Preamble

This pilot project will involve interactions between patients in the pre-admission unit (PAU) who are scheduled to undergo a procedure at the University of Ottawa Heart Institute (UOHI) with our Registered Nurses who deliver the Ottawa Model for Smoking Cessation Program (OMSC) at UOHI, the largest smoking cessation program in Canada. This clinic combines researchers with clinical experts to provide high quality, innovative clinical care to smokers.

1.0 BACKGROUND AND KNOWLEDGE TO DATE

Tobacco use is a principal, causative factor in the development of cardiovascular diseases, including coronary artery disease (CAD) (4). Smokers are more likely to have heart attacks and undergo revascularization procedures such as coronary artery bypass grafting (CABG) (4). Approximately 20% of all patients undergoing CABG are smokers at the time of admission for surgery (5). Smoking is linked to multiple procedural complications including wound infections, respiratory failure, myocardial infarction, stroke; sepsis, shock, and prolonged hospital stay (6). Most smokers about to undergo CABG (> 80%) say they would like to quit; but, long-term follow-up data indicate that < 25% will be smoke-free 6 months after their surgery (7). Nicotine addiction causes compulsive use of tobacco products despite repeated attempts to abstain (8).

Elective procedures provide a unique opportunity for physicians to help smokers quit. Most hospitals use pre-admission units (PAUs) to ensure elective patients are: fit for surgery; prepared appropriately; have made plans for their recovery; and aware of what to expect before and after their procedure. Pre-admission for cardiac procedures at UOHI usually occurs 1-3 weeks before the planned surgical date. Each year at UOHI, approximately 780 patients are evaluated in the PAU. Quitting smoking several weeks (> 4) before surgery has been shown to improve peri-operative outcomes (9).

There is an opportunity to use the pre-admission visit as a venue for the delivery of interventions to help smoker-patients quit smoking. Pharmacotherapy, including Nicotine Replacement Therapy (NRT), is an important component of efficacious smoking cessation practice (10). There is a need to understand the efficacy of NRT, initiated in the PAU prior to surgery, in enhancing long-term abstinence in those undergoing a cardiac procedure. Previous studies have only examined the role of pre-operative NRT use in patients undergoing elective hip and knee replacement surgeries; the benefits in a cardiac population are unknown. In addition, cessation a month or more prior to surgery reduces peri-operative complications and ensures long-term abstinence.

2.0 Research Aim

1. To determine if pre-operative NRT improves the long-term quit rates among smokers undergoing an elective cardiac procedure.
2. To determine the effect of pre-operative NRT on perceived stress and symptoms of nicotine withdrawal at the time of surgery.
3. To assess, retroactively, the impact of pre-operative cessation on peri-operative complications such as infection rates, respiratory failure, myocardial infarction, stroke, sepsis, shock and prolonged hospital stay.

2.1 HYPOTHESES TO BE TESTED

We hypothesize that if NRT is given to smokers during the pre-admission period, they are more likely to be biochemically abstinent from cigarette smoking 6 months after hospitalization and will experience fewer peri-procedural complications.

3.0 METHODS TO BE USED

3.1 Design

A single site, double-blinded randomized controlled trial will be conducted at the University of Ottawa Heart Institute (UOHI). Patients who are identified as a smoker at their initial visit to the PAU will undergo a baseline assessment and be randomly assigned (1:1) to either active or placebo NRT patch. They will wear the patch from that baseline visit until the day of their surgery at UOHI. Following their surgery, they will receive a follow up phone call at 1 and 6 months post-discharge. They will complete a series of short questionnaires to assess their smoking status, stress levels and nicotine withdrawal symptoms. Those who identify themselves as being smoke-free will be asked to complete a carbon monoxide breathing test to chemically validate their smoking status. The study protocol will be reviewed by the Research Ethics board at UOHI and all participants will provide written informed consent prior to undertaking any study activities.

3.2 Participants

60 smokers scheduled to undergo an elective cardiac procedure at UOHI will be recruited at the PAU pre-operative visit. PAU nurses will document smoking status and assess interest in participating in a study addressing smoking behaviour prior to admission. We will offer the intervention to all smokers, not only those interested in quitting.

