation of natural rewards. In support, NRT treatment does not attenuate either stimulus-elicited drug seeking [8] or the reduction in reward-related activity in the striatum of smokers [9]. Here we propose a novel alternative to the steady-state delivery of nicotine (i.e., to the standard patch) for the treatment of smoking cessation. Specifically, we propose to use an oral film to treat smokers wishing to quit with random, rather than steady-state, delivery of nicotine prior to and following the quit date.

2.2 Previous Data

Support for our random delivery hypothesis is provided by both preclinical and clinical data suggesting that yoked (i.e., uncontrollable/unpredictable) delivery of drug impairs the development of cue-drug associations, retards or disrupts responding for drug or alcohol, and can even render the drug aversive. In rats, yoked delivery of ethanol retarded later acquisition of ethanol self-administration [10] and, in our hands, a history of yoked delivery of cocaine [11] disrupted the willingness to work for the drug on a progressive ratio schedule of reinforcement. Although fixed ratio (FR) responding appears normal in rats with a history of yoked delivery of cocaine, the averaged data occlude the fact that rats yoked to high drug-takers actually took only about 4 infusions/hour on the FR schedule. To be effective, however, yoked delivery of drug needs not only delay acquisition in drug inexperienced rats, but must effectively rescue subjects with a strong drug habit. In accordance, Twining and Mueller (in preparation) found that yoked delivery of cocaine rescued cocaine-experienced rats by reducing drug seeking during extinction and by reducing drug-taking during subsequent FR testing. In humans, Donny et al. [12] reported that yoked delivery of cocaine led to an increase in mean systolic and diastolic

blood pressure in response to the drug because of a lack of cue-supported tolerance. Scheduled availability of ethanol led to a marked decrease in intake of ethanol in a controlled setting [13]. Finally, a meta-analysis showed that pre-cessation treatment with a standard (i.e., steady state) nicotine patch doubled the odds of quitting smoking relative to subjects that received only post-cessation treatment with the nicotine patch ([14] but see [15, 16]). Rose and Behm [17], too, found abstinence enhanced by pre-cessation treatment with the nicotine patch and, in an early study, Foulds reported that use of the nicotine patch while smoking led to a 14% reduction in expired carbon monoxide (CO), reduced satisfaction from smoking, and fewer and weaker reported urges to smoke [18]. These marked effects are thought to be due, at least in part, to separation of blood nicotine levels from the act of smoking [16]. Dissociation of smoking behavior and cues from nicotine is expected to be even greater with random nicotine delivery.

2.3 Study Rationale

There is, as yet, no 'random patch'. Random delivery via a subcutaneously placed chip or pump is conceivable, but would be invasive and expensive. Here we propose to test the merits of our hypothesis, simply, by using an oral transmucosal dual-layer film that has been tested and is safe for use in humans [19, 20]. Plasma nicotine levels induced by the nicotine film are on par with those that accompany consumption of a similar dose of Nicorette gum. Preliminary pharmacokinetics studies found that 1mg films increased plasma nicotine levels by less than 2 ng/ml [21]. It has been demonstrated that smokers in a typical smoking day can reach plasma nicotine levels of up to 50 ng/ml [22]. The manufacturer of the film, Dr. Hock Tan, states that the 4mg film has been tested for taste in human nonsmokers and to the best of his knowledge was well-tolerated. Dr. Tan, as a nonsmoker, has also taken an 8mg film without experiencing any ill effects. The film is easy to use and tastes pleasant to humans. No water is required, as the film simply adheres to the roof of the mouth until dissolved (about 5-10 min). Indeed, unlike nicotine gum, there are no complicated instructions regarding how and when to chew. The film can be used to deliver any dose of nicotine desired over time and placebo films are readily available. Finally, if the hypothesis proves correct, this novel treatment should be fairly inexpensive and available over the counter. As such, it will be both accessible and affordable, even for low-income smokers.

If this 'random film' were to work as predicted, cigarette cues would be dissociated from the act of smoking, sensitivity to alternative natural rewards would be enhanced and, most importantly, smokers maintained on the random film would be more likely to achieve cessation. This would be a remarkable advance for the treatment of smoking and would inform the treatment of other addictions as well.

3.0 Inclusion and Exclusion Criteria

3.1 Inclusion Criteria

1. Aged 18 - 55
2. Smoke >9 cigarettes/day for at least the past 12 months
3. Able to understand and consent to study procedures
4. Able to read and write in English
5. Exhaled Carbon Monoxide <12 ppm at in-person screening

3.2 Exclusion Criteria

1. Unstable or significant medical conditions and conditions such as elevated blood pressure (Systolic >140 mm Hg or Diastolic >90mm Hg at baseline), COPD and those that are likely to affect biomarker data such as kidney or liver disease.
2. Individuals with sodium-restricted diet, heart disease, recent heart attack, irregular heartbeat, stomach ulcers, or diabetes as well as those taking prescription medications for depression or asthma as indicated under "Warnings" section on FDA approved NRT Drug Facts Label.

3. More than weekly use in the past 3 months of illegal drugs or prescription drugs that are not being used for medically prescribed purposes or inpatient treatment for these in the past 6 months
4. Use of non-cigarette nicotine delivery product in the prior week (including cigars, pipes, chew, snus, hookah, electronic cigarette and marijuana mixed with tobacco)
5. Use of an FDA approved cessation medication in past week (any NRT, Chantix, Wellbutrin)
6. Women who are pregnant (verified by urine pregnancy test at visit), trying to become pregnant (not using a medically acceptable form of birth control for at least one month prior to visit i.e.: oral contraceptives, intrauterine device, double barrier), or nursing.
7. Uncontrolled serious psychiatric illness or inpatient treatment in the past 6 months
8. [23].
9. Unwillingness to provide blood samples or history of repeatedly fainting during blood draws
10. Any previous adverse reaction to NRT.
11. Any other condition, serious illness, or situation that would, in the investigator's opinion, make it unlikely that the participant could comply with the study protocol.

