BMJ Open  Cost-free pharmacotherapy in smokers with TIA or stroke: QUIT-MED randomised controlled trial

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ABSTRACT
Objective To examine whether cost-free (CF) smoking cessation medication was more effective than a prescription for cessation medication in patients after transient ischaemic attack (TIA) or stroke.
Design Two-site randomised trial.
Setting Stroke prevention clinics (SPCs) in Ontario, Canada.
Participants Smokers with TIA or stroke, willing to quit smoking.
Intervention Smoking status was assessed in SPC attendees. Smokers were advised to quit smoking and received recommendations for cessation medication and counselling. Consenting participants were randomly assigned (1:1) to either a CF medication group or a prescription-only (Rx) group. CF participants immediately received a 12-week supply of cessation medication. Rx participants were given a prescription for 12 weeks of cessation medication. Follow-up counselling was provided for 26 weeks.
Main outcome The primary outcome was 40-week continuous abstinence verified using a carbon monoxide breath test at 52-week follow-up. Secondary outcomes included abstinence at intermediate timepoints, medication adherence and serious adverse events.
Results Hundred and ninety-four participants were randomised and 131 (67.5%) completed the trial. The 40-week continuous abstinence rate at 52-week follow-up was 15.5% in the CF group versus 14.0% in the Rx group (OR=1.13; 95% CI 0.51 to 2.53). The 14-week continuous abstinence rate at 26-week follow-up was 18.6% in the CF group versus 16.8% in the Rx group (OR=1.20; 95% CI 0.56 to 2.55). Seven-day point-prevalence abstinence at 12 weeks was 38.1% in the CF group versus 26.9% in the Rx group (OR=1.76; 95% CI 0.94 to 3.28). Medication adherence was higher in the CF group versus the Rx group (47.4%±41.2% vs 25.5±36.8%, p<0.001). Serious adverse events occurred in 11.1% of participants and were unrelated to treatment.
Conclusions Our findings were inconclusive; we failed to meet our recruitment target and the effect size was smaller than anticipated. CF medication improved medication adherence.
Trial registration number NCT00962988; ClinicalTrials.gov Identifier.

STRENGTHS AND LIMITATIONS OF THIS STUDY
⇒ This is the largest reported randomised controlled trial of a smoking-specific intervention for patients after a transient ischaemic attack or stroke.
⇒ The intervention was codesigned with patients, neurologists and nurses to fit within the context of outpatient stroke prevention clinics.
⇒ The primary outcome was verified, long-term abstinence from smoking measured at 52-week follow-up.
⇒ Our results were inconclusive; we failed to recruit our intended sample size because many smoker-patients were not ready to quit smoking within 30 days of their stroke prevention clinic visit.

INTRODUCTION
Cigarette smoking increases the risk for ischaemic and haemorrhagic stroke and there is a strong dose-dependent relationship between amount smoked and stroke risk.1 Current smokers have a twofold to fourfold increased risk of stroke compared with lifelong non-smokers or individuals who have been smoke-free for 10 years or more.2 Risk is increased by 12% for every five cigarettes smoked per day, and stroke patients who smoke experience an initial stroke 11.4 years earlier than non-smokers (at 61.8 vs 73.2 years of age; p<0.001).3 Mechanisms include effects of cigarette smoke on atherosclerosis, coagulation, endothelial dysfunction and oxidation.4 Cessation of cigarette smoking after a stroke or transient ischaemic attack (TIA) reduces risk of recurrent stroke by half within 3 months5 and reduces stroke, MI and death by 30% over 5-year follow-up.6 Consequently, guidelines recommend interventions to increase smoking cessation after a TIA or stroke.7 8

Many smokers who experience a stroke or TIA continue to smoke. Our systematic review of randomised controlled trials (RCTs) of...
smoking cessation interventions in smokers with cerebrovascular disease (four studies, 354 patients) showed that the long-term cessation rate following a smoking cessation intervention was 23.9% (42 of 176) while without one it was 20.8% (37 of 178).9 A recent review of prospective cohort and clinical trials of smoking cessation after stroke or TIA (25 trials, 1604 to 1920 patients) found self-reported cessation rates of 51%, 44% and 44% at 3-month, 6-month and 12-month follow-up, respectively.10 Higher levels of disability postevent, lower levels of depression and more intensive support were associated with higher rates of cessation.

Nicotine replacement therapy (NRT), bupropion and varenicline, when combined with counselling, can double or even triple long-term smoking abstinence in smokers trying to quit.11–16 Unfortunately, many patients must pay for medication; the cost associated with treatment has been identified as a barrier to use by many smokers, particularly those in the low-income categories. Studies in non-stroke/TIA populations have found that the provision of cost-free (CF) medication increases motivation to quit, the number of quit attempts and long-term smoking abstinence.17–20

We conducted the Cost-free QUITting MEDication for High Risk Smokers with Cerebrovascular Disease (QUIT-MED) study to examine whether the immediate provision of CF smoking cessation medication was more effective than providing a prescription for such medication among patients following TIA or stroke. The main premise of our study was that reducing the time, effort and financial outlay to acquire smoking cessation medications would make it more likely these medications would be used during a quit attempt, and long-term cessation rates would be increased. Interventions were provided by clinic staff to replicate ‘real-world’ conditions.

METHODS
Patient and public involvement
This project was developed in collaboration with clinicians and patients from the stroke prevention clinic (SPC) at the Ottawa Hospital. Patients were first involved in a survey of smokers who attended the SPC. More than 80% of smoker-patients said they intended to quit smoking within 6 months. They identified the cost of smoking cessation medications as a barrier to making a quit smoking attempt. SPC clinicians helped develop study tools to identify patient smoking status, guide cessation counselling and make decisions about cessation medication. Patients participated in a pilot study of methods used in the current trial.21

Design
QUIT-MED was a pragmatic, open-label RCT undertaken at two SPCs (Ottawa and Hamilton) in Ontario, Canada from December 2009 to January 2015. SPCs in Ontario offer early assessment, teaching and follow-up to prevent a recurrent event for people with a recent stroke or TIA, generally within 6 weeks of an index event. The trial protocol and statistical analysis plan appear in online supplemental file 1. Consenting smokers with TIA or stroke were randomly assigned (1:1) to either a CF medication treatment group or a prescription only (Rx) usual care group.

Participants
Individuals were recruited during their visit to the SPC. Current daily smokers over the age of 18 years with a confirmed diagnosis of TIA or stroke who were willing to quit smoking in the next 30 days using an approved smoking cessation medication were invited to participate in the study. We excluded patients: who were pregnant or lactating; with cognitive impairment that would preclude study participation (in the opinion of the attending neurologist); currently using cessation medication; with contraindications to all smoking cessation medications; unavailable for follow-up or unable to speak English or French.

Randomisation and blinding
Participants were stratified by site and time to first cigarette (≤30 min or ≥30 min) and randomly allocated to either a CF or Rx group. Participants were allocated to treatment using a computer-generated randomisation scheme that was concealed to participants, investigators and healthcare providers with codes sealed in opaque envelopes. When a patient was enrolled, an envelope was opened in sequence to disclose the result of the randomisation. Block randomisation (block sizes of 4 to 8) and allocation concealment were performed by a statistical consultant not affiliated with the study. Participants were not blinded. Outcome assessments were performed by research staff unaware of treatment allocation.

