Pilot and Feasibility Studies

STUDY PROTOCOL

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Cytisine compared to combination nicotine replacement therapy to reduce cigarette consumption in relapsed smokers: protocol for a pilot randomized controlled trial

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Abstract

Background Cigarette smoking is a leading cause of death and disease, including those related to the cardiovascular system. Cytisine is a plant-based medication, which works in a similar mechanism to varenicline. It is safe, efficacious, and cost-effective for smoking cessation. While there are effective therapies such as nicotine replacement therapy, bupropion, varenicline, and cytisine for smoking cessation, relapse remains common. It is unclear how best to support these individuals. This study aims to assess the feasibility of randomizing patients who relapse to combination NRT or cytisine after admission to a cardiac hospital.

Study design Randomized, two-group parallel feasibility trial.

Methods This trial will recruit relapsed smokers from the University of Ottawa Heart Institute. Participants will be randomized 1:1 to receive cytisine or combination NRT, alongside counseling and follow-up support. Feasibility outcomes include recruitment rates and treatment completion. Secondary outcomes include smoking cessation rates and adverse events. A total of 60 participants will be recruited using stratified randomization by sex to ensure gender balance. Data will be analyzed descriptively, focusing on feasibility and efficacy measures to inform future trials.

Discussion The primary aim of this study is to evaluate the feasibility of recruiting patients who were recently admitted to the hospital and have relapsed to smoking within 180 days post-discharge. This will inform future studies aimed at recruiting patients who have relapsed to understand how best to support them to quit smoking. This study will also compare the acceptability, efficacy, and safety of cytisine compared to combination NRT, as demonstrated in previous studies in other populations. Notably, cytisine's shorter regimen and natural composition broaden its appeal, potentially supporting a wider spectrum of people who smoke. The study's robust design, infrastructure, and expertise enhance its feasibility. Future research avenues, especially among cardiac patients and relapsed individuals, promise further insights, potentially transforming cessation strategies worldwide.

Trial registration Registered at Clinicaltrials.gov (CT04286295) on 14 March 2022. https://clinicaltrials.gov/study/NCT04286295?locStr=Canada&country=Canada&intr=Cytisine&rank=3.

Keywords Cytisine, Nicotine replacement therapy, Cardiovascular disease, Smoking relapse

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Introduction

Cigarette smoking is a causative factor in the development of cardiovascular disease (CVD) and is the most dangerous form of tobacco use [1]. There are effective treatments for smoking cessation but relapse to cigarette smoking is common, principally due to nicotine addiction and related withdrawal symptoms [2]. Little is known about how best to support people who smoke who have relapsed in subsequent attempts to change their smoking behavior. Pharmacotherapy is effective in achieving smoking cessation and preventing relapse [3–5]. Three drugs are currently employed as first-line medications: combination nicotine replacement therapy (NRT), sustained-release bupropion hydrochloride, and varenicline tartrate [3]. Recent evidence suggests that cytisine is also effective as a cessation aid [6]. However, its efficacy has not been evaluated among patients who have relapsed after a previous quit attempt.

Cytisine is a plant-based smoking cessation medication with more than 50 years of use in central and eastern Europe [7]. It is a partial agonist of the nicotinic acetylcholine receptors (nAChRs), which is central to the effect of nicotine on the reward pathway [8, 9]. Cytisine acts by reducing the rewarding effect of nicotine thus attenuating nicotine withdrawal symptoms [10, 11]. Several studies have highlighted the promising future of cytisine as a smoking cessation treatment [12–14]. It is inexpensive to produce and is currently priced at a fraction of the cost of other first-line cessation medications [15]. It is well-tolerated by smokers [16] and requires a shorter treatment period (i.e., 25 days) than conventional treatments, which may be 12 or more weeks [17]. Because it is plant-based, cytisine may be attractive to smokers who prefer "natural" medicines [18].