3.3 Early Withdrawal of Subjects

3.3.1 Criteria for removal from study

Participation may be discontinued if the principal investigator (PI) determines it is the best decision in order to protect the safety of a participant. The participant may be removed from the research study without his or her permission because the participant does not follow the instructions for the study, has an adverse reaction to the study product (irregular heartbeat, palpitations, tachycardia (resting heart rate persistently greater than 100 beats per minute), has symptoms of nicotine overdose such as nausea, vomiting, dizziness, weakness, or rapid heartbeat, or has symptoms of an allergic reaction.

3.3.2 Follow-up for withdrawn subjects

N/A

4.0 Recruitment Methods

4.1 Identification of subjects

All recruitment for this study will be routed through IRB STUDY00002213 which will also serve as the initial recruitment point of contact.

4.2 Recruitment process

Interested volunteers calling the study center number will first complete the eligibility script and questions for IRB STUDY00002213. If a participant's responses match our study's specified inclusion criteria they will be forwarded to the study coordinator for further screening.

4.3 Recruitment materials

See IRB STUDY00002213.

4.3.1 Eligibility/screening of subjects

Screening 1 (Phone): We will consider the screening process and eligibility questions in IRB STUDY002213 as Screening 1. Then, participants will complete the screening process in two additional steps.

Screening 2 (phone): A full script and screening questions for this study are in the "Consent Forms and Recruitment Materials" section of the IRB application.

Screening 3 (In person): After a participant has met basic eligibility criteria over the phone, they will be scheduled to come in to the study center where they will be

consented to the study and further screened for eligibility. See section 7.2 for further details.

5.0 Consent Process and Documentation

5.1 Consent Process

5.1.1 Obtaining Informed Consent

There will be separate consent forms for Part 1 and Part 2 of the study. Part 1 will accrue 12 participants after which it will be closed to enrollment and participants will only be able to enroll in Part 2, which will also accrue 12 participants. Part 2 will not be open to enrollment until Part 1 is complete. Participants will be informed of the part of the study that is currently open for enrollment.

5.1.1.1 Timing and Location of Consent

When participants attend their visit, they will have the appropriate part (1 or 2) of the study explained to them in detail, have the opportunity to ask questions and then will be asked to sign the appropriate consent form. Participants will be given a signed copy of the form. This will take place in a private clinic room at the Penn State Clinical Research Center (CRC).

5.1.1.2 Coercion or Undue Influence during Consent

Recruitment materials for the study will be broadly distributed throughout the community. Once participants contact the study center, they will be given information about the study and offered the opportunity to participate. The researchers obtaining consent will be instructed to clearly indicate that the participant's enrolling in the trial is purely voluntary and the researchers will not offer comments about whether they believe the participant should enroll in the study or not. Compensation provided to the participant for the study is modest.

5.1.2 Waiver or alteration of the informed consent requirement

N/A

5.2 Consent Documentation

5.2.1 Written Documentation of Consent

An IRB approved consent form will be used to document consent. Both the researcher and the participant will retain a copy of the consent. .

5.2.2 Waiver of Documentation of Consent

Participants who are interested in the study will be asked to consent to allow the researcher to pre-screen them for the study by asking all screening questions of all participants (eligible or ineligible). Participants will be asked if this information can be retained so that the study team will know reasons that participants are not eligible for the study.

In addition, participants who are not eligible for the study, or those who begin the phone screener but are not interested in completing it after learning more about the study, will be asked if they would be interested in being contacted for future studies being conducted by our research team. They will be informed that by providing their name and phone number, they will be consenting to allow the study team to contact them in the future.

5.3 Consent – Other Considerations

5.3.1 Non-English Speaking Subjects
N/A

5.3.2 Cognitively Impaired Adults
N/A

5.3.2.1 Capability of Providing Consent
N/A

5.3.2.2 Adults Unable To Consent
N/A

5.3.2.3 Assent
N/A

5.3.3 Subjects who are not yet adults (infants, children, teenagers)

5.3.3.1 Parental Permission
N/A

5.3.3.2 Assent
N/A

6.0 HIPAA Research Authorization and/or Waiver or Alteration of Authorization

6.1 Authorization and/or Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

Check all that apply:

- **X** Authorization will be obtained and documented as part of the consent process.
- ☐ Partial waiver is requested for recruitment purposes only
- ☐ Full waiver is requested for entire research study
- **X** Alteration is requested to waive requirement for written documentation of authorization

6.2 Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

6.2.1 Access, use or disclosure of PHI representing no more than a minimal risk to the privacy of the individual

6.2.1.1 Plan to protect PHI from improper use or disclosure
All data collected during the screening process will be directly entered into REDCap on a password protected, IT maintained, encrypted computer..

6.2.1.2 Plan to destroy identifiers or a justification for retaining identifiers
All study data will be retained indefinitely. Paper records will be kept in a safe area in Dr. Grigson's locked research office.

6.2.2 Explanation for why the research could not be practicably be conducted without access to and use of PHI
N/A

6.2.3 Explanation for why the research could not practicably be conducted without the waiver or alteration of authorization

In order to screen the participants prior to inviting them into the study center, the investigators are conducting a phone screen to determine if the participants are likely to be eligible for the study.

6.3 Waiver or alteration of authorization statements of agreement

Protected health information obtained as part of this research will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other permitted uses and disclosures according to federal regulations.

The research team will collect only information essential to the study and in accord with the 'Minimum Necessary' standard (information reasonably necessary to accomplish the objectives of the research) per federal regulations.

Access to the information will be limited, to the greatest extent possible, within the research team.

All disclosures or releases of identifiable information granted under this waiver will be accounted for and documented.

