TITLE: Pre to Postoperative Smoking Cessation

NCT: NCT02683161

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JHM IRB - eForm A – Protocol

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1. Abstract

a. Provide no more than a one page research abstract briefly stating the problem, the research hypothesis, and the importance of the research.

Preoperative smoking significantly increases the risk of postoperative complications, most prominently pulmonary (atelectasis, pneumonia) and cardiovascular (myocardial ischemia) problems (Aveyard & Dautzenberg, 2010), increased admission to the intensive care unit, and hospital-based mortality (Delgado-Rodriguez et al., 2003). Pre-surgical smokers also require greater quantities of opioid analgesics to control postsurgical pain (Aydogan et al., 2013; Erden, Basaranoglu, Delatioglu, Hamzaoglu, & Saitoglu, 2005; Marco, Greenwald, & Higgins, 2005; Steinmiller et al., 2012). In contrast, smoking cessation, even short-term, can attenuate the impact of being a smoker on postsurgical complications and opioid analgesic use, and these effects are evident with as little as 4 weeks of pre-surgical smoking abstinence, though longer periods further enhance outcomes (Thomsen, Tonnesen, & Moller, 2009; Thomsen, Villebro, & Moller, 2014; Wong, Lam, Abrishami, Chan, & Chung, 2012). Despite research clearly demonstrating the value of pre-surgical smoking cessation, the only studies to explicitly address that issue have either utilized intensive behavioral counseling or nicotine replacement therapy to reduce smoking, which are associated with modest cessation rates in and of themselves, and the only two pharmacotherapy studies were designed in a way that limited their utility to evaluate sustained preoperative cessation rates. To date, no studies have combined pharmacotherapy with counseling and/or more powerful behavioral interventions, such as the use of monetary incentives to remain abstinent, which yield the best long-term cessation rates. Therefore, it is completely unknown how the most effective tobacco cessation interventions (medication combined with brief counseling and monetary incentives) might synergize with the motivational benefits of the surgical life event to enhance long-term cessation and improve surgical outcomes and expenses. It is also unclear if smokers who quit smoking pre-surgery are able to maintain smoking abstinence for any period of time post-surgery, after the initial motivator of the surgical procedure has passed. To address these research gaps, the proposed open-label pilot study will evaluate the feasibility of integrating an intensive pre- post-surgical smoking cessation intervention (i.e., varenicline + monetary incentives + brief counseling) into a hospital setting, and assess theoretically relevant baseline characteristics (e.g., factors influencing smoking decisions, such as smoking motivation, delayed discounting, and distress tolerance) that may predict postsurgical recovery and smoking cessation outcomes. We expect that this intensive intervention will promote high rates of smoking cessation both pre- and post-surgery, that patients showing longer periods of sustained smoking abstinence will evidence better post-surgical outcomes (including shorter lengths of hospital stay, fewer admissions to ICU, lower total costs of procedure, smaller quantity of opioid analgesic use, and lower 30-day readmission rates), and that relevant decision-making factors at baseline will predict smoking abstinence post-surgery. In addition to enhancing the quality of care and potentially reducing the

cost of surgery and aftercare in surgical patients, we believe that this project will establish the ground-work necessary to develop a sustainable clinical program for other surgical practices to minimize post-surgical complications and overall costs.

2. **Objectives** (include all primary and secondary objectives)
    1. **Evaluate whether an intensive pre- post-surgical smoking cessation intervention will promote smoking cessation both pre- and post-surgery.**
        Hypothesis: An intensive smoking intervention will promote smoking abstinence across the pre- and post-surgical phases. Secondary outcomes will include cessation at 1-month postsurgical follow up and other smoking-related outcomes (withdrawal, craving).

    2. **Assess whether changes in smoking are associated with surgical recovery outcomes.**
        Hypothesis: Patients who show longer periods of sustained smoking abstinence pre- and post-surgery will have better recovery post-surgery as evidenced by the following outcomes: shorter length of stay, fewer admissions to the ICU, lower total cost of procedure, smaller total quantity of opioid analgesic use, and lower 30-day hospital readmission rates.

    3. **Examine baseline decision-making characteristics, including smoking motivation, delayed discounting, and distress tolerance, as predictors of post-surgical recovery and smoking cessation outcomes.**
        Hypotheses: (1) Patients with strongest positive and negative reinforcement-based smoking motives (i.e., patients whose motives to smoke center around experiencing the positive outcomes of smoking, such as mood enhancement and/or ameliorating the cons of abstaining from smoking, including craving and negative affect) will be most likely to resume smoking post-surgery. (2) Patients with steeper discounting curves at study baseline and/or lower distress tolerance will be less likely to abstain from smoking pre-surgery, may request higher quantities of opioid analgesics post-surgery, and will be at the greatest risk of relapsing to smoking post-surgery.

The overall objective of this study is to assess the feasibility of conducting a pre-postoperative smoking cessation study in presurgical patients. If a positive signal is found, then these data will be used to support a large-scale grant application to evaluate this approach using a randomized, controlled study design.

4. **Background** (briefly describe pre-clinical and clinical data, current experience with procedures, drug or device, and any other relevant information to justify the research).

Over 40 million (18.1%) adults in the United States currently smoke cigarettes. Smoking is responsible for 400,000 deaths annually, making it the leading cause of preventable death in the US, and an additional 16 million adults and children are currently suffering from a smoking or second-hand smoking-related disease. Smoking cessation interventions are frequently tailored to meet the needs of specific high-risk or special populations. The importance of such interventions is especially acute in the context of preoperative preparation for invasive surgeries, the outcomes of which depend upon adaptive tissue recovery and rehabilitation, which are disrupted by tobacco use. We propose a novel pre- post-surgical smoking cessation study that will combine gold-standard smoking cessation treatments to maximize quit rates prior to surgery.

Preoperative smoking significantly increases the risk of postoperative complications, most prominently pulmonary (atelectasis, pneumonia) and cardiovascular (myocardial ischemia) problems (Aveyard & Dautzenberg, 2010), wound healing, increased incidence of lower respiratory tract infection, opioid overuse, increased admission to the intensive care unit, and hospital-based mortality (Delgado-Rodriguez et

al., 2003). Smoking is also associated with osteoporosis, because it delays ossification and increases the risk of non-union after bone fractures. In short, being a cigarette smoker is an independent risk factor for experiencing postoperative complications (Moller, Villebro, Pedersen, & Tonnesen, 2002). As a result, presurgical smoking is associated with significant costs. Postoperative complications increase the cost of treatment by 89-148%, and respiratory problems, which have been shown to occur primarily among smokers, are the primary contributor to these costs (Kamath et al., 2012; Vaughan-Sarrazin et al., 2011).