Several randomized controlled trials have demonstrated that cytisine is more likely to result in smoking cessation compared to placebo [13] and combination NRT [14]. While there is a slight increase in any adverse events such as nausea, serious adverse events were uncommon and not significantly different between groups. A recent RCT comparing cytisine to varenicline did not meet the threshold for non-inferiority [17]. However, a Cochrane review comparing these medications did not show a significant difference in efficacy outcomes and highlighted lower rates of adverse events such as nausea and adverse dreams with cytisine compared to varenicline [8] Nonetheless, these trials do not evaluate which medication is preferred in cases of relapse to smoking. In this pilot feasibility study, our long-term goal is to evaluate the efficacy of cytisine compared to conventional treatment (i.e., combination NRT) for smoking cessation among smokers who have relapsed to smoking following hospitalization at a cardiac centre. Prior to conducting a larger, definitive RCT there is a need to conduct a pilot study to better understand the potential feasibility of such a trial.

Methods

Design

A pilot, two-group parallel RCT will be conducted at the University of Ottawa Heart Institute (UOHI). Patients enrolled in UOHI's in-patient smoking cessation program who have relapsed to daily smoking within 180 days of hospital discharge will be recruited through the program's follow-up support services. Eligible participants will be randomized 1:1 to receive a 25-day supply of cytisine capsules or combination NRT (patch and lozenge). All participants will receive counseling and follow-up support from a nurse specialist on days 3, 7, 14, and 21. See Fig. 1 for the flow diagram of the study.

The primary feasibility outcome is the ability to recruit 10 patients per month over the course of recruitment. The secondary feasibility outcome includes a proportion of participants who complete the prescribed treatment course and attrition rate. Additional secondary outcomes include rates of smoking cessation, number of cigarettes smoked, and adverse events. See Table 1 for the primary and secondary objectives of this study.

Participants

A total of 60 participants (30 women, 30 men) will be recruited. We will use quota sampling to ensure our participant sample is balanced based on sex after every 20 participants. Eligibility criteria are presented in Table 2.

Feasibility of recruitment

All patients who smoke and are admitted to UOHI are systematically identified and offered treatment through the Institute's in-patient smoking cessation program. Patients are visited at the bedside by nurse specialists who deliver counseling and initiate treatment with combination NRT (long-acting products such as nicotine patch and short acting products such as gum or lozenge) to reduce nicotine withdrawal symptoms. At hospital discharge, smokers are instructed to continue combination NRT and are enrolled in an automated telephone follow-up system. Calls to patients are placed 3, 14, 30, 90, and 180 days after hospital discharge. If the patient indicates during any call that they have relapsed from smoking or that their confidence in remaining smoke-free is low, they receive a "live" telephone call from the nurse specialist who