7.0 Study Design and Procedures

7.1 Study Design

This will be a randomized, double blind, parallel group pharmacokinetics study that will occur in two parts. The researchers and participants will be blind to the dosing of the nicotine films. Participants may participate in one or both parts of the study.

Part I: Participants are randomized to receive one dose of 0, 2, or 4 mg nicotine films
Part II: Participants are randomized to receive one dose every three hours for a total of four doses of either all 0 mg, all 2 mg or 4,4,0,4 mg nicotine films.

7.2 Study Procedures

Part 1- Screening (Phone)
Participants will be instructed to drink water prior to their visit to help the blood draw process go smoothly. They will also be instructed that they may choose to have a meal from our cafeteria but may also bring snacks if they would like. Participants will also be informed that they can bring personal items such as laptops, books, etc. for use during their visit.

Part 1-Screening (In Person)
Participants will be re-screened for eligibility and informed consent for the appropriate part of the study will be obtained by research staff.

After consent, additional eligibility screening materials will include:

1. A review of medications and medical history
2. NIDA Drug Screener
3. Blood Pressure (systolic must be $\leq$140, diastolic must be $\leq$ 90)
4. Urine pregnancy test (if applicable)
5. Exhaled Carbon Monoxide <12 ppm

Part 1 Visit – 4 Hours

Clinical measures and questionnaires will be conducted as outlined in the table below. An IV will be inserted for access for 11 blood draws in Part 1.

Part 1: Time and Events Table						
	Screening	**Part 1 Procedures**				
Visit Hour	-2	-1	0	1	2	3
Administer Film			X			
Blood Draws (mins)			0-59	60-119	120-179	180-239
Baseline Blood		X				
Hour 0 Blood			Set Minutes: 5, 10, 20,30, 40, 50 Varied by Participant: 1 minute after film dissolves			
Hour 1 Blood				Minute 60		
Hour 2 Blood					Minute 120	
Hour 3 Blood						Minute 180
Measures						
Screener 2	X					
Concomitant Meds	X					
Medical History	X					
NIDA	X					
CES-D		X				
Oropharyngeal Exam		X				X
Blood Pressure & Heart Rate	X	X	Minute 30	Minute 0, 30	Minute 0, 30	Minute 0, 30
CO Reading	X					X
Pregnancy Test	X					
Anthropometrics		X				
Demographics		X				
Nicotine Dependence		X				
Cigarette Details		X				
Tobacco Use History		X				
Minnesota Withdrawal Scale		X	Minute 15, 35, 55	Minute 20	Minute 20	Minute 20
Questionnaire of Smoking Urges		X	Minute 15, 35, 55	Minute 20	Minute 20	Minute 20
Study Product Side Effects			Minute 15, 35, 55	Minute 20	Minute 20	Minute 20
Study Product Evaluation						X
Likelihood of Use Scale						X
Payment						$120

Film Administration, Dose and Blood Draws:
Participants will receive one film at this visit after completing baseline measures (approximately 8 AM). They will be instructed to allow the film to dissolve in their mouth without chewing or swallowing it and to report to the researcher when he or she feels that the film has completely dissolved. Four participants each will receive a randomly allocated dose of either (a) 0mg, (b) 2mg or (c) 4mg oral nicotine film. The Time and Events table above details the order of events and timing for biomeasures, questionnaires and 11 total blood draws. However, if the film dissolves within one minute of a set blood draw time, the blood draw that is to be completed one minute after the film dissolves will be omitted.

Payment:
Participants will receive $120 for completing this visit.

Part 2- Screening (Phone)
Participants will be instructed to drink water prior to their visit to help the blood draw process go smoothly. They will also be instructed that they may choose to have meals from our cafeteria but may also bring snacks if they would like. Participants will also be informed that they can bring personal items such as laptops, books, etc. for use during their visit.

Part 2- Screening (In Person)
Participants will be re-screened for eligibility and informed consent for the appropriate part of the study will be obtained by research staff.

After consent, additional eligibility screening materials will include:

1. A review of medications and medical history
2. NIDA Drug Screener
3. Blood Pressure (systolic must be $\leq$140 mm Hg, diastolic must be $\leq$90 mm Hg)
4. Urine pregnancy test (if applicable)
5. Exhaled Carbon Monoxide <12 ppm

Part 2 Visit- 12 hours

Clinical measures and questionnaires will be conducted as outlined in the table below.
An IV will be inserted for access for 20 blood draws in Part 2. Time and contents of participant meals/snacks will also be recorded so as to enable researchers to assess food intake and timing as it relates to timing of nicotine absorption from the film.

Part 2: Time and Events Table														
	Screening	**Part 2 Procedures**												
Study Hour	-2	-1	0	1	2	3	4	5	6	7	8	9	10	11
Administer Film			X			X			X			X		
Blood Draws														
Baseline Blood		X												
Hour 0 Blood			Min 30, 45											
Hour 1 Blood				Min 0										
Hour 2 Blood					Min 0									
Hour 3 Blood						Set Mins: 0, 30, 45								
Hour 4 Blood							Min 0							
Hour 5 Blood								Min 0						
Hour 6 Blood									Set Mins: 0,30,45					
Hour 7 Blood										Min 0				
Hour 8 Blood											Min 0			
Hour 9 Blood												Set Mins: 0, 30,45		
Hour 10 Blood													Min 0	
Hour 11 Blood														Min 0
Study Hour	-2	-1	0	1	2	3	4	5	6	7	8	9	10	11
Measures														
Screener 2	X													
Concomitant Medications	X													
Medical History	X													
NIDA	X													
CES-D		X												
Oropharyngeal Exam		X												X
Blood Pressure & Heart Rate	X	X	Min 30	Min 0, 30	Min 0, 30	Min 0, 30	Min 0, 30	Min 0, 30	Min 0, 30	Min 0, 30	Min 0, 30	Min 0, 30	Min 0, 30	Min 0
CO Reading	X													X
Pregnancy Test	X													
Anthropometrics		X												
Demographics		X												
Dependence		X												
Cigarette Details		X												
Tobacco Use History		X												
Minnesota Withdrawal Scale		X	Min 50	Min 50		Min 50	Min 50		Min 50	Min 50		Min 50	Min 50	