In contrast, smoking cessation, even short-term, can attenuate the impact of being a smoker on postsurgical complications and opioid analgesic use. Presurgical smoking cessation has been robustly associated in several randomized controlled trials and meta-analytic reviews (Mills et al., 2011; Thomsen et al., 2009; Thomsen et al., 2014; Wong et al., 2012) with improved postsurgical outcomes, and may reduce the rate of complications to those of non- or never smokers (Moore, Mills, Moore, Miklos, & Mattox, 2005). Moreover, these effects are evident with as little as 4 weeks presurgical smoking abstinence, though longer periods further enhance outcomes (Thomsen et al., 2009; Thomsen et al., 2014; Wong et al., 2012).

As of yet, the majority of presurgical cessation trials have utilized intensive behavioral counseling or nicotine replacement therapy to reduce smoking, which are associated with modest cessation rates in and of themselves, and the only two pharmacotherapy studies were designed in a way that limited their utility to evaluate sustained preoperative cessation rates. No studies have combined varenicline or bupropion with counseling and/or more powerful behavioral interventions, such as monetary incentives for sustained abstinence, which yield the best long-term cessation rates. Therefore, it is completely unknown how the most effective tobacco cessation interventions (medication combined with brief counseling and/or monetary incentives) might synergize with the motivational benefits of the surgical life event to enhance long-term cessation and improve surgical outcomes and expenses. It is also unclear if smokers who quit smoking pre-surgery are able to maintain smoking abstinence for any period of time post-surgery, after the initial motivator of the surgical procedure has passed. This represents a critical gap in patient care, as an extended pre-post smoking cessation intervention could simultaneously improve surgical outcomes, reduce cost and suffering associated with surgery, promote extended postsurgical smoking cessation, and reduce long-term health consequences associated with smoking. To address these research gaps, the proposed study will evaluate the feasibility of integrating an intensive pre- post-surgical smoking cessation intervention into a hospital setting, and assess theoretically relevant baseline characteristics (e.g., factors influencing smoking decisions, such as smoking motivation, delayed discounting, and distress tolerance) that may predict postsurgical recovery and smoking cessation outcomes.

In the proposed study, smokers who have scheduled elective surgeries will be enrolled for a 12-week period in an open-label trial to test the feasibility of integrating an intensive smoking cessation intervention in a hospital setting. The intensive intervention will consist of varenicline + counseling + motivational incentives. Motivational incentives are frequently used for treatment-reticent cigarette smokers and consistently produce the highest rates of smoking abstinence reported in hard-to-treat populations, with short-term cessation rates as high as 60% (Sigmon & Patrick, 2012). We have elected to provide this constellation of treatments to increase the efficacy of the intervention and ensure that the highest possible presurgical rates of abstinence are obtained in order to demonstrate the ideal potential effect on surgical outcomes. Incentives will only be available during the presurgical phase; however, varenicline use will be maintained for an additional 4-6 weeks after the surgery to promote continued cessation. It is critical that a powerful cessation intervention be used because the intensity and duration of the intervention has been directly associated with the magnitude of postsurgical outcomes by a meta-analytic review. Specifically, positive outcomes related to wound healing and rate of postoperative complications were only evident among patients who underwent an intensive vs. brief preoperative cessation intervention (Thomsen et al., 2014).

Decision-Making and Tobacco Cessation. There are many factors that my impact patients' abilities to make the decisions necessary to make and maintain healthy behavior changes, such as terminating smoking. A large body of research on the role of decision-making in health behavior change has identified two factors of critical importance: the pros and cons of changing (27). Individual differences in certain patient characteristics may influence the impact that perceived pros vs. cons have on the ultimate decisional balance of changing vs. staying the same. For example, individuals who tend to discount the value of delayed rewards may find it difficult to make the decision to change a behavior, such as smoking, as many of the pros of quitting, such as health improvements and financial savings, tend to be delayed, and therefore, may be undervalued. The use of incentives, as is proposed in the current study, may facilitate the decision to quit smoking initially, but individuals who are particularly steep discounters of delayed rewards may find it difficult to maintain smoking cessation once immediate incentives for abstinence are removed.

Another factor that can impact the decision to quit smoking is one's willingness or ability to tolerate the distress (e.g., withdrawal symptoms, craving) that is likely to accompany smoking cessation. For smokers with low distress tolerance, the cons (uncomfortable symptoms) associated with changing may be particularly likely to outweigh the pros. Additionally, variations in specific motivations to smoke may also impact decision-making related to smoking cessation. That is, individuals who endorse strong motivations to smoke directly due to the pros of smoking (e.g., pleasurable effects of smoking, reductions in craving/withdrawal, affiliative attachment with fellow smokers) may have more difficulty making the decision to quit and to maintain abstinence relative to individuals who endorse smoking motives related more to automaticity/habit. Indeed, all of the factors discussed above (i.e., delay discounting, distress tolerance, and smoking motives) have been shown to predict smoking outcomes in standard smoking cessation trials. However, they have not been directly examined as predictors of smoking outcomes among the unique population of pre-surgical candidates for whom decisions related to their recovery may play a more prominent role in short and/or long-term abstinence behavior.

Ultimately, this study will provide a unique, innovative contribution to the literature because it will be the first to promote both pre- and post-surgical smoking cessation, it will layer varenicline, counseling, and motivational incentives to produce large magnitude effects, it will evaluate decision-making characteristics at baseline that may impact postsurgical decisions to either maintain smoking abstinence or reinitiate smoking, and it will focus on surgical recovery outcomes and rates of opioid analgesic use, as well as smoking cessation. The researchers are uniquely poised to conduct this research. Dr. Dunn has run two incentive-based smoking cessation trials in treatment reticent smokers (Dunn et al., 2008; Dunn et al., 2010), and has worked on two studies administering varenicline for treatment purposes, including an R21 funded study awarded to Co-I Annie Umbricht and conducted here (IRB protocol NA_00074143).

Pilot Data: Post-Surgical Costs and Smoking Status.

We also have data to support our proposal. Table 1 presents data from the Bayview Medical Hospital, collected from all patients in FY14. Among patients seeking voluntary bariatric surgery, 5% were rated as *current* smokers (a total of 23 individuals overall). Despite this large discrepancy in sample size, several variables emerged as being significantly different between the smoker and nonsmoking patients, including the overall length of hospital stay, total cost of the procedure, and likelihood of 30-day readmission. These data indicate a positive signal exists that warrants additional research attention, and provides evidence that there will be sufficient sample size from which to recruit for a pilot project. **The total savings ($14,220.69) between the smoker and nonsmoker groups, regarding total cost and total cost of meds, is enough money to pay 21 participants or to completely run 9 participants**. Please note: Based on population

Table 1.	Smokers N=23	Nonsmokers N=451	P-Value
Bariatric Surgery Patients (2014)			
Length of Stay (Days)	8.2	3.5	**0.005**
Total Cost ($)	34,781.90	21,405.19	**0.024**
Total Cost in Meds ($)	1,364.66	520.68	0.064
30-day Readmission (%)	17%	4%	**0.018**

prevalence alone, we believe this clinical data, likely underestimates the true rate of current smokers among presurgical patients. Many are likely to temporarily quit based on the advice of their surgeons and without any evidence-based intervention in place, relapse rates are likely to be very high.