3.2.1 Inclusion criteria

1. Patients who are (is) currently smoking ≥5 cigarettes/day for the past 30 days; there is no evidence that NRT is useful in those who smoke <5cpd.
2. Patients who are (is) able to participate and willing to provide informed consent; participants will need to follow directions and adhere to the medication usage instructions as outlined in the informed consent document.
3. Patients who are (is) willing to be contacted by phone for follow up at 1 month and 6 months post-discharge; these time points will assess our final outcome of cessation at 6 months post-discharge.

3.2.2 Exclusion criteria

1. Patient is scheduled for a cardiac procedure in <1 day.
2. Patient is currently using a smoking cessation product (i.e. nicotine containing patch, gum, inhaler, lozenge, spray or nicotine containing electronic cigarette, varenicline, buproprion) or has used a smoking cessation aid consistently for more than 72 consecutive hours with the intent to reduce cigarette consumption or quit smoking within 30 days of the baseline PAU visit; this will ensure the effects of the study patches will be assessed without any contamination from other cessation products.
3. Patients is willing to refrain from using any other cessation products (nicotine containing patch, gum, inhaler, lozenge, spray, nicotine containing electronic cigarette, varenicline, buproprion) prior to surgery; this will allow us to track the usage and side effects with the study patches.
4. Patient is allergic to the adhesive on the nicotine replacement therapy patch.

5. Patient is unable to read and understand English or French; study materials will only be supplied in these two languages.
6. Patient has a positive urinary pregnancy test.

3.2.3 Feasibility of recruitment

Pre admission for scheduled procedures usually occurs 1-3 weeks before the planned procedure date. Each year approximately 2058 patients undergoing an elective procedure are evaluated in the PAU. We expect that the recruitment of participants can be completed over a 15 month period.

4.0 Procedures

4.1 Recruitment and baseline assessment

All patients who are identified as a current smoker at their initial PAU visit will be approached by a nurse from the Ottawa Model for Smoking Cessation Program (OMSC) for participation in the study. Patients who are not interested in participating will have the option to meet with the OMSC nurse as would normally happen in the PAU. This is the standard of care for all smoker patients identified in the PAU. If the patient is interested in participating in the study, the OMSC nurse will notify the Research Coordinator (RC) who will come to the PAU to meet with the patient to review and sign the consent form. Following the consenting process, participants will complete questionnaires addressing their smoking history, previous quit attempts, perceived stress, and nicotine withdrawal. The RC will also collect a carbon-monoxide (CO) breath sample using a handheld CO monitor (Bedfont Inc. Smokerlyser) from the participant. If the participant is of childbearing age and has not had a full hysterectomy, a urinary pregnancy test will be completed (prior to randomization). Following the baseline assessment, the Research Coordinator will extract pertinent features of the medical history from the clinical chart including: other diagnoses (e.g. cancer, COPD, diabetes, autoimmune disorders); mental health status; and, previous surgeries/procedures (appendix A).

4.2 Allocation to treatment

On-line software will randomly allocate participants, in a 1:1 fashion, to either the intervention (INT) or placebo (PLB) arm and generate a number identifying a 'medication' supply for the participant. The randomization list will be kept with the research manager, all other staff will be blinded to the treatment allocation. Upon receiving written consent, the research manager will be paged by the RC. The research manager will allot the required medication (# of days to scheduled surgery) to the study nurse who will then dispense the medication to the participant. Active and placebo patches will be identically packaged and stored at UOHI in a secure, temperature monitored, cabinet on the 2nd floor (room 2353).

4.3 Interventions

Intervention at the time of the PAU visit will be identical for all participants. The Anaesthesiologist in the PAU will advise participants to 'fast' from smoking prior to their elective admission. A Nurse from the OMSC program will demonstrate the appropriate use of the NRT patch, discuss tactics for remaining smoke-free and provide a 'tip-sheet' with instructions about patch use and a summary of the nurse's advice (appendix B). Participants will be provided with a diary to record patch use (appendix C) and will be given a set of questionnaires to be completed the day before their scheduled procedure. The questionnaires are identical to the first visit and will assess their smoking status, stress level, and withdrawal symptoms. Those receiving active NRT will receive 21mg patches; identical placebo patches will contain no nicotine. Participants will be instructed to keep the individual patch packages

and return them along with any unused patches when they come in for their procedure. Following the procedure, during their hospital admission, all participants will receive the standard of care UOHI smoking cessation intervention ('The Ottawa Model').