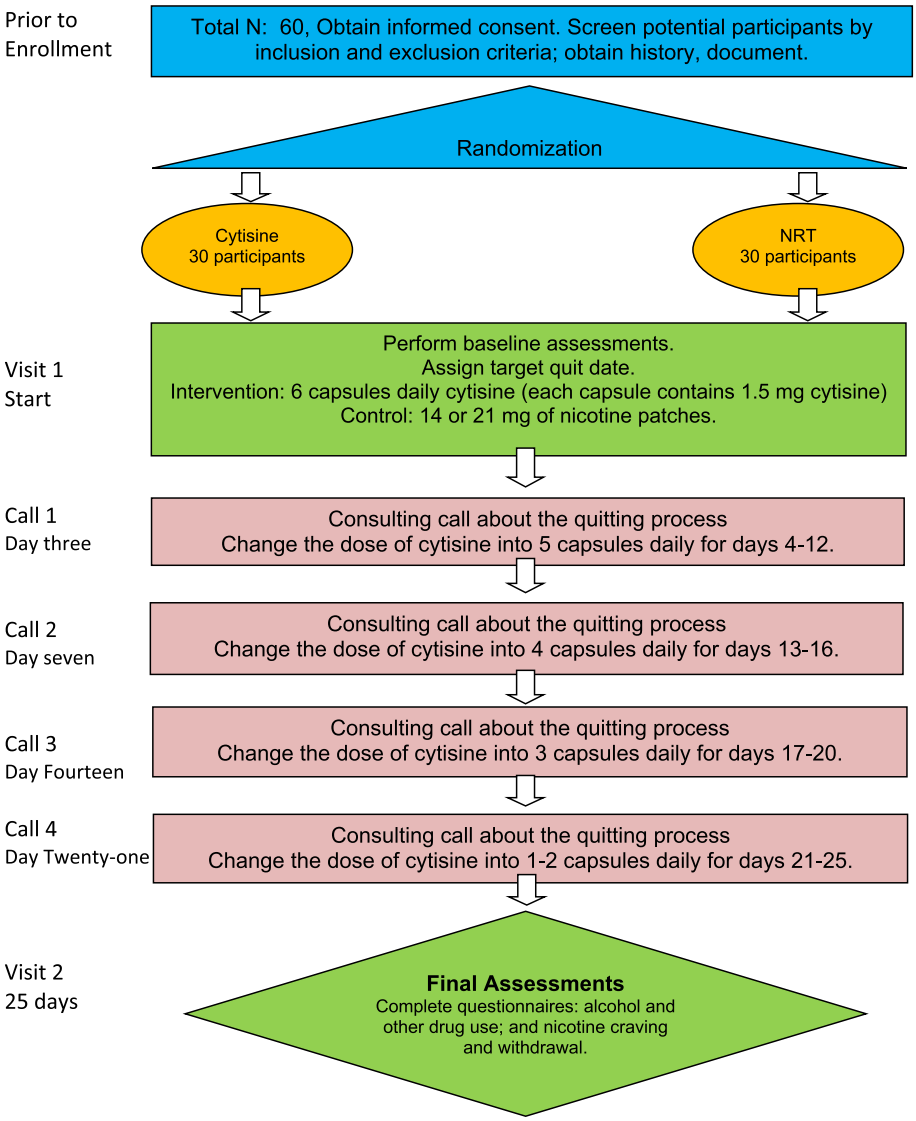

Fig. 1 Flow diagram of study

provides additional support as necessary. Each month approximately 125 smokers receive treatment as part of the in-patient smoking cessation program. Approximately 30% of these individuals relapse to smoking within 180 days of hospital discharge (approximately 30–40 patients per month). These relapsed patients (from calls on day 3 to 180 post-discharge) will form the pool from which the study sample will be drawn. Given the infrastructure, staffing, and patient volumes, recruiting 60 patients should be feasible. The key feasibility outcomes and the associated progression criteria that will determine the feasibility of a larger study are presented in Table 3.

Procedures

Recruitment

Potential study participants will be identified from patients enrolled in the UOHI inpatient program, the Quit Smoking Program (QSP). When the nurse specialist contacts a patient who has relapsed, they will ask if they have returned to daily smoking. If yes, the nurse specialist (within the circle of care) will ask the patient if they are interested in participating in a research study concerning different treatments for smokers who have relapsed. If interested, a research coordinator will contact the patient by phone and conduct a preliminary screening of eligibility criteria. If they are eligible and willing to

Table 1 Cytisine and smoking relapse trial objectives

Primary objective
(a) To evaluate the feasibility of future randomized clinical trial about effect of cytisine for prevent smoking cessation relapse among cardiovascular disease (CVD) patients who smoke daily
Secondary objectives
(b) To recruit 10 relapsed smokers with CVD per month to a study of cytisine vs. combination NRT
(c) To assess any differences in the effectiveness of the form of tobacco used (tobacco smoking only versus a combination of smoking and smokeless tobacco)
(d) To assess any differences in the effect across different CVD severity groups, high and low socio-economic status (SES), gender, and age subgroups
(f) To assess possible adverse effects of cytisine in the target population
(g) To assess all relevant components of the design and delivery of the smoking cessation program as part of a process evaluation

Table 2 Patient eligibility criteria

Inclusion criteria
a. Patient is enrolled in the University of Ottawa Heart Institute (UOHI)'s Quit Smoking Program (QSP) post-discharge follow-up program
b. Patient is currently smoking ≥ 5 cigarettes per day
c. Within 180 days of discharge from UOHI
Exclusion criteria
a. Patient has used cytisine, varenicline, bupropion, or a nicotine-containing vaping device within the past 15 days
b. Patient is unavailable to come on-site to UOHI for 2 assessments
c. Patient is unable to provide informed consent
d. Patient is unable to comprehend the intervention instructions (in the opinion of qualified investigators Pipe or Mir)

participate, a baseline assessment will be scheduled. Prior to the baseline visit, all remaining QSP calls will be cancelled so they do not conflict with the study phone calls.