5. **Study Procedures**
   a. Study design, including the sequence and timing of study procedures (distinguish research procedures from those that are part of routine care).

In this two-year open-label feasibility study, 20 smokers who are planning to undergo elective surgery will complete a 12-week intensive pre- post-surgical smoking cessation intervention, involving three major components: (1) varenicline administration, (2) standardized smoking cessation counseling, and, during the pre-surgery phase, (3) incentives for urine samples that test negative for cotinine. Upon verifying that all study eligibility criteria are met, patients will enter the intervention phase of this study. During this phase, patients will attend weekly study visits to receive the pre-surgical component of the intensive smoking cessation intervention in approximately the 4-6 weeks leading up to surgery, and complete approximately six additional weekly study visits post-surgery in order to continue with the post-surgical varenicline administration component of the intensive smoking intervention for a total of 12 weeks, and to allow for in-person assessment of post-surgical smoking cessation and surgical recovery outcomes. Finally, participants will be scheduled for an in-person follow-up visit approximately one month following completion of the study to assess study outcomes. In some cases, this follow-up period may extend as long as six months to collect data that ensures study outcomes are being met.

Recruitment: We will recruit participants via physician or self-referrals. A number of strategies may be utilized to identify potential participants early in the elective surgical process. We will provide medical departments and physicians detailed information about study eligibility criteria and procedures and encourage them to provide potentially eligible patients with information to contact the study team. We will also post flyer advertising a smoking cessation study for elective surgical patients in common areas and waiting rooms to enable potential participants to contact us directly. All interested individuals will be instructed to call the study team and complete a brief phone screen to establish initial study eligibility before conducting a full screening visit.

Screening: We are proposing to screen 40 individuals and complete 20 people for this initial study, which is consistent with other pilot/feasibility studies and will provide enough data to indicate whether a signal exists that would support further evaluation of this treatment approach in a larger-scale clinical trial study.

All participants will read and sign the informed consent with a trained staff member before conducting the screening visit, which will include self-report of smoking and other related variables, urinalysis verification of recent smoking, illicit drug, and pregnancy status, a medical history to determine medical eligibility, and completion of baseline decision-making measures. Participants will also provide written permission for study staff to access medical records to verify postsurgical outcomes and analgesic use, for study outcome measures.

Screening and Study-related Measures:

The following measures will be utilized during the study to determine eligibility and provide data necessary to complete the study aims. Individuals enrolled into the study will complete assessments weekly during treatment with one follow-up assessment 30 days after study completion. These data will be used to monitor changes in smoking status, mood or behavior changes related to medication or tobacco abstinence, health and pain-related outcomes, and vital signs.

- Time-Line Follow-Back (TLFB; Sobell et al., 1988): a validated self-report measure to record daily behaviors, including medication compliance and use of tobacco, alcohol, and other drugs/medications.

A past 30-day assessment will be conducted at baseline, with weekly assessments during the study

- Smoking History: brief self-report questionnaire of smoking history, quit attempts, use of pharmacotherapy, interest in quitting smoking, perceived ability to quit smoking and perceived health risk of smoking.

- Fagerström Test for Nicotine Dependence (FTND; Heatherton et al., 1991): 6-item self-report measure of nicotine dependence.

- Contemplation Ladder (Biener & Abrams, 1991): graphical description of process of change in relation to the need to quit smoking. Score ranges from 0 (no thoughts of quitting) to 10 (taking action to quit).

- Minnesota Nicotine Withdrawal Questionnaire-Revised (MNWQ-R; Hughes & Hatsukami, 1986): The 15- item self-report measure of nicotine withdrawal with good reliability and validity.

- Questionnaire of Smoking Urges-Brief (QSU-B; Cox et al., 2001): 10-item self-report measure with good reliability and validity for detecting cigarettes craving.

- Medication Adherence Questionnaire (MAQ; Morisky et al., 1986): 4-item self-report measure used to identify potential problems with adherence to a medication regimen including quit smoking aid pharmacotherapies (Toll et al., 2007). Will be given monthly to monitor self-reported compliance with study medication.

- Beck Depression Inventory (BDI, Beck et al., 1961): 21-item self-report measure that evaluates symptoms of depression and suicidal thoughts. Scores are aggregated and categorized as minimal (0-13), mild (14- 19), moderate (20-28) or severe (29-63) depression. Participants who score >20, indicating moderate to severe depression, or who endorse >0 on the suicidal thoughts question (item 9) during screening will be excluded and referred to a clinician for further evaluation and referral if indicated. The BDI will be administered at every study visit to assess ongoing changes to mood.

- Columbia Suicide Severity Rating Scale (C-SSRS; Posner et al., 2003): The C-SSRS is a widely used suicide rating scale that is frequently used in clinical trials that administer varenicline. The C-SSRS will be used at baseline to assess lifetime history of suicidal events, and throughout the study.

- Weekly Update: We will administer a measure designed to assess changes in potential varenicline-mediated side effects over time at every weekly visit. This measure was designed in the context of large-scale trial to assess varenicline for alcohol treatment and was used successfully in a recently completed study to assess varenicline for smoking cessation (NA_00074143).

- Adverse Events Questionnaire: Locally developed measure to query potential side effects and concomitant medications. Specific questions address concerns with new onset of irritable and potentially violent behaviors.

- Medical Assessment: A locally developed questionnaire will be used to collect demographic, education, social history, past medical history, allergies, medication side-effects, and family history. Blood samples for CBC, comprehensive chemistry panel and urine sample for toxicology and urinalysis will be obtained. Vital signs, height, weight, BMI and EKG will be recorded. Medical staff will review the laboratory results, the medical survey, vital signs to ensure that participants qualify for the study and that no exclusionary criteria are violated prior to giving medical clearance for participation in the study.

- Wisconsin Inventory of Smoking Dependence Motives (WISDM-68) Scale: (Piper et al., 2004): WISDM-68 is a 68-item self-report questionnaire that characterizes motivations for smoking.

- Brief Pain Inventory (BPI; Keller et al., 2004): We will administer a brief self-report measure used to document pain outcomes in patients with non-cancerous pain. The BPI will be administered periodically throughout the study to track current pain levels.

- Pain Catastrophizing Scale (PCS; Sullivan et al., 1995): The PCS will be used to measure cognitive intrusion of pain. The PCS includes 14 items and uses a 5-point scale to assess helplessness, rumination, and magnification of pain.

- Patient-Reported Outcomes Measurement Information System (PROMIS Sleep Disturbance Short Form; Yu et al., 2012): The short form from the PROMIS Sleep Disturbance item bank will be used to assess general sleep disturbances in the past 7 days. The PROMIS Sleep Disturbance Short Form is a brief self-report questionnaire that asks participants to rate the frequency and severity of sleep-related symptoms

- PROMIS Global Health (Yu et al., 2012): This scale is a 10 item self-report measure to assess functioning in several domains, to evaluate patient quality of life.