4.4 Medication

Participants will receive the appropriate number of patches based on their scheduled procedure date. They will be instructed to wear one patch per day until their procedure date (appendix B). All participants will receive a call from the RC at the end of the 2nd week of treatment. If their procedure has been delayed, participants will receive additional medication (either sent to participant by courier or picked up by participant). Under these circumstances the RC will provide additional telephone calls every second week based on how long the procedure has been delayed. The medication will be allotted by the research manager in order to ensure study staff remain blinded to treatment allocation. Following their procedure, participants will be permitted to use any nicotine containing cessation product as required, at their own expense. Additional medication usage will be documented during the 1 and 6 month post-discharge follow up. Those participants who discontinue the patch prior to surgery will still be contacted for follow-up. All patches (active and placebo) will be securely stored in a secure, temperature monitored, cabinet on the on the 2nd floor (room 2353) in accordance with the standard operating procedure C-3-006.03 (Management of Clinical Research Products). Participants will be instructed to return all used and unused patches to study staff on the day of their surgery for reconciliation.

4.5 Follow-up assessments

Follow-up will occur at admission, 1 and 6 months post-discharge. At admission, a CO sample will be collected, unused patches and used patch packets will be collected and questionnaires (previously sent home with the participant) will be collected. Following their discharge, the RC will complete a retrospective chart review and assemble evidence of peri-procedural complications. Information will be abstracted using a standardized data collection form (appendix D). The chart review will seek evidence of peri-procedural complications including: sputum volume; respiratory complications including bronchospasm, atelectasis and pneumonia, prolonged intubation; wound infection; duration of hospital stay; and mortality. We will compare complication rates between groups.

The same set of questionnaires administered at the baseline visit will be administered again either in person or by telephone at 1 and 6 months post discharge. Participants who self-report that they are abstinent from smoking will have their smoking status verified using CO monitoring. The CO sample will be obtained as soon as possible in a location of the participant's choosing.

5.0 Measures

See Table 1for study timeline

5.1 Demographic Information and Medical History

At the baseline visit, participants will complete a questionnaire to document their gender, marital status, level of education, employment status and income range. The RC will extract information recorded by the PAU nurse at the initial visit from the participant's chart (age, sex, weight, height, blood pressure and resting heart rate). Cardiovascular history and other co-morbidities (peripheral

vascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, asthma, cancer) will also be extracted.

5.2 Smoking Status

The primary outcome will be CO-confirmed abstinence from smoking 6 months after discharge. This will be the main indicator of success. Participants self-report their smoking status in response to two questions: 1) "Have you smoked any form of tobacco (even a puff) in the past 7 days?" and 2) "Have you smoked any form of tobacco (even a puff) since your cardiac procedure". Self-reports of smoking abstinence will be chemically validated using expired CO levels measured by the Bedfont Smokelyser. CO concentrations < 10 ppm are confirmatory of tobacco cessation. Smoking status and CO levels will also be determined at the time of the baseline PAU visit, date of hospital admission for surgery and 1 month after the participants procedure; these are secondary indicators of success. We will compare quit rates between the NRT and placebo groups. For the purposes of the outcome analysis, drop-outs and participants who cannot be contacted for follow-up will all be considered smokers.

5.3 Smoking History

Smoking history will be assessed at baseline to identify the current forms of tobacco that are being used, the number of cigarettes smoked per day, the number of years the participant has been smoking, the time of day at which the first cigarette is consumed, the presence of other smokers in the home and the total number of quit attempts (lasting 24 hours) in the past year. Using a scale of 1-5 with 5 being the most important, participants will be asked to rate how important they feel it is for them to quit smoking and asked to rate their confidence in being able to quit.