Questionnaire of Smoking Urges		X	Min 50	Min 50		Min 50	Min 50		Min 50	Min 50		Min 50	Min 50	
Study Product Side Effects			Min 50	Min 50		Min 50	Min 50		Min 50	Min 50		Min 50	Min 50	
Study Product Evaluation						Min 0								X
Likelihood of Use Scale						Min 0								X
Dose Awareness														X
Payment														$240

Film Administration, Dosing and Blood draws:
Participants will receive four doses of nicotine film during this visit. Four participants each will be randomly allocated to consume four films over twelve hours in the following orders (a) 0,0,0,0mg (b) 2,2,2,2, or (c) 4,4,0,4. The first film will be administered upon completion of baseline measures (approximately 8AM). Again, participants will be instructed to allow the film to dissolve in their mouth, without chewing or swallowing it and to report to the researcher when he or she feels that the film has completely dissolved. Films will be administered every three hours (approximately 11 AM, 2 PM, and 5 PM). The Time and Events table above details the order of events and timing for biomeasures, questionnaires and 20 total blood draws.

Payment:
Participants will receive $240 for completing this visit.

7.3 Duration of Participation

Duration of participation is dependent on which part of the study the participant is enrolled in. The study visit for Part 1 will last approximately four hours. The study visit for Part 2 will last approximately twelve hours.

7.4 Test Article(s) (Study Drug(s) and/or Study Device(s))

7.4.1 Description

Nicotine orally dissolving films (ODF) will be provided in doses of 0, 2, or 4 mg. The active pharmaceutical ingredient in Nicotine ODF is nicotine polacrilex (20%, USP). The film used in Nicotine ODF has a muco-adhesive property, i.e. it can adhere to the oral mucosa and allow the drug to be absorbed through oral mucosa. After placement in the oral cavity, nicotine ODF dissolves over a 5-10 minute period. The unit-dose dosage is in the form of a 1 in x 1 in square and weighs about 100 mg. Nicotine films are not available in the United States in a non-investigational setting. See table below for composition information.

Nicotine Oral Film Formulations: 0, 2, and 4 mg

Nicotine ODF Dosage		Placebo, 0 mg	2 mg	4 mg
Material Name	Grade	Weight, g		
Sodium Bicarbonate	USP/EP	1.97	1.71	1.64
Propylene Glycol	USP/EP	23.66	20.55	19.68
Nicotine Polacrilex 20%	USP	0.00	17.81	37.72
Purified Water	USP	209.04	205.45	196.80
Ethanol anhydrous	USP	110.44	119.85	114.80

Polyox N10 (Polyethylene oxide)	NF	134.10	116.42	111.52
Saccharin	Food Grade	2.45	2.12	2.03
Cocoa Powder	Food Grade	1.77	1.71	1.97
L-Menthol	USP	9.98	8.66	8.30
Peppermint oil	USP	6.19	5.38	5.15
Methylparaben	NF	0.20	0.17	0.20
Propylparaben	NF	0.20	0.17	0.20
Total		500.00	500.00	500.00

7.4.2 Treatment Regimen

Nicotine films will be administered orally. They are used by placing a film on the tongue, closing the mouth and pressing the tongue gently to the roof of the mouth. The film will dissolve in the mouth within 5-10 minutes. Three doses of nicotine film will be used in this study: 0, 2, and 4 mg. During the first part, participants will receive one dose of either 0, 2, or 4 mg film. After the first part is complete, reactions to dosing will be evaluated and adjustments will be made if necessary before proceeding to the second part. Should adjustments need to be made, modified protocol and consent documents will be submitted to the IRB prior to proceeding to Part 2. During the second part, participants will receive four doses of nicotine film at three hour intervals over the course of twelve hours. There will be three dosing groups and four participants each will receive all 0 mg films, all 2 mg films, or a sequence of 4,4,0,4 mg films.

7.4.3 Method for Assigning Subject to Treatment Groups

Participants will be randomized to one of three dosing groups based on a pre-determined random number sequence generated by the study statistician, Dr. Junjia (Jay) Zhu.

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7.4.4 Subject Compliance Monitoring

Subjects will remain on-site for the duration of each visit and will be given the study product by the researcher who will monitor that the dose was taken as directed.

7.4.5 Blinding of the Test Article

Blinded packages of the test article will be created for each participant prior to their arrival by an unblinded study staff member. Both the participant and the researcher administering the film will be blinded to the dose of the test article.

7.4.6 Receiving, Storage, Dispensing and Return

7.4.6.1 Receipt of Test Article

The test article will be manufactured by Bionex Pharmaceuticals LLC in its North Brunswick, NJ, facility under cGMP conditions, and shipped directly from Bionex to Penn State Hershey. The packaged test article has been tested to be stable at temperatures up to 30°C for 12 months, and therefore will be shipped via courier under room temperature.

Each film (test article) will be individually contained in a sealed, chemical- and moisture-resistant multi-component (polyester/aluminized) laminated pouch. Number of pouches, cartons, and labeling information, will be made according to the Clinical Trial Protocol.

7.4.6.2 Storage

The nicotine films will be stored in the Investigational Drug Pharmacy at Hershey Medical Center in accordance with guidelines provided by the manufacturer.

7.4.6.3 Preparation and Dispensing

The test article will be randomized by an unblinded study team member according to the randomization code created by the study statistician. The study treatment will be administered by blinded study staff who will provide each dose of the study product to the blinded researcher.

7.4.6.4 Return or Destruction of the Test Article

Any remaining study product will be destroyed at the end of the study.