- Daily Diary: At each study visit, participants will be given a brief diary form to complete over the course of the week. Specifically, participants will be asked to rate their average pain, worst pain, negative mood, stress, and cigarette craving on a 0-10 scale, two times per day (once at mid-day, and again at the end of the day). Participants are also asked to record how many hours of sleep they got each night.

- Dietary Adherence Questionnaire: At several points during the study, participants will complete a brief self-report questionnaire to assess the degree to which they are adhering to standard dietary guidelines commonly recommended to patients both presurgery and postsurgery. Patients will be given a list of dietary guidelines and will be asked to rate the degree to which they adhered to each guideline in the past week.

Pain testing: Three procedures will be used at several time points over the course of the study to assess responses to noxious sensory stimuli, and changes as a function of smoking status:

Pressure Pain Threshold: The pressure pain threshold is defined as the kilopascals (kPA) value at which a mechanical stimulus is first judged to be painful. An electronic algometer with a $1cm^2$ hard rubber probe will be applied two times to the muscle belly of the quadriceps muscle (bilaterally), and the proximal third of the brachioradialis muscle of the forearm (bilaterally) in randomized order. Pressure will be applied at a constant rate of 30kPA/s until the participant first reports pain. A 30 second interval will be imposed between each stimulus presentation. The values in kPA will be averaged across administrations and muscle groups to create an index of pressure pain threshold. Administering the stimulus at multiple anatomic locations increases the reliability of the pressure pain threshold. Possible effects of laterality and muscle group will be evaluated to determine if threshold outcome measures should be separated into subgroups.

Conditioned Pain Modulation: We will also conduct a test of conditioned pain modulation, formerly known as diffuse noxious inhibitory controls. Conditioned pain modulation is the process by which the pain induced by a tonic conditioning stimulus inhibits the pain produced by another noxious stimulus at a distal anatomic location. This procedure initiates a robust activation of the endogenous opioid system. Our conditioned pain modulation procedure will measure the change in pressure pain threshold at the trapezius muscle induced by immersion of the contralateral hand in cold water. Two baseline pressure pain threshold readings will be assessed via algometry on the muscle belly of the dominant trapezius. Participants will then immerse their hand in a circulating ice water bath maintained at 10 +/- 1° C and will

not be told the duration of time for which their hand will be submerged. After 20 seconds, with their hand still submerged, participants will rate their pain on a 0-100 numeric rating scale, where 0=No Pain and 100=is Worst Pain Imaginable, and after 45 seconds participants will be asked to remove their hand from the water bath. Simultaneously with hand withdrawal, an algometer will be applied to the contralateral trapezius muscle and pressure pain threshold in kPA will be recorded. This procedure will be repeated on the contralateral hand and trapezius after a 5-minute interval. The order of administration with respect to laterality will be randomized. Conditioned pain modulation will be indexed as the percent change in pressure pain threshold from the baseline administration to the conditioned administration, averaged across the 2 trials.

Mechanical Temporal Summation**.** Temporal summation of pain will be assessed using repetitive mechanical stimuli. The assessment of temporal summation involves rapidly applying a series of identical noxious stimuli and determining the increase in pain across trials; animal studies have suggested that temporal summation occurs centrally in second-order neurons in the spinal cord as a consequence of sustained C-fiber afferent input. For temporal summation of mechanical pain, pain ratings in response to a single punctate noxious stimulus will be compared to pain ratings in response to a sequence of identical punctate noxious stimuli. A weighted pinprick stimulator with a flat contact area will be used to deliver, to the ventral surface of the arm, either a single pinprick stimulus or a train of 10 pinprick stimuli repeated at a constant rate. Following the single stimulus and the 10-stimulus train, the subject is asked to give a pain rating. Single pinprick stimuli are alternated with the trains of 10 stimuli.

Monetary and commodity-based DD tasks will also be administered via computer to participants during the Screening visit and at regular intervals during the study

Finally, the Paced Auditory Serial Addition Task (PASAT) will be administered via computer to assess distress tolerance. For this task, participants are asked to complete a challenging mathematical processing task in which the speed of number presentation is titrated based on participant performance. As the numbers begin to appear more quickly, participants begin to lose points as the task continues and increases in difficulty. Participants also receive automated visual and auditory feedback that is designed to promote mild negative reactions. In the final round, the difficulty level of the task is deliberately set to a level beyond the participants' ability level and participants are provided with an option to quit the task prior to its scheduled end time. Distress tolerance is operationalized as time in seconds to task termination (i.e., higher persistence time before terminating = higher distress tolerance). Participants are told that their performance will influence how much money they get at the end of the session in order to provide a small incentive to persist on the task in the face of aversive feedback. Specifically, participants who persist until the end of the task will be given a $5 bonus at the end of the session.

Intensive Smoking Cessation Intervention: Eligible participants will receive an intensive pre- post-surgical smoking cessation intervention beginning approximately six weeks before their elective surgery is scheduled to occur. The presurgical intervention phase is comprised of six weekly visits that will include varenicline administration, standardized smoking cessation counseling, and monetary-based incentives for urine samples that test negative for cotinine.

The outcome of each urine screen for cotinine will be used only for the purpose of determining whether the patient is eligible to receive their monetary incentive on that particular visit and will not be shared with members of the medical team. Any decisions that are made about whether patients remain eligible for surgery based on their smoking status will be solely at the discretion of the surgical team, as information collected from patients as a part of study procedures will not be shared with their surgeons.

Following the surgery, patients will resume weekly study visits approximately two weeks post-surgery in order to continue with the post-surgical varenicline administrations and to assess post-surgical recovery and smoking cessation outcomes. We will attempt to coordinate with the surgery team to schedule patients' first post-surgical study visit on the same day as their two-week post-surgical follow-up visit with their surgeon

in order to maximize convenience for patients, and participants will be given a 2-week supply of varenicline at the study visit immediately prior to their scheduled surgery so that they can continue taking the full dose while recovering from surgery. Patients will return weekly for a total of six post-surgical study visits. Additional follow-up may occur for six months post-intervention. More details about timing of each of the intervention components are listed below:

1. Brief Behavioral Counseling: All participants will complete a 3-session counseling session with a trained member of our study staff. Brief behavioral counseling is a standard component of RCT evaluations of varenicline for smoking cessation. The first session will occur prior to the target quit-date. Sessions are meant to be 15-20 minutes in duration, and are designed to adequately educate participants about methods for abstaining prior to their quit attempt without requiring a large time commitment. Not only is brief counseling effective (Fiore et al., 2008), but counseling is perceived by participants to be useful. We asked participants in our recently completed trial to rate their perceived value of the counseling component on a scale of 0 (none at all) to 10 (extremely) as part of an exit interview. Of the 56 participants who completed the interview, the mean rating for the counseling was a 7.6 out of 10. A total of 59% (n=33) of participants rated counseling as an 8 or higher, with 29% (n=16) of them rating the counseling at the highest possible value. Only 4% (n=2) rated counseling as a 0, indicating it did not help at all. As part of the counseling, participants will receive a copy of the National Cancer Institute booklet "Clearing the Air: Quit Smoking Today", which is a 39-page self-help guide to quitting smoking that contains information on nicotine dependence, withdrawal, and managing cravings. Participants will also receive a copy of a counseling manual that was developed by our group and has been used by us in multiple previous studies, including a multi-site RCT of the nicotine vaccine for smoking cessation. This brief counseling manual provides more enriched information about the experience of quitting smoking, including a benefits/disadvantage analysis, functional analysis of craving/risk periods, and skills-building exercises to prevent lapse and relapse.