5.4 Nicotine Dependence

Nicotine dependence will be tested at baseline using the 6 question Fagerström Test for Nicotine Dependence scale. Scores range from 0 to 10 with scores ≥ 6 indicating a high level of nicotine dependence. We will compare scores between groups.

5.5 Withdrawal symptoms

Nicotine withdrawal will be measured at each visit using the Minnesota Nicotine Withdrawal Scale (MNWS). The MNWS measures cravings for nicotine as well as levels of depression, insomnia, irritability/frustration/anger, anxiety, difficulty concentrating, restlessness, and increased appetite/weight gain over a 24 hour period. We will compare withdrawal symptoms between groups.

5.6 Perceived Stress

Perceived stress will be measured at each visit using Cohen's 14-item Perceived Stress Scale (PSS-14). The PSS-14 measures the degree to which situations in an individual's life are appraised as stressful. Items are designed to assess how unpredictable, uncontrollable, and overloaded respondents find their lives to be. The scale also includes a number of direct queries about current levels of experienced stress. Perceived stress is an important patient-reported outcome. We will compare stress levels between groups.

5.7 Use of Cessation Resources

Use of cessation resources will be measured at the admission visit, 1 and 6 month follow-ups. Participants will be asked if they have used various forms of pharmacotherapies, joined cessation programs, or had individualized cessation support or counselling sessions since the last contact. We will compare resource usage between groups.

6.0 Adverse Events

All adverse events will be assessed by the Qualified Investigator who will determine whether or not the event is serious in nature. Any adverse event that is life-threatening, persistent or causes significant disability, or that requires re-hospitalization or leads to death will be recorded as a serious adverse event and will be addressed as per SOP C3-007.1 Safety Reporting Requirements.

A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose:

- results in death;
- is life-threatening;
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity; or
- is a congenital anomaly/birth defect.

The qualified investigator will determine whether or not the participant can remain in the trial and what medical treatment they may require as a result of the adverse event.

If participants have any concerns about their health during the pre-operative phase, they will be instructed to contact their PAU nurse, physician or proceed to the emergency department.

6.1 Unblinding

In the event of a serious adverse event, as outlined above, unblinding may be required. In this case, a member of the study team will carry a 24 hour pager and upon notification, they will open up the randomization envelope for that participant. A note to file will be generated to document the unblinding and an adverse event report will be completed.

7.0 Analysis of Results

This is a pilot study that will inform a larger, definitive trial. It will provide information on recruitment rates, completion of treatment and drop-outs rates, as well as a preliminary estimate of the effect size of the intervention. The minimal clinically important difference for clinical trials of smoking cessation is a 7% absolute difference in quit rates between groups. With 30 participants per group, we will have 10% power to detect a 7% difference between groups assuming the quit rate in the placebo group is 15%. We realize that this pilot study is not powered to provide a definitive answer to our research question, rather its results will inform the design of a larger trial.

8.0 Anticipated results and conclusions

This project has the potential to impact patient related outcomes, clinical practice and the healthcare system. Smoking cessation is the most effective way to reduce morbidity, re-admissions and mortality in CAD patients (1). Successful cessation can also result in improved quality of life, and reduced rates of cancer, respiratory diseases and/or dementia (4). Cross-sectional surveys indicate that very few smokers receive appropriate smoking cessation advice and assistance from anesthesiologists before surgery (2). If more people receiving active NRT quit smoking compared to those receiving placebo it

will indicate that NRT should become a standard element of pre-admission care of patients. This study will provide evidence to support changes in clinical practice and provider behavior (3).

This patient population was selected as cardiac procedures provide a teachable moment during which health care providers can intervene. UOHI has a state-of-the-art, inpatient smoking-cessation program ('The Ottawa Model') but the program has not been adapted for the PAU setting. There will be significant health benefits if we can develop and deliver more effective treatments for smoking cessation in this context. Smokers who quit before and remain smoke-free after their cardiac surgery will derive significant health benefits. Smoking cessation has been shown to significantly reduce morbidity, readmissions, and mortality in those with cardiovascular disease (1,4,5,8).