Interventions
Prior to study initiation, the SPCs implemented systematic processes and tools to identify and assist smoker-patients based on the Ottawa Model for Smoking Cessation.22 SPC neurologists and nurses received training regarding processes for identifying smokers, providing counselling and prescribing smoking cessation medication.

Current smokers were identified at clinic check-in using a waiting room screening questionnaire. SPC neurologists advised all smoker-patients to quit smoking, indicated that effective cessation treatments were available, and assessed patient interest in making a quit attempt within 30 days. Patients willing to make a quit attempt met with an SPC nurse to complete a smoking cessation consultation. The nurse helped to select cessation medication (NRT monotherapy, combination NRT, varenicline or bupropion), provided practical counselling about quitting (such as anticipating challenges, preparing to quit) and worked with the patient to set a quit date. At the end of the consultation, a prescription for cessation medication was prepared and signed by the SPC neurologist (Nota Bene: NRT does not require a prescription in Ontario;
however, if a patient presents a prescription for NRT at a pharmacy, the pharmacist will assist the patient to find the specified medication and dosage). At the end of the consultation, the SPC nurse asked eligible patients if they were interested in participating in a study of smoking cessation medication. If interested, informed consent was obtained. Participants were then randomly assigned to treatment groups.

Participants in the CF experimental group were immediately provided with a CF 12-week supply of cessation medication. Participants in the Rx usual-care group were provided with a prescription for a 12-week course of medication to fill at a pharmacy at their own cost.

All participants were registered in a centralised smoker follow-up system, staffed with nurse-cessation specialists.23 24 The follow-up system automatically placed follow-up telephone calls to participants 7 days before their target quit date and then 3, 14, 30, 60, 90, 120, 150 and 180 days after. Automated calls typically lasted 1–2 min. During the calls, if participants identified that they were unprepared for quitting, had resumed smoking or expressed low confidence in remaining smoke free (<3 on a 5-point scale); a nurse cessation specialist contacted the participant and provided additional assistance, using standardised counselling scripts. The automated calling system has been evaluated in an RCT and improved long-term verified continuous abstinence rates from 29.5% to 38.0% in smokers with heart disease compared with no follow-up counselling.23

Baseline and follow-up assessments

At baseline, information about medical history and comorbidities was abstracted from the patient chart. Questionnaires were used to gather information about current pharmacotherapies, smoking history, level of nicotine dependence,25 previous attempts to quit and insurance coverage for smoking cessation medication. At 26-week and 52-week follow-up, participants returned to the study site and completed an interview with a research assistant blinded to group assignment. The interviewer asked about smoking status since week 12 and over the previous 7 days. Participants who reported they were smoke free were asked to provide a breath sample for carbon monoxide determination. Information was also gathered concerning medication use and serious adverse events (SAEs) since last contact.

Outcomes

The primary outcome was continuous abstinence from smoking (self-report of not having smoked >5 cigarettes during the 40-week period preceding the 52-week follow-up) that was verified using a carbon monoxide breath test (<10 ppm).26 Participants lost or unavailable for follow-up or carbon monoxide validation were considered smokers for analysis purposes. Secondary abstinence outcomes included verified continuous abstinence during the 14-week period preceding the 26-week follow-up and 7-day point prevalence abstinence at 12, 26 and 52 weeks. Other secondary outcomes included medication adherence, duration of medication use (weeks), participation in counselling calls and SAEs. These outcomes were obtained from study records, enrolments in the telephone follow-up system, nurse-counsellor records and in person assessments completed at 26 and 52 weeks. Medication adherence was self-reported and calculated as the number of doses taken divided by the number of doses prescribed over the initial 12-week medication treatment period. SAEs were defined as any adverse event that was life-threatening or resulted in hospitalisation, persistent or significant disability, incapacity or death. An independent data-safety and monitoring committee reviewed all SAEs to determine whether there was any relationship to study participation.

Sample size

A total of 562 participants were to be included in the study. The primary end point used in the sample size determination was the 40-week continuous abstinence rate measured at 52 weeks. The sample size calculation assumed that the cessation rate in the Rx control group would be 30% compared with 40% in the CF group, with 80% power and an alpha level of 0.05. This base rate assumption was based on quit rates observed among patients with cerebrovascular disease participating in a pilot study with similar intervention.21

Statistical methods

The statistical analysis was guided by a prespecified analysis plan. All patients randomised were included in the intent-to-treat analysis, except those who died or moved to an untraceable address.26 For the primary endpoint analysis, we used logistic regression with verified 40-week continuous abstinence status (smoker or non-smoker) at 52-week follow-up as the dependent variable and treatment group and recruitment site as independent variables. Secondary analyses were conducted using similar techniques with verified 14-week continuous abstinence at week 26 and 7-day point prevalence abstinence at 12, 26 and 52 weeks as dependent variables of interest. The post hoc analysis of self-reported 7-day point prevalence abstinence assessed at 12 weeks was not prespecified. Medication adherence and duration of medication use over the first 12 weeks were compared between group using \( \chi^2 \) tests. The proportions of participants using at least one dose of medication, using all recommended doses and using medication at 26-week and 52-week follow-up were compared between groups using \( \chi^2 \) tests. SAE rates were described by group using descriptive statistics. Multiple comparisons increase the potential for type I error. Findings for the analyses of secondary outcomes should be viewed as exploratory.

RESULTS

Figure 1 shows the numbers of patients who were enrolled and the numbers who were excluded. The
The principal reasons for exclusion were that the patient did not have a diagnosis of TIA or stroke or was not willing to quit smoking in the next 30 days. We failed to recruit our intended sample size. After inviting 294 eligible patients, 194 agreed to participate and were randomly assigned to treatment: 99 to the CF group and 95 to the Rx group.
Table 1 shows demographic, clinical and smoking-related characteristics of patients by treatment group. Baseline characteristics were balanced across groups.

Table 2 summarises participation in intervention components. Most participants (53.5%) were advised to use combination NRT, followed by varenicline (26.3%), NRT monotherapy (14.8%) and bupropion (5.2%). Just over half of all Rx participants (52.6%) filled their prescription, leading to lower medication use in this group during the initial medication treatment phase. Medication adherence rates were nearly double in the CF group versus the Rx group (47.4%±41.2% vs 25.5%±36.8%, p<0.001) and using all recommended doses of medication (23.2% vs 11.6%; p=0.03) was higher in the CF group compared with the Rx group. Considering only those participants who took at least one dose of medication, the CF group tended to use medication for more weeks than the Rx group. Some participants were still using cessation medications at 26 weeks and 52 weeks. Of the nine scheduled automated follow-up calls, participants completed an average of 6.1±2.7 calls. In response to flagging from the automated calling system, participants completed an average of 3.6±2.5 ‘live’ nurse cessation specialist calls during the study; the average length of each of these calls was 15.5 min. There were no differences between groups for number of automated calls or nurse cessation specialist calls completed (see table 2).

The follow-up rate for the primary outcome was 67.5% (131 participants), and there was no evidence of a significant difference in the follow-up rate between study groups. Following randomisation, one participant in each group died and one participant in each group moved to an unknown address; these participants were removed from the outcome analysis as per convention in studies of smoking cessation interventions.