2. Varenicline: Varenicline will be administered as clinically indicated and will begin approximately 4-6 weeks prior to surgery. All participants will receive a 1-week dose induction period (0.5mg QD Days 1-3, 0.5mg BID Days 4-7) before transitioning to a full maintenance dose (1mg BID). The target-quit date (TQD) will be on Day 8 (week 2) and will coincide with the 1st day of the maintenance dose, consistent with recommended guidelines. Participants will receive a 1-week supply of varenicline (with 3 days of extra doses in the event of an unpredicted event) in blister packs at each study visit. This will enable us to better track medication adherence and adverse events, and will help encourage participants to attend weekly visits. There is nothing experimental about the use of varenicline in this study. Participants will receive a 2-week supply of varenicline (with 3 days of extra doses) at the visit immediately prior to the participants' scheduled surgery in order to allow participants to continue taking the full maintenance of varenicline uninterrupted, while also allowing for ample healing time before returning for the first study visit post-surgery.

3. Incentives: Incentive payments will begin on the TQD (week 2) and will be in place for 5 weeks or until surgery (whichever is sooner). Participants will receive monetary based incentives for biochemical evidence of smoking abstinence. Abstinence will be determined via breath carbon monoxide (CO) ratings during Week 2, and via urinary cotinine for the duration of the study. The transition from CO to cotinine is a common procedure that provides a method for awarding incentives to participants who have recently begun abstaining from smoking but will still test positive for cotinine (because of the long elimination half-life of cotinine). Cotinine-based testing will be used as the definition of abstinence during weeks 3-12. CO will be tested using mobile meters and abstinence will be

Table 2. Incentive and Compensation Structur

Study Week	Study Visit	Incentives	Visit Payments
Screening			$30
1	-6		$20
2	-5	$20	$20
3	-4	$40	$20
4	-3	$60	$20
5	-2	$80	$20
6	-1	$100	$20
7	1		$50
8	2		$60
9	3		$70
10	4		$80
11	5		$90
12	6		$100
Follow-up			$50
Total:		**$300**	**$650**

defined as ≤4ppm. Cotinine will be tested using hand-held dipsticks and abstinence will be defined as ≤100ng/ml. Incentives will be awarded immediately onsite for biochemical samples that meet the abstinence criteria during weeks 2-6. Table 2 displays the schedule of payments, which have been arranged strategically to maximize the impact of the incentives. In other words, research has shown that incentive payments that escalate over time, are high in magnitude, and include reset contingencies for positive samples are the most effective in promoting behavior change. Total possible incentive payments will be $300. Though this value may seem high, it is important to make the incentive magnitude for this initial study high enough to determine whether it will produce the expected effect on smoking cessation and to accurately assess the study outcome measures; future studies can be conducted that vary the magnitude of the incentive to reduce overall cost of the intervention. Further, this approach will help us to determine whether the cost expenditure associated with this study will be recovered by the cost savings that we hypothesize will result from smoking cessation and the associated decrease in complications, analgesic use, and hospital readmissions, which run in thousands of dollars per complication.

In addition to the visit payments and incentives displayed in Table 2, participants will have the chance to win $5 in bonus money at the end of each session that includes an administration of the PASAT to assess distress tolerance.

Biochemical Testing: It is important to note that results of biochemical testing will not be conveyed with the surgical team. The reason for this is that we need to ensure that patients will not falsify or attempt to misrepresent their smoking status out of concern that their results may have a negative impact on their surgery plans. All results obtained from these patients will be kept confidential from the surgical team and the surgical team will continue to assess smoking in the manner that had been used prior to the study.

Urine will be tested for the primary outcome measure, cotinine. Cotinine testing will be conducted immediately onsite via a CLIA-waived semi-quantitative cotinine urine dipstick, NicAlert (Jant Pharmacol Corporation; Encino, CA). NicAlert provides a semi-quantitative rating of cotinine on scale of 0 (0 mg/mL) to 6 (≥1000 mg/mL), and abstinence is defined as having a cotinine level ≤2 (corresponding to ≤100mg/mL). According to the package insert, NicAlert has no cross-reactivity with other nicotine-like compounds (niacinamide, nicotine, nicotinic acid, nicotinic acid n-oxide), and is not affected by numerous other commonly-used compounds (e.g., aspirin, acetaminophen, caffeine) or changes in urine conditions (e.g., pH, specific gravity, glucose, bacteria). NicAlert has been used successfully in a previous smoking cessation incentive intervention (Schepis et al., 2008). NicAlert also shows high sensitivity (88%-92.2%) and specificity (92%-97.6%) for detecting nicotine use (Bernert, Harmon, Sosnoff, & McGuffey, 2005; Marrone et al., 2011), as well as 96% agreement with GC-MS quantitative testing, and 94% agreement with semi-quantitative EMIT testing (Gaalema, Higgins, Bradstreet, Heil, & Bernstein, 2011). Urine-based NicAlert also demonstrated higher levels of sensitivity and specificity for detecting smoking compared to saliva-based NicAlert in a between-group comparison of nicotine detection methods in smokers and non-smokers (Marrone et al., 2011).

b. Study duration and number of study visits required of research participants.

Study Visits: Participants will attend an initial in-person screening visit, described above, and will return to the clinic on approximately a weekly basis during study weeks 1-12 to receive the intensive pre- post-surgical smoking cessation intervention. Visits during the surgical week will occur prior to the surgery to allow for postsurgical recovery time and we will provide 2 weeks of medication at that visit to allow participants to continue using the medication during their recovery period and provide general flexibility to participants who are unable to complete a visit during their first postsurgical week. Each visit will include collection of a urine sample (that will be tested for urinary cotinine and illicit drug use), a breath CO sample, and self-report questionnaires. None of the data collected during study visits will be shared with the patients' surgical team. Participants will be contacted via phone approximately 3 weeks after study

completion and asked whether they are still abstaining from smoking. Those who endorse continued abstinence will be asked to complete a follow-up visit, during which they will provide a urine sample that will be tested for evidence of cotinine. Participants may be contacted over an additional six month period for follow-up questions pertaining to treatment outcome. Participants will be compensated for attending study visits and completing brief questionnaires and tasks; session payment values will escalate after surgery to encourage continued retention (a standard practice in our treatment protocols) and the total possible study visit compensation will be $650.

c. Blinding, including justification for blinding or not blinding the trial, if applicable.