7.4.6.5 Prior and Concomitant Therapy

A medical history and evaluation of all concomitant medications will be reviewed prior to participant starting the study. Participants currently using FDA approved cessation medications will be excluded.

8.0 Data and Specimen Banking For Future Undetermined Research

After the blood is analyzed, it will be destroyed.

8.1 Data and/or specimens being stored

N/A

8.2 Location of storage

N/A

8.3 Duration of storage

N/A

8.4 Access to data and/or specimens

N/A

8.5 Procedures to release data or specimens

N/A

8.6 Process for returning results

N/A

9.0 Statistical Plan

9.1 Sample size determination

Initial testing by Dr. Tan (a principal investigator on the project and co-inventor of the oral nicotine film) has demonstrated that the plasma nicotine levels produced by oral nicotine film are comparable in size to those produced by consumption of a similar dose of Nicorette gum. Pharmacokinetic studies have shown that Nicorette gum has robust effects on plasma nicotine concentration that are readily detectable in sample sizes that are approximately the same as (e.g., Benowitz, Jacob, & Savanapridi, 1987; Lunell & Lunell, 2005), or smaller than (e.g., Shiffman et al., 2009), the one proposed here (n=12). Based upon such work, we are confident that we will have sufficient power to achieve the aim of the proposed research.

9.2 Statistical methods

Paired sample t-test (or nonparametric Wilcoxon Rank-Sum test) will be used to examine the changes in the outcome measures (plasma nicotine, subjective measures, HR, BP) from the baseline.

10.0 Confidentiality, Privacy and Data Management

10.1 Confidentiality

All study data will be collected and managed using REDCap (Research Electronic Data Capture). REDCap is a secure web application designed to support data capture for research studies, providing user-friendly web-based case report forms. REDCap is HIPAA compliant. Data are stored on a secure server at Hershey Medical Center and data in REDCap are encrypted. Access to the database requires authentication (a unique username and password) and a user matrix will be used to ensure that only appropriate data are accessed based on the individual's role on the project. Every interaction with the data is logged in REDCap creating an audit trail.

10.1.1 Identifiers associated with data and/or specimens

The following personal identifiers will be collected:

- Name
- Address
- Phone numbers
- Email addresses
- Date of birth
- Social security number

10.1.1.1 Use of Codes, Master List

All study data will be collected in REDCap including a participant record number and a study specific code number. The list connecting the participant data to the code numbers will be stored electronically in REDCap and will not be destroyed. The PIs, Study Coordinators, Research assistants and Lab Manager will have access to the list.

10.1.2 Storage of Data and/or Specimens

- **Electronic data:**
  - Your research records will be labeled with a code number and will be kept indefinitely in a secure Research Electronic Data Capture System (REDCap) on a password protected, IT maintained, encrypted computer in Dr. Grigson's locked research office.
  - A list that matches your name with your code number will be kept in a password protected electronic file.
- **Paper records:**
  - Your paper records (e.g. consent forms) will be kept in a safe area in Dr. Grigson's locked research office Paper records may also be scanned and uploaded into participant records in REDCap. Paper will be retained until the end of the study after which it will be destroyed.
- **Specimens:**
  - Specimens will be stored with a code number attached.
  - Prior to processing, samples will be placed in a refrigerator by the study nurse, research assistant or study coordinator in the key-card secured lab on the third floor of the Cancer Institute.

- Within 24 hours, samples will be processed by a lab manager and will then be secured in a freezer located in a locked room within the research laboratory on the 3rd floor of the Cancer Institute.

10.1.3 Access to Data and/or Specimens

Study data in REDCap: Primary study personnel including: Primary Investigators, Study Coordinators, Research Assistants, and the Lab Manager will have access to the REDCap data. However, a REDCap user matrix will limit access to data based on the researcher's role in the study.

Specimens: Only the lab manager will have access to the specimens once they have been processed and secured in the locked freezer room.

10.1.4 Transferring Data and/or Specimens

N/A

10.2 Privacy

The research team will only have access to data that a participant provided during data collection contacts. HIPPA guidelines will be followed for all participants and they will be provided with the institution's written Privacy Notice at their screening visit. Participants will be informed that they can refuse to answer any questions that make them feel uncomfortable. The majority of personal data that the participants provide will be entered directly into REDCap by the participant. All study visits, data collection and procedures will be completed in private consult rooms at the Penn State Hershey CRC.

11.0 Data and Safety Monitoring Plan

11.1 Periodic evaluation of data

The study coordinator will be responsible for the daily oversight of subject safety. The principal investigators, Drs. Grigson, Foulds, and Wilson, will discuss the progress of the study (overall) and review any potential pattern of adverse effects that might indicate any risks or concerns that had not been anticipated when the study was designed. Entrance criteria will be reviewed following screening. Medical history will be reviewed by the research coordinator for any contraindications for the treatment products. Subjects will be under supervision while in the study and seen on an ongoing basis by our research staff who will assess adverse events and make appropriate referrals to a physician. The NIH-funded Penn State Hershey Clinical Research Center has trained nursing staff who are American Cardiac Life Support certified, the CRC has a crash cart on site and the nursing staff is trained in its use. The study physician, Dr. Sciamanna is Board Certified in Internal Medicine and he or his designee will be present on site. In addition the CRC is located in the same building as our Emergency Department, which is a level a Level I Regional Trauma Center, and fully equipped to manage any severe adverse events."

11.2 Data that are reviewed

Data that will be reviewed include:

- Accrual and retention
- Adverse events and serious adverse events
- Protocol deviations/violations
- Changes in subjective effects (particularly dizziness and nausea, the most common nicotine effects)
- Changes in heart rate and blood pressure
- Oropharyngeal changes

11.3 Method of collection of safety information

All data, including safety data, will be coded directly into REDCap electronic case report forms during study visits.

11.4 Frequency of data collection

Safety data will be collected intermittently at each study visit.