The primary smoking cessation results are shown in table 3. The 40-week continuous abstinence rate at 52-week follow-up was 15.5% in the CF group compared with 14.0% in the Rx group (OR=1.13; 95% CI 0.51 to 2.53). The 14-week continuous abstinence rate at 26-week follow-up was 18.6% in the CF group compared with 16.8% in the Rx group (OR=1.20; 95% CI 0.56 to 2.55). The 7-day point prevalence abstinence rates at 12, 26 and 52 weeks were 38.1%, 21.6% and 22.7% in the CF group versus 26.9%, 18.3% and 17.2% in the Rx group.

Because a high percentage of Rx participants did not fill their prescriptions, we conducted an exploratory analysis to compare those who filled their prescription to those who did not. Prescription fillers were older (mean age 58.0 vs 54.7 years), with higher nicotine dependence scores (5.0 vs 4.1 Fagerstrom Test of Nicotine Dependence points), and more likely to have insurance coverage for smoking cessation medication (24.0% vs 15.9%). The verified continuous abstinence rate at 52 weeks among prescription fillers was 14.0% compared with 14.6% among non-fillers (OR=0.972, 0.29 to 3.26; p=0.96).

SAEs occurred in 11.1% of participants (table 4). Ten patients in the CF group experienced a total of 16 SAEs; four patients experienced more than one event. Twelve patients in the Rx group experienced a total of 16 SAEs; two patients experienced more than one event. An independent data safety and monitoring committee determined that all observed SAEs were unrelated to study participation.

**DISCUSSION**

Our study was inconclusive as to whether immediate and CF smoking cessation medication was more effective than providing a prescription for smoking cessation
medication for patients following TIA or stroke. The absolute improvement in the long-term, verified continuous abstinence was 1.5% with CF medication (15.5% vs 14.0%), but our CI did include larger effect sizes that could be clinically important. We failed to meet our recruitment target and the effect size was smaller than the 10% absolute improvement in continuous abstinence anticipated. Fewer patients with stroke and TIA attending the SPCs were willing to quit smoking within 30 days than we anticipated (43% actual vs 63% expected). Participants in the CF intervention group used significantly more medication during their initial quit attempt primarily because a high proportion or patients in the Rx control group (47.4%) failed to fill their prescription. SAEs occurred in 11% of participants over 52-week follow-up; these events were not related to group assignment or smoking cessation medication.

Although we failed to meet our recruitment target, this is the largest reported RCTs to date of a smoking cessation intervention in the context of secondary stroke prevention. The cessation intervention was delivered with high fidelity by regular SPC staff assisted by nurse cessation specialists, rather than research staff, demonstrating that these interventions can be incorporated into SPC routines. Blinding of participants was not possible; however, outcome assessors were unaware of treatment assignment. Carbon monoxide measured in expired breath was used to validate self-reports of non-smoking.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cost-free group</th>
<th>Prescription group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>99</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>NRT monotherapy</td>
<td>13 (13.1)</td>
<td>16 (16.8)</td>
<td>0.61</td>
</tr>
<tr>
<td>NRT combination</td>
<td>52 (52.5)</td>
<td>52 (54.7)</td>
<td></td>
</tr>
<tr>
<td>Varenicline</td>
<td>27 (27.3)</td>
<td>24 (25.3)</td>
<td></td>
</tr>
<tr>
<td>Bupropion</td>
<td>7 (7.1)</td>
<td>3 (3.2)</td>
<td></td>
</tr>
<tr>
<td>*Prescription filled, n (%)</td>
<td>N/A</td>
<td>50 (52.6)</td>
<td></td>
</tr>
<tr>
<td>Used at least one dose, n (%)</td>
<td>72 (72.7)</td>
<td>45 (47.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Medication adherence, mean±SD</td>
<td>47.4±41.2</td>
<td>25.5±36.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Used all recommended doses, n (%)</td>
<td>23 (23.2)</td>
<td>11 (11.6)</td>
<td>0.03</td>
</tr>
<tr>
<td>†Duration of medication use, mean weeks±SD</td>
<td>7.7±4.2</td>
<td>6.3±4.5</td>
<td>0.09</td>
</tr>
<tr>
<td>Using smoking cessation medication at 26 weeks, n (%)</td>
<td>13 (13.1)</td>
<td>19 (20.0)</td>
<td>0.20</td>
</tr>
<tr>
<td>Using smoking cessation medication at 52 weeks, n (%)</td>
<td>10 (10.1)</td>
<td>15 (15.6)</td>
<td>0.23</td>
</tr>
<tr>
<td>Number of automated calls completed, mean±SD</td>
<td>6.4±2.6</td>
<td>5.9±2.9</td>
<td>0.21</td>
</tr>
<tr>
<td>Number of nursing counselling calls provided, mean±SD</td>
<td>3.5±2.6</td>
<td>3.6±2.5</td>
<td>0.78</td>
</tr>
</tbody>
</table>

*Includes only participants in the prescription group.
†Includes only participants who used at least one dose of medication.
NIA, nicotine replacement therapy.

<table>
<thead>
<tr>
<th>Outcome†</th>
<th>Number (%)</th>
<th>Cost-free</th>
<th>Prescription</th>
<th>Adjusted ORc</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participants</td>
<td>97</td>
<td>93</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verified continuous 40-week abstinence at 52-week follow-up</td>
<td>15 (15.5)</td>
<td>13 (14.0)</td>
<td>1.13 (0.51 to 2.53)</td>
<td>0.77</td>
<td></td>
</tr>
<tr>
<td>Self-reported 7-day point prevalence abstinence at 12-week follow-up</td>
<td>37 (38.1)</td>
<td>25 (26.9)</td>
<td>1.76 (0.94 to 3.28)</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>Verified 7-day point prevalence abstinence at 26-week follow-up</td>
<td>21 (21.6)</td>
<td>17 (18.3)</td>
<td>1.25 (0.61 to 2.56)</td>
<td>0.54</td>
<td></td>
</tr>
<tr>
<td>Verified continuous 14-week abstinence at 26-week follow-up</td>
<td>18 (18.6)</td>
<td>15 (16.8)</td>
<td>1.20 (0.56 to 2.55)</td>
<td>0.64</td>
<td></td>
</tr>
<tr>
<td>Verified 7-day point prevalence abstinence at 52-week follow-up</td>
<td>22 (22.7)</td>
<td>16 (17.2)</td>
<td>1.41 (0.69 to 2.89)</td>
<td>0.35</td>
<td></td>
</tr>
</tbody>
</table>

c = adjusted for recruitment site (Ottawa or Hamilton)
†Abstinence was defined as not having smoked more than five cigarettes for the entire 40-week period preceding the 52-week follow-up, which was verified biochemically by an expired carbon monoxide level of less than 10 ppm.
†An assumption was made that all participants with missing data for smoking status were still smoking.
Table 4  Serious adverse events

<table>
<thead>
<tr>
<th>Number (%)</th>
<th>Cost-free</th>
<th>Prescription</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participants</td>
<td>99</td>
<td>95</td>
</tr>
<tr>
<td>Participants with any serious adverse event</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>Total number of serious adverse event</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>Died</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Stroke</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Worsening stroke symptoms</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>TIA</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Carotid endarterectomy</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Unstable/stable angina</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Cardiac revascularisation</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>ICD insertion</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Other, requiring hospitalisation (eg, cancer, orthopaedic)</td>
<td>6</td>
<td>8</td>
</tr>
</tbody>
</table>

ICD = implantable cardioverter defibrillator

It is surprising that among these smokers wanting to quit, with strong health risks for continued smoking, captured at a teachable moment, that only about half filled their prescription. Cost of medication may have been a factor in the low fill rate in the Rx group. At the time the study was conducted, average medication costs for a 12-week supply were $CDN294, $588, $286 and $134, for NRT monotherapy, NRT combination, varenicline and bupropion, respectively. Our exploratory analysis of prescription fillers versus non-fillers showed more filling among those with insurance coverage illustrating that having to pay for cessation medication reduces their use. Clinically important improvements in point prevalence abstinence rates in favour of the CF group were noted at 12 weeks (38.1% vs 26.9%).