Baseline assessment

Remote informed consent will be obtained by the Research Coordinator before any data is collected. Demographic information will be collected from each participant on a questionnaire. Medical history information and current medications will be obtained from the electronic patient record. All participants will have an in-person or virtual consultation with a study doctor or the study nurse prior to randomization to assess their general cardiac and respiratory health. Participants will complete questionnaires concerning gender roles; alcohol and other drug use; smoking and quitting history, and nicotine craving and withdrawal. A breath sample will be obtained to determine carbon monoxide concentration. Participants will be provided with a log sheet to record all their cigarettes smoked over the 25-day treatment period along with the use of the assigned cessation product. Participants will be given a $40 gift card for completing the baseline assessment. We aim to perform an analysis to assess any differences in the effect across various subgroups, including different CVD severity groups, socioeconomic status (high and low SES), gender, and age.

Allocation to intervention groups and blinding

After baseline assessment, participants will be stratified by sex and randomly allocated in a 1:1 ratio to a cytisine or combination NRT group. The randomization scheme will be computer-generated by the Cardiovascular Research Methods Centre at UOHI using a random sequence program with concealed allocation. A log will be maintained for all randomization encounters in REDCap to ensure consecutive allocation. Participants will be immediately informed of their treatment group assignment at the end of their baseline visit.

Trial interventions

The treatment period will last 25 days. Participants will be asked to choose a target quit date and to aim to be smoking zero cigarettes within 5 days of this date. All participants will receive telephone-based nurse counseling calls on days 3, 7, 14, and 21 following their target quit date. During each counseling session, the nurse will ask about the use of the assigned medication or product and will ask about side effects or adverse reactions, including cardiac symptoms and signs of acute respiratory illness. The nurse will also reinforce the proper use of the assigned medication and will remind all participants not to share or alter their medication in any way.

Cytisine Cravv™ (Zpharm, Waterloo) is a natural health product licensed by Health Canada to assist with smoking cessation; each oral capsule contains 1.5 mg of cytisine. The dosing is as follows: 6 capsules daily for the first 3 days; 5 capsules daily for days 4–12; 4 capsules daily for days 13–16; 3 capsules daily for days 17–20; and 1–2 capsules daily for days 21–25. Cravv™ capsules will be ordered from the UOHI Pharmacy. All participants will follow this dosing schedule however, if a patient is not tolerating the medication, the number of capsules taken each day can be decreased based on the direction provided by the study nurse.

Combination NRT The Nicoderm® patch plus Nicorette® gum or Thrive® Lozenge will be provided to participants in the combination NRT group. Participants smoking less than 15 cigarettes per day will be provided with 14 mg patches while those smoking 15 or more cigarettes per day will receive 21 mg patches. Participants will be told to apply a new patch each morning. Participants will be instructed to use lozenges as needed (up to 15 per

Table 3 Key feasibility outcomes and the associated progression criteria

	Go	Amend	Stop
Recruitment			
1. Screened/month	10 or more	5 to 9	4 or fewer
2. Recruited/month	7 or more	4 to 6	3 or fewer
3. % recruited of screened	70% or more	31% to 69%	Less than 30%
Engagement			
4. Research visit (2 of 2)	70% or more	31% to 69%	Less than 30%
5. Nurse counselling visit (at least 3 of 4 attended)	70% or more	31% to 69%	Less than 30%
Adherence			
6. Adherence to drug allocation assignment	80% or more	50% to 79%	Less than 50%
7. Adherence to cytisine taper	80% or more	50% to 79%	Less than 50%
8. Study surveys completed	80% or more	50% to 79%	Less than 50%
9. Log if cigarette use	80% or more	50% to 79%	Less than 50%
10. Biochemical verification of smoking status	80% or more	50% to 79%	Less than 50%
Retention			
11. Loss to follow up	Less than 20%	20% to 50%	More than 50%
Intervention Assessment			
12. Feasibility of nurse counselling visit (at least 3 visits offered)	70% or more	31% to 69%	Less than 30%

• 9 or more (75% +) "Go"—minor revisions prior to proceeding

• 6 to 8 (50–75%) "Go"—major revisions prior to proceeding

• 5 or fewer (Less than 50%) "Go"—stop proceeding

day) to overcome nicotine cravings. All participants will be given the 2 mg or 4 mg lozenge dose.