11.5 Individual's reviewing the data

The study coordinator will be responsible for the daily oversight of subject safety and will provide updates to the Principal Investigators to review participants' progress and their experiences with the study, including any adverse events.

In the event of adverse event(s) during the conduct of the study, we have a mechanism in place to ensure that the event(s) will be assessed by the Principal Investigators and the study physician and reported to the PSU IRB and NIH in a timely manner. All adverse events (AEs) occurring during the course of the study must be collected, documented, and reported to the Principal Investigators and Dr. Sciamanna, Professor of Medicine and Chief of Division of Internal Medicine at Penn State Hershey,. All AEs will be assessed by the Principal Investigator to determine if they meet criteria for a serious adverse event (SAE). Serious adverse events, as defined by the FDA, will be systematically evaluated at each clinic visit. Any SAE, whether or not related to study participation, will be reported to the IRB, and NIDA. The initial SAE report will be followed by submission of a completed SAE report. Outcome of SAEs will be periodically reported to NIDA. A summary of the SAEs that occurred during the previous year will be included in the annual progress report to NIDA. Each week a study investigator will review the AE Forms from the previous week for events that were reported as new or continuing. The study investigators will follow all AEs to the point of a satisfactory resolution. A study participant may have their participation discontinued if the PI determines it is the best decision in order to protect the safety of a participant.

Where any participant had a serious adverse event (systolic BP>160, vomiting or any other symptoms requiring their participation in the study to be interrupted/terminated), Dr. Chris Sciamanna will immediately review the case and make a recommendation both on management of that individual case but also continuation of the study at the planned doses.

The study leadership group (Drs. Grigson, Foulds, Wilson and Sciamanna) will make appropriate recommendations for changes in protocol, if needed. All product related adverse events of a non-serious nature will be reported to the IRB at the time of renewal. Serious adverse events will be reported by telephone to the IRB within the 2 business days of our receipt of information regarding the event and written reports will be submitted within 10 days. The study leadership group will review all serious or unexpected adverse events and provide recommendations.

We will inform NIH of any significant action taken as a result of findings of reviews of serious AEs. We will inform the subjects of any changes in risk.

Responsibility for data quality, provision of reporting of AEs to the IRB and NIH, and appropriate response to recommendations of the leadership group lies with the PI. The PI will provide a summary of the DSM report to NIDA on an annual basis as part of the progress report. The DSM report will include the participants' socio-demographic characteristics, expected versus actual recruitment rates, treatment retention rates, any quality assurance or regulatory issues that occurred during the past year, summary of AEs and SAEs, and any actions or changes with respect to the protocol.

11.6 Frequency of review of cumulative data

All the data from the first part of the study (including the results of the blood nicotine analyses) will be reviewed by the leadership group, including Dr. Sciamanna, before initiation of the next part. If necessary, the doses planned for the next part or the timing of the blood samples may be adjusted accordingly and a modification of study protocol submitted to the IRB.

11.7 Statistical tests

Statistical methods will be used to analyze the safety data to determine whether harms are occurring. Paired sample t-test (or nonparametric Wilcoxon Rank-Sum test) will be used to examine the changes in the outcome measures (plasma nicotine, subjective measures, HR, BP) from the baseline.

11.8 Suspension of research

Due to the low risk of the intervention, it is unlikely that there will be a need to suspend the research. However, should the study doctor (Dr. Sciamanna) identify any issues after reviewing the data, they can develop stopping rules for the trial and these recommendations will be followed.

12.0 Risks

Potential risks for subjects are minimal. The nicotine films which will be administered to subjects have been previously tested in humans and we do not expect them to provide higher nicotine levels than subjects routinely receive from their smoking. Subjects will have a review of their medical history prior to entry into the study. Subjects will be under supervision throughout their participation in the study and adverse symptoms will be recorded and monitored by the Project Leaders. The major risks associated with the study are related to the use of nicotine (which is similar to the nicotine received from smoking) and nicotine withdrawal.

Additional potential risks include:

- **Nicotine withdrawal symptoms:** It is possible for subjects to experience short-term nicotine withdrawal symptoms (e.g. irritability, restlessness, difficulty concentrating, anxiety). Those receiving placebo films may experience more serious nicotine withdrawal symptoms.
- **Risk to fetus and breast fed infants:** Nicotine is known to be harmful to the developing human fetus, either from cigarettes or at the dose being used in this study. For this reason women must not be pregnant or nursing in order to participate in the study.
- **Risks of IV catheter for blood draw:** The discomfort associated with the IV insertion by venipuncture (by needle then catheter into a vein) for removing blood is a slight pinch or pin prick when the sterile needle enters the skin. The risks include mild discomfort and/or a black and blue mark at the site of puncture. Less common risks include a small blood clot, infection or bleeding at the puncture site, and on rare occasions fainting during the procedure.
- **Loss of confidentiality:** There is a risk of loss of confidentiality if information is obtained by someone other than the investigators. Precautions will be taken to prevent this including direct coding of data in REDCap.
- **Randomization:** Participants will be assigned to a treatment program by chance.
- **Discomfort from questionnaires:** It is possible that some of the questions in the questionnaires may make participants uncomfortable. They will be instructed that they are free to skip any questions that make them uncomfortable.
- **Nicotine film side effects:** Excess nicotine can cause mild symptoms such as nausea, dizziness, diarrhea and rapid heartbeat. Occasionally these symptoms are more severe (e.g. vomiting) such as when an individual receives more nicotine than they are accustomed to. This, however, is unlikely to occur with the doses used in this study. Additional side effects of the film may include hiccups.