We observed a non-significant increase in 1.5% in the long-term continuous abstinence rate in our CF intervention group compared with the Rx control group (15.5% vs 14.0%). We expected to see an absolute increase in 10% with the CF intervention, based on our pilot study.21 Both groups received active cessation treatment that included both counselling and a prescription for a first-line quit-smoking medication, based on best practice guidelines, making it difficult to demonstrate incremental benefit.

Government policy regarding coverage for smoking cessation prescriptions made it more likely that prescriptions would be filled by people in the Rx group. This would have reduced differences between groups.

The timing of our intervention may have been suboptimal. We identified and recruited smokers during visits to outpatient SPCs; these visits are typically scheduled to occur in the immediate days to weeks after initial hospital presentation for TIA or stroke. Evidence from studies of hospitalised smokers suggests that interventions should be commenced in the hospital (or in the emergency room), as motivation to quit smoking may be highest at these ‘teachable moments’.32 In addition, patients seen in SPCs typically have cerebrovascular events that resolve fully or result in non-disabling symptoms. Higher levels of disability are associated with higher cessation rates.10

Our results point to a new direction for research. If the true difference in long-term abstinence with CF medication compared with prescription is only 1.5%, a sample size of several thousand per group (>8000) would be required to definitively test a between-group difference of this magnitude. Also, changes in government policy have resulted in expanded access to CF medication, making our original question less relevant, at least in Canada. Since most of the 45 SPCs in Ontario have still not introduced systematic processes to identify smokers and deliver smoking cessation interventions, a better next step might be to evaluate a practice-level intervention like the Ottawa Model for Smoking Cessation enhanced...
to include strategies for both patients interested and not interested in quitting (ie, a quit date would not be required). Such an intervention could include strategies such as motivational enhancement and ‘reducing-to-quit’ approaches for those not ready to quit at the time of presentation to the SPC. Cluster randomised trials are well suited to the evaluation of health system interventions. They are ideal for testing interventions when the decision about whether to implement the intervention will be taken on behalf of a group.

CONCLUSIONS

Most smokers with TIA and stroke are still smoking 1 year later. The present study of CF medication was inconclusive because we failed to meet our recruitment target; the effect size was smaller than anticipated. Additional work is needed to better understand how to implement these lifesaving interventions in patients after TIA and stroke. A cluster randomised trial should be conducted to evaluate the effectiveness of practice-level interventions for smoking cessation in SPC in Ontario.

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Contributors RR, SP, SG, AB, MAL, DA, K-AM, AP and MS were involved in the development of the intervention and made substantial contributions to the concept and design of the study and protocol. AA, AG, AB, MAL, DS, GS and MS were involved with the acquisition of data. RR, LC and K-AM analysed the data. SP, SG, AB, MAL, DS, GS, AP, HM and MS made substantial contributions to data interpretation. RR and LC wrote the paper with assistance from SP, SG, AB, MAL, DA, AA, DS, GS, K-AM, AP, HM and MS who critically revised the manuscript and approved the final version. RR acts a guarantor.

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Competing interests RR, AP, K-AM, DA have intellectual property rights in the Ottawa Model for Smoking Cessation. RR, AP and SP have received speaking fees and research support from Pfizer. RR and AP have received speaking fees from Johnson and Johnson.

Patient and public involvement Patients and/or the public were involved in the design, conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Ethics approval Ethics approval was given by the The Ottawa Hospital (reference 2009430-01H) and Hamilton Health Sciences (reference 09-454). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Anonymized data will be shared by request from any qualified investigator.

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REFERENCES


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Efficacy and cost-effectiveness of cost-free pharmacotherapy for smoking cessation for high-risk smokers with cerebrovascular disease

Preamble
A randomized controlled trial is planned to test the hypothesis that providing cost-free smoking cessation medication is more efficacious and more cost-effective than simply providing a prescription for smoking cessation medication for high-risk smokers with a history of transient ischemic attack (TIA) or stroke. The primary outcome will be carbon monoxide (CO)-confirmed continuous abstinence from weeks 10 to 52 following a target quit date. The proposed study will build upon the results of a pilot study that is currently underway that is employing similar methods. The two co-principal investigators, Drs. Robert Reid and Michael Sharma, are Canadian leaders in clinical smoking cessation and stroke treatment, respectively. They are supported by an experienced team of co-investigators with extensive know-how concerning the introduction of systematic approaches to smoking cessation in high risk populations. This research has important implications for the management of smokers at high risk for stroke and the organization of stroke care across Canada.

1.0 BACKGROUND AND KNOWLEDGE TO DATE

1.1 Stroke and transient ischemic attacks
A stroke occurs when there is an interruption in the blood supply to any part of the brain. This can happen when a blood vessel that supplies the brain becomes blocked by a blood clot (ischemic stroke) or when a blood vessel breaks open, allowing blood to leak into the brain (hemorrhagic stroke). A TIA is caused by a temporary interruption in the blood supply to the brain. This, in turn, can cause a sudden, brief reduction in brain function. By definition, the symptoms of a TIA go away within 24 hours, usually within 1 hour. About one third of people who experience a TIA go on to have a stroke later.1

1.2 Smoking and the importance of cessation in patients with cerebrovascular disease
Cigarette smoking continues to grow in global importance as a leading preventable cause of morbidity and premature mortality. 2 The epidemiological evidence to date has unequivocally confirmed the association between smoking and cardiovascular disease. With respect to stroke and TIA, cigarette smoking has been established as a major independent risk factor for ischemic stroke, hemorrhagic stroke, and TIA. 3-5 In healthy persons smoking is associated with a doubling and even quadrupling of the excess risk of stroke compared with non-smokers. 4, 6, 7 Growing evidence indicates that smoking is also a risk factor for recurrent stroke 8, 9 and those who continue to smoke after stroke have double the risk of death compared to non-smokers and ex-smokers. 10 In addition, smokers have been found to experience poorer functional outcomes (greater global disability and functional impairment) than non-smokers after acute ischemic stroke providing further impetus for increasing the efforts directed at supporting smoking cessation in patients who smoke and advocating for stronger tobacco control measures. 11

Overwhelming evidence exists to support the cardiovascular benefits of smoking cessation. Smoking cessation has been shown to completely reverse the risk of cardiovascular disease from smoking, making it potentially the single most effective and lifesaving intervention available for those at risk or with existing cardiovascular disease. 12 The benefits of cessation begin almost
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immediately after a smoker quits, with a significant reduction of the risk of cardiovascular events, including fatal strokes, generally observed within 5 years after cessation of cigarette smoking. Smoking cessation is also associated with significant reductions in stroke related hospitalizations and associated health care costs. Given that patients with stroke have 15 times higher risk of recurrence of stroke than the general population, and that this risk is further enhanced in the presence of lifestyle-related risk factors, which include smoking, smoking cessation is strongly recommended and is now considered a ‘best practice’ secondary stroke prevention strategy.