Follow-up assessment

All participants will return to the UOHI after the 25-day treatment period (within ± 2 weeks). Participants will complete questionnaires concerning alcohol and other drug use; and nicotine craving and withdrawal. Changes in medication will be recorded. A breath sample will be obtained to determine carbon monoxide concentration. Log sheets will be collected, and all unused capsules, patches, and lozenges will be counted. Participants will be given a $40 gift card for completing the follow-up assessment. Trial schedule of enrolment, interventions, and assessments are presented in Fig. 2.

Measures

Feasibility

The primary feasibility outcome will be the ability of the research team to recruit 10 patients who smoke per month. Secondary feasibility outcomes include the proportion of patients that complete the prescribed treatment, reach 25-day follow-up, keep a log of their cigarette use, and provide biochemical verification of smoking status. Unused cytisine capsules, nicotine patches, and nicotine lozenges will be collected at follow-up and counted.

Smoking behavior (measured on days 3, 7, 14, 21, and 25)

Participants will be asked to self-report how many cigarettes they smoked on each of the 3 days prior to each assessment. The mean number of cigarettes smoked will be recorded. Self-reported cigarette consumption will be checked against the number of cigarettes recorded on the log sheet returned at the day 25 visit. In addition, all participants will be asked at baseline and follow-up to provide a carbon monoxide breath sample measured by the Bedfont Smokelyzer. CO concentrations of < 10 ppm at follow-up will confirm tobacco cessation. Smoking status will follow the Russell Standard (11). Self-reported and biochemically verified smoking cessation rates serve as the key efficacy outcomes.

Gender role (measured at baseline and follow-up)

The BEM Sex Role Inventory questionnaire will be used to assess participants' feelings towards their own gender role identity. Participants will rate themselves on a scale of 1–7 (never to always) for all 60- items and will be categorized as being masculine, feminine, androgynous, or undifferentiated.

		STUDY PERIOD							
	Enrolment	Allocation	Post-allocation						Close-out
TIMEPOINT**	$-t_1$	0	Day 1 t_1	Day 3 t_2	Day 7 t_3	Day 14 t_4	Day 21 t_5	Day 25 t_6	After Day 25 t_x
ENROLMENT:									
Eligibility screen	X								
Informed consent	X								
Medical Assessment	X								
Allocation		X							
INTERVENTIONS:									
Cytisine			←	—	—	—	—	→	
Nicotine Replacement Therapy			←	—	—	—	—	→	
Counselling				X	X	X	X		
ASSESSMENTS:									
Carbon Monoxide (ppm)	X								X
BEM Sex Role Inventory	X								X
Heaviness of Smoking Index (HSI)	X								X
Demographics	X								
Alcohol and Substance Use	X								X
Smoking History	X								X
Withdrawal Symptoms	X								X
Self-reported CPD	X			X	X	X	X		X
Unused medication									X
reconciliation									

Fig. 2 Cytisine vs. NRT trial schedule of enrolment, interventions, and assessments

Nicotine addiction and withdrawal (measured at baseline and follow-up)

Cravings for nicotine will be measured using the Heaviness of Smoking Index (HSI). This is a 2-item questionnaire that asks about the time to first cigarette and the number of cigarettes smoked per day. A score of 0–2 indicates a low nicotine addiction, 3–4 indicates a moderate addiction and 5–6 indicates a high addiction.

Alcohol and substance use (measured at baseline and follow-up)

Participants will be given a single questionnaire to assess the use of alcohol and various forms of illicit substances. Responses to the questions include yes/no and frequency of use.

Safety

All adverse events will be assessed by the study physician who will determine whether the event is serious in nature. Any adverse event that is life-threatening, persistent, or causes significant disability, or that requires hospitalization or leads to death will be recorded as a serious adverse event. The study physician will determine whether the participant can remain in the trial and what medical treatment they may require as a result of the

adverse event. A Data Safety Monitoring Board (DSMB) will be established and will meet before study recruitment begins. The Board will meet at specific time points based on recruitment and will review all adverse events, side effects, toxicities, and issues related to participant safety. The board will consist of 3 members with expertise in cardiac health and tobacco addiction. During each meeting, any new literature or emerging evidence related to the products used within this project will be reviewed. If there is evidence that indicates that one of the products used within this study is no longer safe for use, the treatment will be discontinued. All participants will be notified, and a subsequent medical assessment will be completed by the study physician to assess potential adverse reactions and a side-effect report will be sent to Health Canada via their online reporting portal.