This project is innovative in three key ways:

1) There have been no previous placebo-controlled trials of NRT in the pre-operative phase prior to CABG surgery. Previous investigations have been conducted in populations undergoing elective hip and knee replacement and general surgery. We will be able to assess the efficacy of such interventions and to assess if NRT is a critical element of smoking cessation treatment initiated in the PAU.

2) The long-term cessation benefits of interventions initiated more proximal to the date of a cardiac procedure are not known. While it is clear that quitting a month or more beforehand has benefits, we will find out if there are benefits to quitting closer to the date of various procedures.

3) We will offer the intervention to all smokers, not just to those that are interested in quitting (i.e. interest in quitting smoking will not be an inclusion criterion). We will position the intervention as a `fast' from smoking that will contribute to the success of the the procedure and recovery. By including smokers not interested in quitting, we will be maximizing the generalizability of our findings.

We are confident that if proven successful the delivery of structured approaches to smoking cessation in the PAU will become a new pattern of practice with obvious implications for the health of our patients -- and subsequent utilization of health-care resources.

9.0 POSSIBLE PROBLEMS

Trials involving behavioural interventions come with a series of challenges, especially in a pre-operative group of patients. Because of the nature and severity of CAD, patients may be unwilling to not only enroll in the study, but reluctant to give up smoking completely. Those that do enroll could be biased, as those who join may be more inclined to want to quit smoking. We have however conducted a number of successful inpatient-based smoking cessation clinical trials that have helped inform this current study. We are therefore confident that we can in fact recruit our entire sample as planned. Another problem we may counter involves the study medication. It is the responsibility of the patient to take the medication as directed from the initial assessment until their surgery. They could at any time discontinue the study medication prior to their procedure or, in an effort to have a successful cessation attempt, introduce other cessation products such as the electronic cigarette or seek support from another health care provider. This contamination would also impact the final outcome. Finally, participants must agree to not only complete their follow up visits after their procedure, but they must agree to have their smoking status validated if they are found to be smoke free. In order to minimize this potential challenge, we will allow the participants to select where such validation occurs, either at UOHI, at their home, or at a location of their choosing in the community.

10.0 ASSEMBLED RESEARCH TEAM AND TIME ON PROJECT

This project is a collaboration between the Division of Prevention and Rehabilitation and the Division of Anaesthesia at the UOHI. Dr. Andrew Pipe is the former Chief of Prevention and Rehabilitation who continues to run his practice as well as lead various research. Dr. Pipe is an international expert on nicotine addiction and its treatment. He is a principal developer of the Ottawa Model for Smoking Cessation (along with Co-I Reid). Dr. Pipe will oversee the trial and coordinate knowledge translation activities post-trial. Dr. Peter Wilkes is an anaesthesiologist in the Division of Cardiac Anaesthesia. Dr. Wilkes is an example of a knowledge user in that it is his responsibility to oversee procedures to address tobacco use among patients processed through the PAU. He has informed development of the research questions and the study methodology. He will assess study eligibility, advise on clinical issues in PAU, and provide advice to quit to smoker-patients in the trial. Dr. Robert Reid is Deputy Chief of the Division of Prevention Rehabilitation and an experienced clinical trialist. He will oversee randomization and data analysis and assist with end-of-trial knowledge translation. Ms. Marta Klepaczek is an Advance Practice Nurse in the Quit Smoking Program. Ms. Klepaczek will train the nurse-specialists to deliver the counseling intervention to PAU smoker-patients. Ms. Evyanne Wooding is the Research Manager in the Division of Prevention and Rehabilitation. Ms. Wooding will: develop study standard operating procedures; assist with ethics submission and the design of study database; and supervise the research assistant working on study.

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Table 1 – Study timeline

	Baseline (in person)	**Procedure Admission** (in person)	**1M Post-Op** (phone)	**6M Post-Op** (phone)
Consent	x			
Randomization	x			
Smoking Status	x	x	x	x
CO Sample	x	x*	x*	x*
Questionnaires**	x	x	x	x
Counseling	x			
Patch usage	x			

*CO sample only obtained if participant reports being smoke free

**Questionnaires include: Perceived Stress Scale-14, Minnesota Nicotine Withdrawal Scale, Fagerstrom Scale for Nicotine Dependence, Use of Cessation Resources