Given that this is an open-label pilot study, all participants will receive the same intensive pre to post-surgical smoking cessation intervention in order to collect the data necessary to illustrate the feasibility of incorporating such an intensive intervention into the hospital setting. This pilot data will be used to support the need for future funding to complete larger randomized controlled trials, and/or multi-site trials. Given that no comparison condition is being included in the current pilot study, the issue of blinding is not applicable at this time.

d. Justification of why participants will not receive routine care or will have current therapy stopped.

There is no standard and/or routine access to smoking cessation in elective surgical patients. This study will not disrupt any ongoing routine care associated with the participant's surgery.

e. Justification for inclusion of a placebo or non-treatment group.

N/A

f. Definition of treatment failure or participant removal criteria.

Participants failing to continue to meet any of the inclusion/exclusion criteria will be removed from the study and an appropriate clinical referral provided. For example, subjects developing a psychiatric disorder or symptoms requiring treatment (e.g., mania, suicidality, and psychosis), major medical illnesses or serious injuries, which would preclude further participation, will be withdrawn. Subjects who consistently fail to show up for the first treatment session may also be withdrawn.

g. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.

Participants will be debriefed after completing the 1-month follow-up, 6-month follow-up, or premature removal. They will be fully informed about all treatment options for smoking cessation and provided with additional referrals as needed. Any participant who is discharged or voluntarily leaves the study will be provided referrals for obtaining assistance with smoking cessation. The participants will continue meeting with their surgical team, consistent with routine practice for post-surgical patient care and independent of the study.

6. Inclusion/Exclusion Criteria

Inclusion Criteria: We will recruit cigarette smokers who have scheduled an elective surgery to participate in the study. Inclusion criteria will include having a surgery scheduled 5-10 weeks in advance, reporting regular cigarette smoking (smoking 3 times a week or more) and providing a cotinine-positive urine sample.

Exclusion Criteria: Exclusion criteria will include being contraindicated for varenicline use, using products other than cigarettes as a primary nicotine product (including e-cigarettes), providing an illicit drug-positive urinalysis test without evidence of concurrent prescription (e.g., for narcotic pain medications, for example), being pregnant or breastfeeding, or a score >20 on the Beck Depression Inventory-II or a score $\geq$0 on the suicide question of the BDI, past year suicidal ideations or behavior on the C-SSRS, being

unwilling/unable to adhere to the study schedule, be unwilling to provide study access to medical records, having a serious and/or untreated medical and/or psychiatric illness that may jeopardize study participation, or being otherwise judged by the study team to be inappropriate for study participation.

7. Drugs/ Substances/ Devices

a. The rationale for choosing the drug and dose or for choosing the device to be used.

We have selected varenicline for this study because it is a gold-standard pharmacotherapy for smoking cessation, it produces the highest levels of smoking cessation of all FDA-approved medications, and because it has fewer medication interactions relative to the other common smoking-cessation pharmacotherapy bupropion. This will minimize the likelihood that participants will be required to end varenicline administration following surgery due to a new prescription related to their surgery. There is nothing experimental about the use of varenicline in this study.

Varenicline will be administered as clinically indicated for a 12-week period and will begin approximately 4-6 weeks prior to surgery. All participants will undergo the standard 1-week dose induction period (0.5mg QD Days 1-3, 0.5mg BID Days 4-7) before transitioning to a full maintenance dose (1mg BID). The target-quit date (TQD) will be on Day 8 (week 2) and will coincide with the 1st day of the maintenance dose, consistent with recommended guidelines. Varenicline will be packaged into blister packs by our research pharmacy. Participants will receive a 1-week supply of varenicline (with 3 days of extra doses in the event of an unpredicted event) in blister packs at each study visit (except at the study visit immediately prior to the participants' scheduled surgery, at which time they will receive a 2-week supply with 3 days of extra doses). Dispensing medication at weekly intervals (vs. monthly prescriptions) is a standard approach in our research unit that allows us to more closely track medication adherence and adverse events, and will help encourage participants to attend weekly visits for primary data collection purposes.

Varenicline adherence will be assessed using a weekly medication adherence self-report questionnaire. We will also save an aliquot of urine from each weekly visit that will be tested for evidence of varenicline by a commercial laboratory. Percent medication adherence rate may be used as a covariate in the study analyses.

b. Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed.

N/A

c. Justification and safety information if non-FDA approved drugs without an IND will be administered.

N/A

8. Study Statistics

Outcome Measures: We will collect a variety of outcome measures to enable a full characterization of decision-making factors at baseline, and the impact of this intervention on smoking status, postsurgical outcomes, opioid analgesia utilization, and cost.

a. Primary outcome variable.

Smoking Outcomes: Our primary outcome variable will be smoking status. Smoking abstinence will be defined as a negative biochemical sample + self-report of no smoking for the past 7 days, mean % negative samples, and mean continuous negative samples. Smoking will be evaluated within each pre and post-surgical phase, and collapsed over the 11-week targeted cessation period (following the TQD during week 2). Point prevalence smoking abstinence at the follow-up will be defined as a negative cotinine sample + self-report of no smoking for the past 7-days.

b. Secondary outcome variables.

Secondary smoking outcomes will include ratings of nicotine withdrawal and craving, using standardized measures, and frequency of adverse events judged to be related to varenicline or smoking cessation.

Surgical Recovery Outcomes: A variety of postsurgical outcomes will be evaluated. These will include length of hospital stay, overall quantity and frequency of opioid analgesic use, pain ratings of during the recovery period, types and frequency of post-operative complications, frequency of admission into the intensive care unit, and 30-day hospital readmission rates.

c. Statistical plan including sample size justification and interim data analysis.

Since this is an open-label study design, results will be analyzed in a mostly descriptive method.

Smoking Outcomes: Smoking outcomes will be evaluated as a function of time over the 11-week intervention. Smoking cessation rates will also be compared from the pre to post-intervention phases.

Surgical Recovery Outcomes: Surgical outcomes will be evaluated as a function of percent biochemically-confirmed smoking abstinence, to assess whether the duration and/or magnitude of smoking abstinence is statistically associated with 30-day readmission rates, opioid analgesic use, and other surgical outcomes.

Study-related Measures: We will generate summary scores for each of the study measures and evaluate whether baseline values were positively associated with smoking outcome, and whether there were any changes in measures over time as a function of smoking status. These data will be used to help identify which measures may be most sensitive to change over time for a full-scale trial.