Stroke prevention guidelines for smoking cessation recommend that healthcare providers strongly advise every patient who smokes and is at high risk for a stroke or TIA to quit, and provide specific assistance with quitting including counselling and pharmacotherapy. Despite the evidence supporting the importance of smoking cessation, there is a well documented practice gap in the rates at which smoking cessation is being addressed by practitioners, even for the high-risk groups such as stroke survivors. While rates at which patients are advised to quit are estimated to be between 50-70%, the rates at which assistance with quitting (i.e. set quit date, provide self-help materials, recommend pharmacotherapy) is provided is estimated to be less than 20%. Not surprisingly then, high proportions (i.e., as high as 89%) of stroke and TIA patients identified as smokers at the time of their event are often found to continue to smoke 12-months later. These findings are consistent with the results of an audit conducted recently at the Stroke Prevention Clinic at the Ottawa Hospital, which showed that 73% of smokers with TIA and stroke seen in the clinic were still smoking when contacted six months later.

Despite the importance of smoking cessation as a secondary prevention strategy among stroke and TIA patients, the research on smoking cessation in patients with cerebrovascular disease has been limited. One uncontrolled prospective study specifically examining the effects of a smoking cessation education intervention after stroke found that at 3 months post-event 43% of smokers had quit smoking compared with 28% of smokers previously reported in the literature. In another study, which involved in-hospital initiation of secondary stroke prevention therapies including smoking cessation, 83% of those identified as smokers at the time of the event remained smoke free at 3-month follow-up. Although both studies demonstrate that structured smoking cessation interventions can be effective for secondary prevention in stroke and TIA patients, the fact that the follow-up period did not extend beyond 3 months limits conclusions about the long-term maintenance of this beneficial effect. In contrast, there was no improvement in smoking quit rates of patients with stroke or TIA at 3-month follow-up after a multiple risk factor modification intervention led by a stroke nurse specialist in a single-blind randomized controlled trial. Given the paucity of smoking cessation trials in stroke and TIA patients, further research over longer follow-up periods is needed to properly evaluate the efficacy of interventions.

1.3 Effectiveness of treatments for smoking cessation

Providing smoking cessation treatment is challenging given that tobacco dependence is a chronic relapsing condition, which usually requires repeated interventions, including both pharmacotherapy and counselling before successful long-term abstinence is achieved. The evidence for a wide-range of smoking cessation interventions has recently been reviewed and

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summarized in the 2008 update of the US Cessation Guidelines, Treating Tobacco use and Dependence. Evidence from placebo-controlled clinical trials consistently shows that nicotine replacement therapy (NRT), bupropion and varenicline, when combined with counselling, can double or even triple long-term smoking abstinence in smokers. Moreover, smoking cessation medications have also been found to be highly cost-effective. Economic evaluations estimate that NRT is associated with $1,000-$3,000 per quality adjusted life year gained. It is unfortunate that, at present, the majority of persons who make an attempt to quit smoking do not use quit smoking medications. Low utilization and compliance may be the result of the cost of treatments, patient misconceptions, and the lack of medical and social support.

1.4 The potential role of cost-free pharmacotherapy

In Ontario, drugs that are proven effective in supporting smoking cessation are not covered by the Ontario Drug Benefit Plan or through many extended health insurance plans. Thus, patients often have to pay for nicotine replacement therapy, bupropion and varenicline themselves. Since smoking cessation pharmacotherapy is generally more expensive than tobacco products, the costs associated with the treatment have been identified as a barrier to many smokers, particularly those in the low income categories, making effective smoking cessation therapy prohibitive to many of those who need it. While there have been no trials to evaluate the efficacy of providing cost-free quit smoking medications to stroke or TIA patients, studies in the general population have found the provision of a cost-free medications increases motivation to quit, increase quit attempts as well as smoking abstinence in the general population. For example, there is evidence suggesting that the provision of cost-free NRT increases the number of smokers using NRT, compliance with therapy, and quit rates. A systematic review including 3 trials examining the benefit of covering the cost of smoking cessation treatment (primarily the cost of pharmacotherapy) found that cost-free treatment increased the odds of achieving abstinence by 60% (OR = 1.6; 95% CI 1.2 to 2.2) compared to having smokers pay for their own treatment. One additional trial, completed after the meta-analysis described above, found that providing cost-free effective smoking cessation pharmacotherapies to smokers in primary care increased the odds of quitting 12 months after recruitment almost 5-fold (OR = 4.77; 95% CI 2.0 to 11.2).

1.5 Pilot-testing of the study procedures by the investigative team and other experience conducting clinical trials of smoking cessation interventions

In preparation for the proposed trial, smoking cessation experts from the University of Ottawa Heart Institute (UOHI) have worked closely with clinical staff from the Stroke Prevention Clinic at the Ottawa Hospital to gain a clearer understanding of the issue of smoking and cessation among smokers with TIA and stroke. We first conducted a cohort study to establish the prevalence of smoking and the ‘spontaneous’ cessation rate within this population. We surveyed a consecutive sample of 139 TIA and stroke patients and found that 26/139 (19%) were smokers; when contacted 6 months later, 7/26 (27%) reported that they were no longer smoking. Next we examined smoking-related variables and willingness to make an attempt to quit smoking in a consecutive sample of 178 current smokers with TIA or stroke (mean age = 60.1 ± 12.0 years; 52% male). On average, these smokers had long smoking histories (39.8 ± 11.9 years smoked); 73% smoked more than 10 cigarettes per day and 80% smoked their first cigarette of the day within 30 minutes of awakening. Overall, 81% of these smokers (145/178) reported that they were interested in making an attempt to quit smoking. We then worked to develop a smoking status screening form for the waiting room, smoking cessation consult form, and patient Quit
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Smoking Plan (see Appendices A, B and C) that we tested for usability with clinic staff (neurologists, nurses and clerks). Recently, we have begun a pilot test of the exact procedures described in the “Methods” section of this proposal. A total of 6/50 pilot participants have been recruited over the past 2 weeks. This has provided information on the potential participation rate and accrual for the definitive trial described in this proposal.

Our investigative team has extensive experience conducting clinical trials evaluating the efficacy of behavioural and pharmacological intervention for smoking cessation in patients with cardiovascular disease. In the present trial, we will be using an interactive voice-response (IVR)-mediated telephone follow-up system to track participants in the process of quitting smoking that was developed and evaluated under a previous grant from the Heart and Stroke Foundation of Ontario. We will also be using telephone counseling scripts developed as part of the UOHI-managed Ontario Network of Hospital-Based Smoking Cessation Programs.