- **Possible effects on the oral cavity.** In order to assess local toxicity of the study product, the CRC nurse assisting with the clinic visit will perform an oropharyngeal exam at the beginning of the visit prior to the participant receiving the study product as well as at the end of the visit after study product use is complete. Any changes will be assessed and documented. During the visit, after each film administration, participants will be asked to report side effects including any mouth discomfort or irritation via a questionnaire. If indicated, participant would discontinue study product use. Lesions of the oral mucosa are not anticipated as daily dissolution of several 2 mg sublingual nicotine tables (range 1-12/day over a 6 month period) led to only mild and transient effects on the oral mucosa[24]
- **Incidental Finding:** None of the tests carried out in this study are intended to provide diagnoses for clinical purposes, but participants will be alerted to findings that should be discussed with a healthcare provider (such as high blood pressure)

The participant may be removed from the research study without his or her permission because the participant does not follow the instructions for the study, has an adverse reaction to the study product (irregular heartbeat, palpitations, tachycardia (resting heart rate persistently greater than 100 beats per minute), has symptoms of nicotine overdose such as nausea, vomiting, dizziness, weakness, or rapid heartbeat, or has symptoms of an allergic reaction.
Participants are instructed to please call the Principal Investigator, Patricia Sue Grigson, Ph.D., at 717-531-5772 during business hours or 717-350-4508 after business hours if they:

- Experience any symptoms after the study is completed that they believe may be related to participation in the study
- Have questions, complaints, or concerns about the research

13.0 Potential Benefits to Subjects and Others

13.1 Potential Benefits to Subjects

There are no guarantees of benefit for participation in this research.

13.2 Potential Benefits to Others

The main benefit to society and others from the study is the possibility of a greater scientific understanding of the safety and efficacy of nicotine film.

14.0 Sharing Results with Subjects

This study is not designed to diagnose any disease or condition. However, if during the course of conducting clinical procedures (e.g., blood pressure) a participant is found to have a result outside of clinical norms, the result will be discussed with the participant at the visit where the result is identified. The participant will be given a letter indicating what procedure was done and will direct them to contact a medical provider for further evaluation.

15.0 Economic Burden to Subjects

15.1 Costs

There are no costs that subjects will be responsible for related to the research.

15.2 Compensation for research-related injury

It is the policy of the institution to provide neither financial compensation nor free medical treatment for research-related injury. In the event of injury resulting from this research, medical treatment is available but will be provided at the usual charge. Costs for the treatment of research-related injuries will be charged to subjects or their insurance carriers.

16.0 Number of Subjects

Participants will be screened until twelve participants have completed each part of the study protocol. Participants may elect to participate in one or both parts. We anticipate that fifty participants will be enrolled in order to account for screen failures after the consent form is signed.

17.0 Resources Available

17.1 Facilities and locations

All participant visits will take place in the Penn State Hershey CRC.

17.2 Feasibility of recruiting the required number of subjects

The smoking prevalence in South Central Pennsylvania is 19% of the adult population. Our recruitment strategy is designed to broadly disseminate information about the study to members of the community

17.3 PI Time devoted to conducting the research

Drs. Grigson and Wilson are funded at 15% time to this study. Dr. Foulds is funded at 5% time for this study.

17.4 Availability of medical or psychological resources

Any urgent health problem will require accompanying the participant to the emergency room, which is located in the same building.

17.5 Process for informing Study Team

Regular team meetings will be conducted where study procedures, questions and issues will be discussed and resolved.

18.0 Other Approvals

The FDA will require submission of an IND (Investigational New Drug) application.
The Institutional Biosafety Committee Review and Registration

19.0 Subject Stipend (Compensation) and/or Travel Reimbursements

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Part 1: Subjects will be compensated $20 for attending the study visit regardless of whether or not they are eligible to continue after in-person screening. Subjects will receive an additional $100 for completing the study. Participants have the option of being provided lunch from our cafeteria if their appointment falls during this time.

Part 2: Subjects will be compensated $20 for attending the study visit regardless of whether or not they are eligible to continue after in-person screening. Subjects will receive an additional $220 for completing the study. Participants have the option of being provided lunch and dinner from our cafeteria.

20.0 Multi-Site Research

N/A

20.1 Communication Plans

N/A

20.2 Data Submission and Security Plan

N/A

20.3 Subject Enrollment
N/A

20.4 Reporting of Adverse Events and New Information
N/A

20.5 Audit and Monitoring Plans
N/A

21.0 Adverse Event Reporting

21.1 Adverse Event Definitions

For drug studies, incorporate the following definitions into the below responses, as written:	
Adverse event	Any untoward medical occurrence associated with the use of the drug in humans, whether or not considered drug related
Adverse reaction	Any adverse event caused by a drug
Suspected adverse reaction	Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than "adverse reaction". • *Reasonable possibility.* For the purpose of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event.
Serious adverse event or Serious suspected adverse reaction	Serious adverse event or Serious suspected adverse reaction: An adverse event or suspected adverse reaction that in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
Life-threatening adverse event or life-threatening suspected adverse reaction	An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator (i.e., the study site principal investigator) or Sponsor, its occurrence places the patient or research subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that had it occurred in a more severe form, might have caused death.
Unexpected adverse event or Unexpected suspected adverse reaction.	An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure, general investigational plan, clinical protocol, or elsewhere in the current IND application; or is not listed at the specificity or severity that has been previously observed and/or specified.

21.2 Recording of Adverse Events
All adverse events (serious or non-serious) and abnormal test findings observed or reported to study team believed to be associated with the study drug(s) or device(s) will be followed until the event (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the investigator.

An abnormal test finding will be classified as an adverse event if one or more of the following criteria are met:

- The test finding is accompanied by clinical symptoms

- The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention; including significant additional concomitant drug treatment or other therapy
- The test finding leads to a change in study drug dosing or discontinuation of subject participation in the clinical research study
- The test finding is considered an adverse event by the investigator.