Sample Size Considerations: Our proposed sample of 20 completers is consistent with other open label studies of this kind. Additionally, our pilot data on bariatric patients from FY 2014 included only 23 smokers and still provided enough power to show a signal regarding the effects of smoking status on duration of hospital stay, total costs, and 30-day hospital readmissions. As such, we believe 20 completers will be a large enough sample to demonstrate an effect of the intensive intervention on promoting smoking cessation and minimizing post-surgical complications, and will also be a feasible sample size to recruit within the 2-year study period.

d. Early stopping rules.

This study will be stopped if we have evidence that enrolling participants into the study puts them at undue risk of experiencing complications during their surgery. We do not anticipate this happening, however since this is the first study of its kind in this population, we will monitor the data closely to verify safety of the participants.

9. Risks

a. Medical risks, listing all procedures, their major and minor risks and expected frequency.

Varenicline Administration:

Side-effect risks associated with varenicline administration (21): Allergic reactions to varenicline can be life-threatening and are generally characterized by a swelling of the face, mouth, and throat that can cause trouble breathing. *GI:* Nausea is the most frequent side-effect of varenicline and is present in approximately 30% of participants taking varenicline (versus 10% of participants taking placebo). The nausea associated with varenicline is generally transient, dose-dependent, of moderate intensity, and leads to dose discontinuation in only 3% (0.6% - 9%) of people who begin taking varenicline. Constipation, flatulence, and vomiting are more rare but possible side-effects. *Sleep complaints:* Insomnia (12% in

varenicline versus 10% in placebo group), and vivid or abnormal dreams. *Neurologic*: headache. *Cardiovascular*: A meta-analytic review concluded that varenicline increased the risk of cardiovascular events compared to placebo (22), however a clinical trial demonstrated that varenicline was safe for use in patients with stable cardiovascular disease (23) and an updated meta-analysis concluded that varenicline did not increase the risk of cardiovascular adverse events (24).

Psychiatric risks associated with varenicline: Cigarette smoking itself has been associated with suicidality, and there have been concerns raised regarding whether smoking cessation aids (including varenicline) increase the risk of depression and suicidal ideation and/or behavior (25). A series of case studies also reported a trend towards impulsive and unpredictable aggressive behavior among patients receiving varenicline for smoking cessation (26). These concerns prompted several meta-analytic reviews of psychiatric events following varenicline administration; all three meta-analyses concluded there was no increased risk of psychiatric events following varenicline administration for smoking cessation (26-29). A further, prospective study also reported no emergence of aggressive events among people receiving varenicline for smoking cessation (30). Therefore, though the incidence of neuropsychiatric symptoms among patients taking varenicline are of serious concern, they are expected to be rare.

Potential Drug-Drug Interactions: There is a general risk that varenicline might have an adverse reaction with another medication. The only known interactions for varenicline is bupropion (Wellbutrin, Zyban), and we will exclude all participants taking bupropion (which is another potential smoking cessation medication) from this study.

Smoking: It is possible that participants may not respond to the intervention and may continue to smoke cigarettes. Smoking incurs health risks in general and increases the risk of poor recovery, specific surgery-related side effects post-surgery, and decreased sensitivity/response to narcotic pain medications.

Discomfort from Pain Testing: Participants will likely find the pain testing procedures uncomfortable for a brief period of time. This effect is expected to be transient and to produce only mild levels of discomfort.

Hospitalization for Non-study Related Injury or Illness: It is likely and expected in this study that some participants will be rehospitalized while still enrolled in the study. We anticipate these hospitalizations will be related to their surgery and will be generally unlikely they will be related to study participation. Nevertheless, in the event of a confirmed hospitalization, study and medical staff will evaluate the event and determine whether it meets criteria for immediate reporting. Events that meet these criteria will be promptly reported to the IRB and NIH in accordance with reporting guidelines of severe adverse events (SAE). The medical monitor of the study will determine whether it is safe for the participant to remain on the study medication or resume its use based upon the specific adverse event.

Pregnancy: There is risk that female participants may become pregnant while enrolled in the study and taking varenicline. Varenicline has been assigned to pregnancy category C drug, indicating there are no adequate and well-controlled studies in humans to assess the safety of varenicline in pregnant women, and therefore is contraindicated for women who are pregnant or breastfeeding. Female participants who plan to become pregnant or who refuse to use adequate methods of birth control during the study will be excluded. Female participants will be tested for pregnancy monthly and if found to be pregnant will be discontinued from the study and varenicline will be stopped immediately.

Questionnaires and Decision-Making Tasks: Minimal risks associated with completing the questionnaires and decision-making tasks are subject fatigue and the possibility of minor psychological distress associated with answering sensitive questions regarding psychological functioning. Participants will be informed that they may choose not to answer any questionnaires that cause discomfort.

Violation of Confidentiality: The risk of violation of confidentiality exists because human subjects are giving personal information.

b. Steps taken to minimize the risks.

In order to maintain minimal risk we have established exclusion criteria to rule out individuals who might be at more than minimal risk for participating. This includes individuals having a serious and/or untreated medical and/or psychiatric illness. All personnel involved in study procedures will be fully trained in the protocol. Regarding any discomfort that may result from completing study questionnaires or tasks, participants will be informed that they are free to refrain from answering any questions that make them uncomfortable or that they perceive as being particularly personal or sensitive. No participant will be considered ineligible due to declining to answer certain items or specific questionnaires. If information gathered during the study indicates that an individual is in need of emergent psychiatric care (e.g., expressed suicidality), the investigators will place the need for treatment above research considerations. In such cases, the participant will be referred for psychiatric care at Johns Hopkins or in their home community as appropriate.

Specific Protection Against Risks:

Varenicline Administration: To minimize risks associated with varenicline administration, all participants who are deemed high-risk for experiencing varenicline-associated problems will be excluded from study participation. Participants will be informed of the risk and symptoms of an allergic reaction and will be instructed to stop taking varenicline and immediately contact medical staff if they experience any swelling or tingling in the mouth, develop a rash, or observe swelling, redness and/or peeling of the skin. Participants who meet eligibility criteria will be informed of potential varenicline-associated side effects prior to signing the informed consent. Participants will also be able to discuss any potential side effects with a medical professional or qualified study team member prior to providing informed consent to participate. Participants will be informed of the risk of nausea that is associated with varenicline administration and provided methods for alleviating or avoiding nausea (e.g., dose titration as scheduled, consuming divided doses of the medication and consuming varenicline with water and/or food).