Over the past six years, UOHI-based investigators have developed and disseminated a highly successful program for the systematic identification, counselling, treatment and follow-up of hospitalized smokers. The is program has become known as the Ottawa Model for Smoking Cessation. The Ottawa Model has led to an absolute 15% improvement in the long term quit rate for tobacco users admitted to our institution (from 29% to 44% at 6-months; the 1-year quit rate is 46%).

2.0 RESEARCH AIMS AND HYPOTHESES TO BE TESTED

2.1 Research Aims
The aims of this research study are to determine whether cost-free smoking cessation pharmacotherapy:
1. Helps smokers with TIA or stroke to quit smoking over the long-term, compared to simply providing a prescription for these medications;
2. Is a more cost-effective alternative to providing a prescription only for these medications in this high risk population.

2.2 Hypotheses to be Tested
The hypotheses to be tested include the following:
1. The CO-validated continuous abstinence rate for weeks 10 to 52 following a target quit date will be at least 10% higher for the cost-free smoking cessation pharmacotherapy intervention group compared to the prescription only usual care group;
2. Cost-free smoking cessation pharmacotherapy will have a greater cost-effectiveness (i.e., cost/quit) than providing a prescription only.

3.0 METHODS TO BE USED

3.1 Design
This will be a 52-week, multi-site, parallel, two-group, open label, experimental study. Smokers with TIA or stroke attending a Stroke Prevention Clinic and willing to quit smoking within 30 days of the clinic visit will be randomly assigned (1:1) to either a prescription only (PO) usual care group or a cost-free (CF) pharmacotherapy experimental group. All participants will
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receive identical advice regarding smoking from the attending neurologist, nurse counseling for smoking cessation, and follow-up tracking and telephone-based support for up to 26 weeks after the target quit date. Non-treatment follow-up will continue to week 52 after the target quit date. The primary outcome will be the biochemically confirmed (exhaled CO ≤ 10 ppm) self-reported continuous abstinence for weeks 10 to 52 following the target quit date. The total costs of smoking cessation treatment will be tracked over the duration of the follow-up. Adverse events and serious adverse events will be tracked throughout the study. The study protocol is currently under review by the Research Ethics Board at the Ottawa Hospital and all participants will provide written informed consent.

3.2 Settings
The trial will be conducted at two Stroke Prevention Clinics in Eastern Ontario, as well as at least one other large Stroke Prevention Clinic in Central or Western Ontario. (We are currently in discussion with several other clinics in the province concerning their participation). The Eastern Ontario clinics are located at the Ottawa Hospital and Hawkesbury and District General Hospital. Co-PI Sharma is Medical Director of the Regional Stroke Centre at the Ottawa Hospital.

3.3 Participants
A total of 562 participants will be included in this study. The sample size calculation is provided in Section 3.6. Eligibility criteria are outlined below.

3.3.1 Inclusion criteria
Inclusion criteria will include the following:
1. Patient is a current smoker (≥ 5 cigarette per day in the month preceding the visit to the Stroke Prevention Clinic);
2. Patient has a diagnosis of TIA or stroke;
3. Patient is able, in the opinion of the neurologist, to comprehend and participate in the smoking cessation interventions
4. Patient is 18 years of age or older;
5. Patient is willing to set a date to quit smoking within the 30 days following the visit to the Stroke Prevention Clinic;
6. Patient is willing to provide informed consent

3.3.2 Exclusion criteria
Exclusion criteria will include the following:
1. Patient is unable to read and understand English or French;
2. Patient is pregnant, lactating or planning to become pregnant during the study period;
3. Patient is currently using a smoking cessation medication (NRT, bupropion, varenicline);
4. Patient has contraindication(s) to all of the following smoking cessation medications:
   a. Nicotine replacement therapy (allergy to adhesive, serious cardiac arrhythmias (e.g., tachycardia), vasospastic disease (e.g., Buerger’s disease, Prinzmetal’s variant angina);
   b. Bupropion (history of seizure disorder or head trauma; presently taking Wellbutrin; previous reaction to bupropion/Zyban/Wellbutrin; pre-existing or current eating disorder; taking anti-depressants, antipsychotics, corticosteroids, MAO inhibitors, theophylline, cocaine or diet pills; taking a quinalone antibiotic (e.g., ciprofloxacin, levoflozacin);

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currently using oral hypoglycemic product or insulin; severe hepatic impairment; CNS tumour; and
  c. Varenicline (renal failure; use of cimetidine; previous reaction to varenicline).
5. Patient lives more than 1.5 hours from any of the study sites.

Between April 2007 and March 2008, approximately 1750 patients with TIA or stroke were seen in the Stroke Prevention Clinics in Ottawa and Hawkesbury, combined. As described above in section 3.2, we are also in the process of recruiting at least one other large Stroke Prevention Clinic in Central or Western Ontario that would approximately double this volume. Pilot testing has established that the prevalence of smoking among TIA and stroke patients in these clinics is approximately 20% (i.e., there will be a pool of 700 smokers per year from which the sample can be drawn). During pilot testing, we have found that 60% of smokers are willing to make a quit attempt within 30 days and we estimate that 80% of these smokers are willing to participate in a randomized evaluation of cost-free pharmacotherapy. (The participation rate among eligible participants in our pilot study has been 100% to date). Based on these assumptions, we believe we can recruit 336 participants per year to the study. The required sample size can be recruited over a 20-month period.

3.4 Procedures

3.4.1 Baseline information and initial smoking cessation treatment
The staff of the Stroke Prevention Clinics (neurologists, nurses and clerks) participating in the proposed trial will receive training and support from members of the investigative team to help them incorporate a number of best practices for smoking cessation treatment into their usual care practices. Key elements are described below.

Identification of Smokers. All patients attending the participating Stroke Prevention Clinics will complete a smoking status screening form in the waiting room; the form will be provided to the patient by the clinic clerk who checks in patients when they arrive at the clinic. This form asks about current smoking status and, if the patient is a smoker, includes additional questions relating to smoking history, concerns about quitting, nicotine dependence, and insurance coverage for smoking cessation medications. The form will be returned by the patient to the clerk and placed in the patient chart. If the patient is a current smoker, a sticker will be placed on the chart indicating to the neurologist that they should address smoking with this patient during their consultation. A smoking cessation consult form will be placed in the chart.

Consultation with the neurologist. The smoking cessation consult form will be used to guide the interaction with the smoker and the neurologist will be responsible for the advise and assess portions of the form. During their consultation with the smoker, the neurologist will advise the patient to quit smoking in a clear and unambiguous manner, indicate that effective treatments for smoking cessation are available through the clinic, and then assess the patient’s interest in making an attempt to quit smoking within the next 30 days. If they are not willing to make a quit attempt within the next 30 days, the neurologist will indicate that the patient can access smoking cessation assistance through the clinic in the future if they decide they want to quit smoking later.
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Consultation with the nurse. After their consultation with the neurologist, patients willing to make a quit attempt within the next 30 days will meet with a research nurse to complete the remainder of the smoking cessation consult form. The nurse will assist the patient by guiding them through the selection of appropriate pharmacotherapy, taking into account contraindications and patient preference. A prescription for pharmacotherapy will be prepared and signed by the neurologist. The nurse will also provide practical counseling about quitting (i.e., anticipating challenges, preparing to quit) and work with the patient to set a quit date. This information will be summarized in a Quit Smoking Plan that will be provided to the patient. The research nurse will also arrange follow-up for the patient by enrolling them in the IVR-mediated telephone follow-up system, and describe what to expect during these calls. Additional details concerning the follow-up system are outlined in the section 3.4.5.