Sample size and justification

The purpose of this pilot is not to prove the superiority of one treatment over another, but rather to test the feasibility of a larger trial. As pilot trials do not have the same objectives as a main trial, setting the sample size in the same way—using formal power considerations—is usually not necessary. The primary outcome of this study is feasibility. However, efficacy and safety outcomes are also measured and can help inform future sample size calculations. As such, we have used approximation rules for estimating sample size for pilot randomized trials with continuous outcome measures; power = 90% and $\alpha = 0.05$ [19]. Given the efficacy of NRT is 30% and the efficacy of cytisine is 40%, we expect a small effect size of cytisine over NRT. Accordingly, we aimed to have at least 25 participants in each arm. To account for a 15% loss to follow-up rate, we increased the sample size from 50 to 60 participants (30 in each group).

Data analysis plan

The number of months required to recruit the entire sample will be recorded. Treatment completion in the group will be calculated from the amount of medication provided and returned at the end of treatment. The attrition rate will be calculated from the number of participants failing to return for follow-up. Descriptive statistics will be used to compare cigarettes per day 25 days after treatment initiation between groups and measures of arterial stiffness. The proportion of participants reporting zero cigarettes per day will also be compared between groups. Feasibility will be determined by comparing observed recruitment, treatment completion, attrition, and quit rates with our proposed progression criteria. See Table 3 for the key feasibility outcomes and associated progression criteria.

Registration and ethics approval

The trial was granted full ethics approval by the Ottawa Health Science Network Research Ethics Board (OHSN-REB) (Reference number 20190720-01H) and it is registered to Clinicaltrials.gov (CT04286295).

Protocol revisions

Since drafting the original study protocol, a few revisions were required. Due to the COVID-19 pandemic, we enabled virtual means of obtaining informed consent and conducting medical assessments. Initial recruitment has been lower than expected and therefore the eligibility criteria were adjusted to augment recruitment. This included the removal of patients needing to have coronary heart disease, reducing the number of cigarettes per day (from 10 to 5), extending the time from discharge from UOHI (from 90 to 180 days), and the removal of an exclusion criteria for those using NRT at the time of eligibility assessment. Arterial stiffness testing and interpretation are no longer available and 4 mg lozenges were also unavailable, thus revisions were made accordingly. The adjustments made to the initial protocol were also updated on clinicaltrials.gov and summarized in Table 4.

Discussion

Cytisine presents a promising alternative to traditional nicotine replacement therapy (NRT) for smoking cessation and preventing relapse. It is more efficacious, has a similar side effect profile, and is significantly less expensive when compared to a combination of NRT and other cessation aids. It will have major implications as a cost-effective cessation aid with global implications. Despite significant strides in reducing smoking rates in Canada over the past two decades, a substantial portion of the population continues to smoke daily, highlighting the ongoing need for effective cessation interventions [20]. Moreover, the rise in nicotine dependency and the use of alternative nicotine delivery systems pose additional challenges for healthcare systems [21], further highlighting the importance of accessible interventions like cytisine. With its shorter treatment regimen and natural composition, cytisine could appeal to a broader spectrum of smokers seeking to quit, potentially leading to even greater reductions in smoking rates and relapse instances [22]. By providing evidence of its efficacy, this study stands to influence policy decisions, potentially saving millions of lives worldwide annually.

There are several strengths to this study. To the best of our knowledge, this is the first pragmatic RCT to comprehensively assess the safety, effectiveness, and cost-effectiveness of cytisine in this patient population. The study design is strong, comparing the currently approved and available dose of cytisine in Canada with combination

Table 4 Revisions made to the original protocol

Revision number	Date of revision	Revision	Reason
1	October 21, 2021	Medical assessments may be conducted virtually at the baseline visit	Lockdowns and social distancing due to the COVID-19 pandemic affected on-site visits
2	April 1, 2022	Removed the criteria that the patient must have coronary heart disease	More inclusive of other forms of heart disease seen at UOHI
3	May 30, 2022	4 mg lozenges were removed so all patients in the NRT arm only received 2 mg lozenges	4 mg lozenges were no longer available
		"Thrive" brand of lozenges was added in addition to Nicorette	Ensure adequate medication availability and choice for patients
4	July 6, 2022	Inclusion criteria changed: Daily smoking of 5 cpd (rather than 10 cpd) Within 180 days of discharge from UOHI (rather than 90 days)	Expand eligibility criteria to help augment recruitment given lower-than-expected recruitment
5	March 22, 2023	Study objective change: removed measure of arterial stiffness	Testing and interpretation are no longer available at UOHI
		Removed NRT as an exclusion criterion Added remote means of obtaining informed consent	Expand eligibility criteria to help augment recruitment given lower-than-expected recruitment
		Added in study windows (i.e., follow-ups to be done within 2 weeks of finishing 25-day treatment)	Clarity for participants and study staff