21.3 Causality and Severity Assessments

The investigator will promptly review documented adverse events and abnormal test findings to determine 1) if the abnormal test finding should be classified as an adverse event; 2) if there is a reasonable possibility that the adverse event was caused by the study drug(s) or device(s); and 3) if the adverse event meets the criteria for a serious adverse event.

If the investigator's final determination of causality is "unknown and of questionable relationship to the study drug(s) or device(s)", the adverse event will be classified as associated with the use of the study drug(s) or device(s) for reporting purposes. If the investigator's final determination of causality is "unknown but not related to the study drug(s) or device(s)", this determination and the rationale for the determination will be documented in the respective subject's case history.

21.4 Reporting of Adverse Reactions and Unanticipated Problems to the FDA

21.4.1 Written IND Safety Reports

The Sponsor-Investigator will submit a written IND Safety Report (i.e., completed FDA Form 3500A) to the responsible new drug review division of the FDA for any observed or volunteered adverse event that is determined to be a serious and unexpected, suspected adverse reaction. Each IND Safety Report will be prominently labeled, "IND Safety Report", and a copy will be provided to all participating investigators (if applicable) and sub-investigators.

Written IND Safety Reports will be submitted to the FDA as soon as possible and, in no event, later than 15 calendar days following the Sponsor-Investigator's receipt of the respective adverse event information and determination that it meets the respective criteria for reporting.

For each written IND Safety Report, the Sponsor-Investigator will identify all previously submitted IND Safety Reports that addressed a similar suspected adverse reaction experience and will provide an analysis of the significance of newly reported, suspected adverse reaction in light of the previous, similar report(s) or any other relevant information.

Relevant follow-up information to an IND Safety Report will be submitted to the applicable review division of the FDA as soon as the information is available and will be identified as such (i.e., "Follow-up IND Safety Report").

If the results of the Sponsor-Investigator's follow-up investigation show that an adverse event that was initially determined to not require a written IND Safety Report does, in fact, meet the requirements for reporting; the Sponsor-Investigator will submit a written IND Safety Report as soon as possible, but in no event later than 15 calendar days, after the determination was made.

21.4.2 Telephoned IND Safety Reports – Fatal or Life-threatening Suspected Adverse Reactions

In addition to the subsequent submission of a written IND Safety Report (i.e., completed FDA Form 3500A), the Sponsor-Investigator will notify the responsible review division of the FDA by telephone or facsimile transmission of any unexpected, fatal or life-threatening suspected adverse reaction.

The telephone or facsimile transmission of applicable IND Safety Reports will be made as soon as possible but in no event later than 7 calendar days after the Sponsor-Investigator's receipt of the respective adverse event information and determination that it meets the respective criteria for reporting.

21.5 Reporting Adverse Reactions and Unanticipated Problems to the Responsible IRB

In accordance with applicable policies of The Pennsylvania State University Institutional Review Board (IRB), the investigator will report, to the IRB, any observed or reported harm (adverse event) experienced by a subject or other individual, which in the opinion of the investigator is determined to be (1) unexpected; and (2) probably related to the research procedures. Harms (adverse events) will be submitted to the IRB in accordance with the IRB policies and procedures.

21.6 Unblinding Procedures

A subject's record will be unblinded if the study doctor (Dr. Sciamanna) feels it is necessary in order to further assess a serious adverse event. This will be reported along with the serious adverse event in accordance with the safety monitoring plan.

21.7 Stopping Rules

In the event of unexpected or serious adverse events that the study doctor (Dr. Sciamanna) believes are related to the study product, the IRB will be notified and their recommendations will be followed.

22.0 Study Monitoring, Auditing and Inspecting

22.1 Study Monitoring Plan

22.1.1 Quality Assurance and Quality Control

Data will be collected from participants and coded directly by either using the REDCap survey tool (participant entered data) or through REDCap data entry forms (researcher entered data). The codes that link the name of the participant and the study ID will be kept confidential in REDCap. Any paper forms (consent) will be securely transported to the PI's data entry center.

Study data will be managed using REDCap (Research Electronic Data Capture). REDCap is a secure web application designed to support data capture for research studies, providing user-friendly web-based case report forms, real-time data entry validation (e.g. for data types and range checks), audit trails and a de-identified data export mechanism to common statistical packages (SPSS, SAS, Stata, R/S-Plus). The system was developed by a multi-institutional consortium which includes The Pennsylvania State University and was initiated at Vanderbilt University. The database is hosted at the Penn State Hershey Medical Center and College of Medicine data center, which will be used as a central location for data processing and management. REDCap data collection projects rely on a thorough study-specific data dictionary defined in an iterative self-documenting process by all members of the research team. This iterative development and testing process results in a well-planned data collection strategy for individual studies.

REDCap is HIPAA compliant. Data are stored on a secure server; data in REDCap are encrypted; access to the database requires authentication (a unique username and password); data are accessed based on the individual's role on the project; every interaction with the data is logged, creating an audit trail.

Random data entry checks will be implemented regularly to identify problems with data entry. Data quality tools included in REDCap will be utilized to identify incorrect data types, out of range data and outliers. In addition, electronic edit checks, and random internal quality and assurance checking will be performed manually. Data quality will be monitored by random inspection of the completed electronic forms by one of the research assistants and any problems detected will be discussed with the PI. If necessary, re-training of researchers will be conducted.

The responsibility for data quality and study conduct lies with the PI.

22.1.2 Safety Monitoring

The Principal Investigator will confirm that all adverse events (AE) are correctly entered into the AE case report forms by the coordinator; be available to answer any questions that the coordinators may have concerning AEs; and will notify the IRB, FDA, sponsor and/or DSMB of all applicable AEs as appropriate. All assessments of AEs will be made by a licensed medical professional who is an investigator on the research.

The research coordinator will ensure that AEs are correctly entered into REDCap and complete the appropriate report form and logs; assist the PI to prepare reports and notify the IRB, FDA, and/or DSMB of all Unanticipated Problems/SAE's.

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