Patients who are prescribed NRT will be advised to use NRT for an initial 10 weeks. The initial dosage will be determined from the average number of cigarettes smoked each day. Patients smoking 11-20 cigarettes per day will be prescribed 14 mg/24 hours for 6 weeks and then nicotine patch 7mg for 4 weeks. Those smoking ≥ 20 cigarettes per day will be prescribed 21 mg/daily for 6-weeks and then nicotine patch 14mg/daily for 2 weeks and then nicotine patch 7 mg/daily for 2-weeks. Doses may be titrated during based on patient response to therapy and combination therapy (e.g. gum, inhaler prescribed) may be prescribed based on individual need. For patients who are prescribed varenicline, they will start the medication 8 days before the quit date using the following regime: Days 1-3: 0.5mg once/day; Days 4-7: 0.5 mg BID; Day 8-12 weeks 1.0 mg twice daily. For patients who are prescribed bupropion, they will start the medication 8 days before the quit date using the following regime: Days 1-3: 150 mg daily (in the morning); Day 4-30: 150 mg BID for 3 months.

3.4.2 Recruitment

At the end of the consultation with the research nurse, the nurse will ask the patient if they are interested in participating in the proposed study of the effects of cost-free medication for smoking cessation. If the patient is interested, the nurse will explain the study and obtain informed consent. If the patient consents to participate, the research nurse will abstract information from the patient chart (which now includes the waiting room screener and smoking cessation consult form) onto a case report form. Information to be abstracted will include the medical history, medications, smoking history, concerns about quitting, insurance coverage for smoking cessation medications, nicotine dependence and previous quit attempts.

3.4.3 Allocation to Treatment

Participants will be stratified by site and time to first cigarette of the day (<30 minutes or ≥ 30 minutes) and randomly allocated to either the PO usual care group or the CF intervention group. For treatment allocation, the research nurse will use a web-based allocation program, operated by the UOHI Clinical Epidemiology Unit. The nurse will enter the patient data into the program and receive the treatment allocation back immediately. The program maintains a log of all randomization encounters. Because of the nature of the interventions, participants will not be blinded to the intervention.
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3.4.4 Interventions

3.4.4.1 Prescription Only Usual Care Group
Participants assigned to the prescription only usual care group will be asked to have their prescription for smoking cessation pharmacotherapy filled at their own cost at their local community pharmacy.

3.4.4.2 Cost-Free Pharmacotherapy Experimental Group
Participants assigned to the cost-free pharmacotherapy group will be provided with a 10-week supply of NRT, or a 12-week supply of bupropion or varenicline. The pharmacotherapy will be provided by the research nurse to the patient immediately.

3.4.5 IVR Contacts and Nurse Counseling
The IVR system will automatically conduct a follow-up telephone call to participants 7 days before their target quit date and then 5, 14, 30, 75 and 120 days after to check on their: 1) preparation to quit (call 7 days before target quit date); or 2) their smoking status, potential concerns, use of pharmacotherapy and other quitting resources, and their risk of relapse (calls after the target quit date). If patients identify that they are inadequately prepared for quitting, have resumed smoking or indicate that their confidence in remaining smoke-free is low (< 7 on a 10-point scale), they will be contacted by the research nurse and provided additional assistance over the phone.

3.4.5 Post-assessment and follow-up data collection
All participants will return to the study site 26 and 52 weeks after their specified target quit date and complete a standardized interview with a study coordinator asking for information on their current smoking status. The study coordinator will be blind to the participant’s treatment allocation. Participants who claim that they are non-smokers at each follow-up will be asked to provide a breath sample for CO determination. Information will also be gathered concerning medication compliance and adverse events since the last contact. Participants will be asked to return any unused medication.

3.5 Study End-Points

3.5.1 Continuous abstinence from smoking
The primary outcome will be the biochemically confirmed self-reported continuous abstinence between weeks 10 and 52. Abstinence will be defined according to the Russell Standard, as a self-report of smoking not more than five cigarettes from week 10 to week 52 supported by a negative CO test (exhaled CO ≤ 10 ppm). The standard abstinence question asked at the follow-up points will be: ‘Have you smoked at all since (date of start of the abstinence period) A: No not a puff; B: 1-5 cigarettes; C: More than 5 cigarettes?’ Answers A or B and negative CO test will be required for the participant to be classified as abstinent. Continuous abstinence for weeks 10 to 26 will also be assessed as secondary outcome of interest.

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3.5.2 Medication compliance
Compliance with pharmacotherapy will be examined at the 26 and 52 week follow-up assessments. Compliance will be calculated as the number of doses taken divided by the number of doses prescribed over the treatment period.

3.5.3 Adverse events
Self-reported or observed adverse events will be recorded at each follow-up point. Serious adverse events will be defined as any adverse event that is life-threatening or results in hospitalization, persistent or significant disability, incapacity or death.

3.5.4 Costs associated with smoking cessation treatment
The costs associated with smoking cessation treatment will be collected during the study period. All costs will be expressed in Canadian dollars for the year 2009 and evaluated from the perspective of the health care system. Costs will be based on real resource use and will include the sum of the costs associated with cost-free pharmacotherapy, patient advice and counselling, and follow-up telephone contacts by IVR and live nurse counselors. For the purpose of the present evaluation, costs incurred by patients will not be considered.

3.6 Anticipated Results and Sample Size Calculations
A total of 562 participants will be included in the study. The primary end point used in the sample size determination was the continuous abstinence rate between weeks 10 and 52. The sample size was calculation based on the assumption that the proportion in the PO group will be 0.30 compared to 0.40 in the CF group. This base rate assumption was based on quit rates observed among CVD patients participating in the Champlain Network of Hospital-Based Smoking Cessation Programs (directed by PI Reid). The sample size required to detect this difference in abstinence rates between the PO and CF group is 2N=562. The calculation was based on a one-sided test with 80% power and an alpha level of 0.05. The sample size was not increased to account for loss to follow-up since participants who do not return for follow-up will be considered smokers for the purposes of the analysis.

3.7 Analysis of Results
All patients randomized to receive treatment will be included in the intent-to-treat analysis, except those that have died and those documented as having moved to an untraceable address. 51 We will compare the two groups at baseline to assess any chance imbalances that may have occurred. The primary outcome will be the biochemically confirmed continuous abstinence for weeks 10 to 52. Participants who are not available for follow-up will be considered smokers. For the analysis of the primary endpoint, a logistic regression model will be ‘fitted’ to the continuous abstinence status for weeks 10 to 52 (smoker or non-smoker) and will include treatment group as the independent variable. Adjusted analyses will be considered based on chance baseline differences between groups. Secondary analyses will be conducted using similar techniques with abstinence for weeks 10 to 26 as the dependent variable. Treatment compliance, adverse events and serious adverse event rates will be compared between treatments.