NRT. By using combination NRT (as opposed to single NRT), this study strengthens the control group and ensures that cytisine is being compared to the standard of care NRT dosing. Multi-pronged efforts have been made to maximize feasibility. There is a strong infrastructure, staffing, expertise, and patient volumes at UOHI. The study team has research expertise in conducting large, impactful research related to smoking cessation [23–25]. Further, there is adequate access to funding, medications, and staff (clinical and research) to complete the study.

The findings from this innovative trial will inform future studies evaluating cytisine for smoking cessation, especially among cardiac patients and those who have relapsed. These studies will have the potential to revolutionize smoking cessation strategies, offering healthcare systems a natural, safe, efficacious, and cost-effective tool to improve cessation rates and overall health outcomes for millions of people who smoke in Canada and across the World.

Conclusion

This pilot feasibility study will be the first randomized controlled trial evaluating the efficacy and safety of cytisine compared to combination nicotine replacement therapy for patients who relapse to smoking. The findings will inform the design of a larger study to assess the optimal approach to support patients who relapse to smoking.

Acknowledgements
Not applicable

Authors' contribution
Hassan Mir contributed to the conception, supervision, and design of the research; Ashley Baldwin, and Evyanne Quirouette contributed to the screening, recruitment, and data gathering; Javad Heshmati acquired and analyzed the data; Kerri-Anne Mullen, Andrew Pipe, and Robert Reid contributed to the interpretation of the data; Hassan Mir, Robert Reid, Javad Heshmati, and Kerri-Anne Mullen drafted the manuscript. All authors critically revised the manuscript, agreed to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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Data availability
Data will be available upon request and consent of the corresponding author.

Declarations

Ethics approval and consent to participate
The trial was granted full ethics approval by the Ottawa Health Science Network Research Ethics Board (OHSN-REB) (Reference number 20190720-01H) and it is registered to Clinicaltrials.gov (CT04286295).

Consent for publication
Not applicable—no identifying images or other personal or clinical details of participants are presented here or will be presented in reports of the trial results. The participant information materials and informed consent forms are available from the corresponding author on request.

Competing interests
The authors declare that they have no competing interests.