Protection Against the Emergence of Neuropsychiatric Symptoms: The most worrisome potential side-effects of varenicline is the occurrence of rare neuropsychiatric symptoms (suicidal thoughts). Monitoring for such potential side effects will take place via multiple mechanisms. First, participants will be screened with specific questionnaires to history of suicidal thoughts and/or behaviors. Participants with severe prior or current psychiatric symptoms such as psychosis, suicidal behaviors, will be excluded from the study. Second, eligible participants will be informed of the risks for neuropsychiatric side effects and will be instructed to inform a study staff member immediately following any observed change in mood or worrisome thoughts, and will be assessed as clinically indicated. Third, trained staff members will meet with participants on a weekly basis to assess for adverse events using open-ended questions, as well as any emergency room visits and/or hospitalizations that may have occurred. Medical staff will be consulted if the participant endorses any behaviors or thought patterns that signify threats to patient safety or the safety of others, or any adverse event requiring medical attention including vital signs that are out of the norm. Adverse events will be reported to the IRB and the funding agency in accordance with reporting guidelines, and will be recorded as secondary outcome measures. Participants will complete a weekly assessment and the BDI at each study visit. Any endorsement of suicidal thoughts (at any level) on the BDI will prompt administration of the more comprehensive C-SSRS measure to fully characterize suicidal ideation. Any changes in weekly updates, regarding agitation, sadness, or hostility will also prompt assessment by a trained and qualified study investigator. A psychiatrist is always available to assist study staff in the evaluation and management of individual cases. In addition, the Emergency Department and Community Psychiatry department are located on the same campus as the BPRU smoking cessation clinic and are available to provide additional care to participants as needed. Following endorsement of any past 30 day suicidal ideations and/or behaviors, or if determined otherwise necessary by a trained member of the study staff, the individual will be escorted by a staff member to the Emergency Room (located across the street from the BPRU) for further evaluation and/or treatment. Participants will be reminded that they can stop

taking the study medication at any time. Participants who request to stop taking the study medication because of potential medication-related side effects may be permitted to continue participating in the study. This will be determined on an individual basis by the study team members.

Protection Against Risks Associated with Continued Cigarette Smoking: All participants in this study will receive access to cognitive behavioral therapy for smoking cessation, which is a standard-of-care for smoking cessation and will be informed of the potential negative impact of smoking on their surgery. Despite this, some participants may not respond to the smoking cessation intervention. We will also encourage all applicants who are not eligible for this study, participants who are discontinued or participants who have completed the study to contact the Maryland Quit Line, which is a free service that provides access to NRT products as an alternative to study participation.

Protection Against Risks Associated with Pain Testing: It is likely that participants will experience some acute and transient discomfort from the pain testing session, however we will work to mitigate that risk as much as possible. First, participants will be informed of the pain testing procedure during the informed consent and will be able to make an informed decision regarding their study participation. Second, we chose pain tests (pressure pain and conditioned pain modulation) that will produce short-lived effects, and are unlikely to produce any residual pain. Third, we will stop pain administration as soon as participants report the first incidence of "pain" (operationalized as 50% on a scale of 0% (no pain) to 100% (extreme pain)). Time to first pain will serve as our dependent variable in the analyses. Fourth, we will enforce an upper limit on both pain measures to prevent any tissue damage from occurring (e.g., hand cannot be in cold pressor task for >150 seconds). Finally, participants will be informed that they can revoke their consent to participate in the pain testing at any time without penalty

Protection Against Risks Associated with Hospitalization For Non-Study Related Injury: We fully expect some participants to be rehospitalized while enrolled in the study (30-day readmission is an outcome measure), and we expect this hospitalization to be associated with their primary surgery. As part of the study enrollment procedure, we will require permission to review each patient's EMR and therefore will be able to easily assess the reason for rehospitalization. The IRB and NIH will be informed of the event as per the standard reporting guidelines for serious adverse events. Further, each participant will be provided with a medical card that will identify them as being a member of a research study, and if necessary the hospital will be able to contact the study staff to break the blind on the medication and determine whether active study drug (e.g., varenicline) may be contributing to the problems. We will work with the hospital to have the study drug continually administered whenever possible, however in circumstances where study medication dosing has been disrupted for a period of >8 days, the varenicline dose would be adjusted for the first 3 days of treatment by the pharmacist to re-establish the maintenance dose of 1 mg/BID, according to a preset schedule. If a new medical condition occurs while the participant is enrolled in the study that is contraindicated with further study participation, the participant will be discontinued from the study. Because of the possibility of treatment interruptions described above, a participant may be enrolled in the study a few days longer than initially scheduled.

Protection Against Pregnancy: Female participants will complete a pregnancy test during the Screening visit and at monthly assessments. Female participants will be asked to agree to utilize an active form of birth control while participating in the study. If a participant becomes pregnant during study participation, varenicline will be discontinued immediately and she will be withdrawn from the study protocol.

Protection Against Questionnaires and Decision-Making Tasks: Participants will be informed that they may choose not to answer any questionnaires that cause discomfort.

Protection Against Risks associated with Breach of Confidentiality: To protect confidentiality, all research participants will be assigned unique participant identification codes that will be used on study–related

forms. Documents that include the participants' full names (e.g., signed informed consent forms) will be stored in an independent binder, consistent with FDA Good Clinical Practice Guidelines, and will be kept in a locked room. All research data will be stored in locked areas that are accessible only to research staff and that will not be left unattended. Documents with confidential information will be shredded before being discarded. Confidential information will never be shared with anyone outside of the research program without the explicit written permission of the research participant. Only selected designated staff members will be approved to share confidential information after explicit written permission is obtained from the participant and the participant can revoke written permission at any time. In accordance with IRB requirements, all research staff will be formally trained in these procedures. Finally, no identifying participant information will be used in written reports, manuscripts and/or conference presentations.

c. Plan for reporting unanticipated problems or study deviations.

All unanticipated problems will be reported to the IRB consistent with IRB reporting requirements.

d. Legal risks such as the risks that would be associated with breach of confidentiality.

We have not identified any known legal risks associated with breach of confidentiality at this time.

e. Financial risks to the participants.

None.

10. Benefits

a. Description of the probable benefits for the participant and for society.

Participants enrolled in the study will have the benefit of receiving a substantially more intensive smoking cessation intervention than is currently provided as a standard measure for smokers seeking elective surgery, which may increase their likelihood of quitting smoking before surgery, remaining quit post-surgery, and avoiding smoking-related post-surgical complications.

11. Payment and Remuneration

a. Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol.

Participants have the potential to earn up to $950 in combined study visit payments (up to $650) and potential pre-surgical monetary incentives for negative urine cotinine screens (up to $300) (see Table 2 for complete timeline of participant remuneration).

In addition, participants will have opportunities to earn a $5 bonus based on their performance on each administration of the PASAT.

Table 2. Incentive and Compensation Structur

Study Week	Study Visit	Incentives	Visit Payments
Screening			$30
1	-6		$20
2	-5	$20	$20
3	-4	$40	$20
4	-3	$60	$20
5	-2	$80	$20
6	-1	$100	$20
7	1		$50
8	2		$60
9	3		$70
10	4		$80
11	5		$90
12	6		$100
Follow-up			$50
Total:		**$300**	**$650**

12. Costs

a. Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.

There are no costs to study participants.

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