We will calculate the incremental cost effectiveness as the incremental cost of the CF treatment compared to PO treatment divided by the incremental effectiveness (i.e., abstinence rate) of the CF treatment compared to the PO treatment. We will use a Markov simulation model for the
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effectiveness analysis. The time horizon used will be 7 and 10 years. All costs will be expressed in Canadian dollars for the year 2009 and evaluated from the perspective of the health care system. The model will incorporate the intervention efficacy, and the lifetime probability of relapse after 1-year abstinence, program delivery and health care costs. Existing long-term follow-up data suggest that approximately 35% of smokers who have been abstinent for 1 year will relapse sometime during their lifetime.52, 53 We will use previously published results regarding the saving in health care expenditures.17, 18 A sensitivity analysis will be conducted for all of the input variables. We will use a 3% discount rate in our base case analysis, with a range of 0% to 5% for the sensitivity analysis.

4.0 SIGNIFICANCE OF THIS RESEARCH

Quitting smoking is potentially the most effective and lifesaving intervention available for smokers with TIA and stroke. Stroke has a devastating effect on patients and their families, often leading to long-term disability, and strokes are costly for the health care system. Efforts to prevent stroke have to be of high priority. Despite being at high risk for future stroke, smokers with TIA and previous stroke are unlikely to quit smoking on their own. If cost-free pharmacotherapy for smoking cessation can be proven to be effective for improving quit rates, it will become a sound investment for the stroke care system in Ontario. The proposed study will also yield a complete ‘toolbox’ of materials (e.g., waiting room screener, smoking cessation consult form, patient Quit Smoking Plan, IVR follow-up system, telephone counseling scripts) that will allow the knowledge gained to be quickly transferred to other Stroke Prevention Clinics. This approach is also suitable for use with other high risk patient populations in the outpatient setting. The investigative team is plugged into networks in the stroke and smoking cessation domains that will allow rapid dissemination of results. For example, UOHI (under the direction of Reid and Pipe) manages a network of > 30 hospitals in Ontario that have implemented the Ottawa Model for Smoking Cessation for inpatient smokers. These approaches are now being expanded to the outpatient setting.

5.0 POSSIBLE PROBLEMS

There may be concerns about the feasibility of recruitment and loss-to-follow-up. Concerning recruitment, we will put in place standard care procedures in each of the Stroke Prevention Clinics that ensure that all clinic attendees are screened for smoking status in a consistent way. During pilot testing, using identical eligibility criteria, we have found that virtually all smokers meeting the other eligibility criteria are willing to participate in a trial where they have a 50:50 chance of receiving cost-free pharmacotherapy to help them quit smoking. Our research team has previously recruited similar size sample of smokers to other clinical trials.47, 54, 55 Over the years, we have devised methods to reduce loss-to-follow-up, incorporating mail and telephone reminders as well as home visits. We anticipate that we will be able to keep loss-to-follow-up to ≤ 15%, based on previous clinical trials of smokers with cardiovascular disease.

6.0 ASSEMBLED RESEARCH TEAM

The first co-PI, Robert Reid (PhD, MBA), is Associate Director of the Minto Prevention and Rehabilitation Centre at UOHI. He has extensive experience conducting RCTs of pharmacological and behavioural interventions for smoking cessation.47, 49, 54, 55 He is one of the principal architects of the Ottawa Model for Smoking Cessation. He is a past recipient of the HSFC’s New Investigator Award and in 2005 he was awarded the James Hogg Award from the
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CIHR’s Institute for Circulatory and Respiratory Health for his contributions to population and clinical health research. Dr. Reid will share overall responsibility for conduct of the trial. The second co-PI, Michael Sharma (MD, FRCPC, M.Sc.) is a neurologist and clinical epidemiologist who is Medical Director of the Regional Stroke Centre at the Ottawa Hospital. He is key member of the Ontario and Canadian Stroke Networks. Dr. Sharma will share responsibility for the overall conduct of the trial, will manage medical issues related to trial conduct, and serve as the principal medical liaison with the other participating Stroke Prevention Clinics. Andrew Pipe (CM, MD) is Director of the Director of the Minto Prevention and Rehabilitation Centre at UOHI, and Associate Professor in the Department of Family Medicine and Division of Cardiac Surgery at the University of Ottawa. Dr. Pipe is recognized as one of Canada’s leading experts in cardiovascular disease prevention, physical activity, and health, and smoking cessation. Dr. Pipe’s research interests have included pharmacological and non-pharmacological interventions for smoking cessation and hospital-based approaches to smoking cessation. Dr. Pipe will be responsible for training clinical staff from the Stroke Prevention Clinics regarding treatments for smoking cessation. He will also oversee knowledge translation activities. Sophia Papadakis, (MHA, Ph.D. candidate) is a Research Associate in the UOHI and is a 3rd year doctoral student in the Department of Health Studies and Gerontology at the University of Waterloo. Ms. Papadakis’ is a doctoral trainee in CIHR Strategic Tobacco Research Program and has expertise in program design and evaluation, smoking cessation, behaviour change, and economic evaluation. Ms. Papadakis will provide support to the implementation of the study protocols, project management, analysis, and report generation.

Debbie Aitken (RN, BScN) is a Tobacco Dependence Treatment Specialist and Manager of the in-patient and out-patient smoking cessation programs at UOHI. Ms. Aitken will be responsible for training the study staff and nursing staff at the Stroke Prevention Clinics regarding treatments for smoking cessation. Kerri-Anne Mullen (M.Sc.) is a Tobacco Dependence Treatment Specialist and Project Leader for the Ottawa Model for Smoking Cessation, Hospital-Based Network in Ontario. Ms. Mullen will provide training and assistance for study staff and nursing staff at the Stroke Prevention Clinics participating in the trial. Sophia Gocan (RN, BScN, CNN(C)) is a Stroke Prevention Nurse Specialist with the Regional Stroke Program at The Ottawa Hospital. She has expertise in behaviour change, smoking cessation and stroke risk factor management. Sophia will provide advice on nursing issues relating to the proposed study and will provide support to the implementation of the study protocols at the participating Stroke Prevention Clinics. Mary Ann Laplante, (RN, BScN) is a Stroke Prevention Nurse Specialist with the Regional Stroke Program at The Ottawa Hospital. She has expertise in behaviour change, smoking cessation and stroke risk factor management. Mary Ann will provide advice on nursing issues relating to the proposed study and will provide support to the implementation of the study protocols at the participating Stroke Prevention Clinics. Co-investigators Papadakis, Aitken, Mullen, Gocan and Laplante have lead the pilot investigations that have informed the design of the present study and prepared and tested the study materials (i.e., waiting room screening form, smoking cessation consult form, Quit Smoking Plan. Isabella Moroz (Ph.D.) is an analyst at the UOHI-PRC. After receiving her Ph.D. in Psychology (Behavioral Neuroscience) from Concordia University in Montreal (2003), Isabella completed two post-doctoral fellowships during which she researched the therapeutic efficacy pharmacological and non-pharmacological rehabilitative treatments in experimental models of stroke. Isabella also has also been involved in research on quality improvement interventions in primary care. She will provide assistance with quantitative research design, analysis, report and publication writing.
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REFERENCES

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42. Smeth L, Fowler G. Nicotine replacement therapy for a healthier nation. Nicotine replacement is cost effective and should be prescribable on the NHS. *BMJ (Clinical research ed.)*. 1998;317(7168):1266.
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