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References

1. Barua RS, Rigotti NA, Benowitz NL, Cummings KM, Jazayeri M-A, Morris PB, et al. 2018 ACC expert consensus decision pathway on tobacco cessation treatment: a report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. J Am Coll Cardiol. 2018;72(25):3332–65.
2. Reid RD, Pritchard G, Walker K, Aitken D, Mullen K-A, Pipe AL. Managing smoking cessation. CMAJ. 2016;188(17–18):E484–92.
3. Aubin HJ, Luquiens A, Berlin I. Pharmacotherapy for smoking cessation: pharmacological principles and clinical practice. Br J Clin Pharmacol. 2014;77(2):324–36.
4. Yilmazel Ucar E, Araz O, Yilmaz N, Akgun M, Meral M, Kaynar H, Saglam L. Effectiveness of pharmacologic therapies on smoking cessation success: three years results of a smoking cessation clinic. Multidisciplinary respiratory medicine. 2014;9:1–5.
5. Aldi GA, Bertoli G, Ferraro F, Pezzuto A, Cosci F. Effectiveness of pharmacological or psychological interventions for smoking cessation in smokers with major depression or depressive symptoms: A systematic review of the literature. Substance abuse. 2018;39(3):289–306.
6. Tutka P, Vinnikov D, Courtney RJ, Benowitz NL. Cytisine for nicotine addiction treatment: a review of pharmacology, therapeutics and an update of clinical trial evidence for smoking cessation. Addiction. 2019;114(11):1951–69.
7. Paduszyńska A, Banach M, Rysz J, Dąbrowa M, Gąsiorek P, Bielecka-Dąbrowa A. Cytisine-from the past to the future. Curr Pharm Des. 2018;24(37):4413–23.
8. Livingstone-Banks J, Fanshawe TR, Thomas KH, Theodoulou A, Hajizadeh A, Hartman L, Lindson N. Nicotine receptor partial agonists for smoking cessation. Cochrane Database Syst Rev. 2023(5).
9. Quintanilla ME, Rivera-Meza M, Berríos-Cárcamo P, Cassels BK. Reduction of nicotine and ethanol intake in alcohol-preferring (UChB) female rats by the α4β2 nicotinic acetylcholine receptor partial agonists 5-bromocytisine and cytisine. Drug Alcohol Depend. 2023;250: 110900.
10. Tutka P, Zatoński W. Cytisine for the treatment of nicotine addiction: from a molecule to therapeutic efficacy. Pharmacol Rep. 2006;58(6):777.
11. Zatonski W, Cedzynska M, Tutka P, West R. An uncontrolled trial of cytisine (Tabex) for smoking cessation. Tob Control. 2006;15(6):481–4.
12. Beard E, Shahab L, Cummings DM, Michie S, West R. New pharmacological agents to aid smoking cessation and tobacco harm reduction: what has been investigated, and what is in the pipeline? CNS Drugs. 2016;30(10):951–83.
13. West R, Zatonski W, Cedzynska M, Lewandowska D, Pazik J, Aveyard P, Stapleton J. Placebo-controlled trial of cytisine for smoking cessation. N Engl J Med. 2011;365(13):1193–200.
14. Walker N, Howe C, Glover M, McRobbie H, Barnes J, Nosa V, et al. Cytisine versus nicotine for smoking cessation. N Engl J Med. 2014;371(25):2353–62.
15. Gotti C, Clementi F. Cytisine and cytisine derivatives. More than smoking cessation aids. Pharm Res. 2021;170:105700.
16. Hajek P, McRobbie H, Myers K. Efficacy of cytisine in helping smokers quit: systematic review and meta-analysis. Thorax. 2013;68(11):1037–42.
17. Courtney RJ, McRobbie H, Tutka P, Weaver NA, Petrie D, Mendelsohn CP, et al. Effect of cytisine vs varenicline on smoking cessation: a randomized clinical trial. JAMA. 2021;326(1):56–64.
18. Thompson-Evans TP, Glover MP, Walker N. Cytisine's potential to be used as a traditional healing method to help indigenous people stop smoking: a qualitative study with Māori. Nicotine Tob Res. 2011;13(5):353–60.
19. Whitehead AL, Julious SA, Cooper CL, Campbell MJ. Estimating the sample size for a pilot randomised trial to minimise the overall trial sample size for the external pilot and main trial for a continuous outcome variable. Stat Methods Med Res. 2016;25(3):1057–73.
20. Hammond D, Rynard VL, Reid JL. Changes in prevalence of vaping among youths in the United States, Canada, and England from 2017 to 2019. JAMA Pediatr. 2020;174(8):797–800.
21. Gholap VV, Kosmider L, Golshahi L, Halquist MS. Nicotine forms: why and how do they matter in nicotine delivery from electronic cigarettes? Expert Opin Drug Deliv. 2020;17(12):1727–36.
22. Pastorino U, Ladisa V, Trussardo S, Sabia F, Rolli L, Valsecchi C, et al. Cytisine therapy improved smoking cessation in the randomized screening and multiple intervention on lung epidemics lung cancer screening trial. J Thorac Oncol. 2022;17(11):1276–86.
23. Coja M, Mullen K, Pipe A, Reid R. 1442 Implementation and outcomes of systematic approaches to tobacco treatment: the Ottawa Model for Smoking Cessation. Eur Heart J. 2019;40(Supplement_1):ehz748. 0077.
24. Reid RD, Malcolm J, Wooding E, Geertsma A, Aitken D, Arbeau D, et al. Prospective, cluster-randomized trial to implement the ottawa model for smoking cessation in diabetes education programs in Ontario. Canada Diabetes Care. 2018;41(3):406–12.
25. Reid RD, Mullen K-A, Slovinec D'Angelo ME, Aitken DA, Papadakis S, Haley PM, et al. Smoking cessation for hospitalized smokers: an evaluation of the "Ottawa Model." Nicotine Tob Res. 2010;12(1):11–8.

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