Electronic cigarettes for smoking cessation: randomised controlled trial.

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Summary

Background
Electronic cigarettes (ECs) can deliver nicotine, mitigate tobacco withdrawal and are used by many smokers to assist quit attempts. We investigated whether ECs are more effective than nicotine patches at helping smokers to quit.

Methods
In this pragmatic randomised controlled superiority trial conducted in New Zealand (NZ) between 2011 and 2013, smokers wanting to quit were randomised to Elusion nicotine ECs, placebo ECs (no nicotine), or to nicotine patches (21 mg patch, one daily), from one week before until 12 weeks after quit day, with low intensity behavioural support. The primary outcome was biochemically verified continuous abstinence at six months (intention to treat, ITT); secondary outcomes were cigarette consumption, withdrawal, time to relapse, and adverse events. The trial is registered with the Australian NZ Clinical Trials Registry (ACTRN12610000866000).

Findings
657 people were randomised and included in the ITT analysis. Verified abstinence rates were 7·3% (nicotine ECs), 5·8% (patches) and 4·1% (placebo ECs). While there was no support for superiority of nicotine ECs over patches or placebo ECs (risk difference [RD] nicotine EC *vs* patches 1·51 [95% CI -2·49 to 5·51]; nicotine EC *vs* placebo EC 3·16 [95% CI -2·29to 8·61], cigarette consumption halved or more in 57% of the participants allocated to nicotine ECs *vs* in 41% in the patches group (RD 15·39 [95% CI 7·38 to 23·40]), and 45% in placebo ECs. Median time to relapse was twice that in participants allocated to nicotine ECs than patches (Log-rank test P=0·0001) or placebo ECs. No significant differences in adverse events were observed.

Interpretation
ECs, with or without nicotine, were modestly effective at helping smokers quit, with few adverse events over 13 weeks use, similar to patches. Nicotine ECs were more effective than patches and placebo ECs at aiding cessation, but the differences were not statistically significant.

Funding
Health Research Council of New Zealand (HRCNZ).

Trial registration
Australian NZ Clinical Trials Registry (ACTRN12610000866000) https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=336091

Contributors
All authors were involved in the design and development of the study. CB and CH oversaw the conduct of the study and data collection. VP undertook the statistical analysis, with all other authors interpreting the data. CB led the writing of the first draft of the manuscript and all authors were involved in subsequent drafts and reviewing the final manuscript.

Conflicts of interest
The ECs, cartridges and batteries were Elusion™ brand provided by PGM International Ltd, NZ, which had no role in study design, data collection, analysis, interpretation, or writing of the publication. All authors declare that (1) no authors have received support from any companies for the submitted work; (2) (2) ML, via his company HealthNZ, previously undertook research funded by Ruyan (an EC manufacturer). CB and HM have undertaken research on Ruyan ECs independently of Ruyan, funded by HealthNZ. HM has received honoraria for speaking at research symposia and received benefits in kind and travel support from, and has provided consultancy to the manufacturers of smoking cessation medications. NW has provided consultancy to the manufacturers of smoking cessation medications, received honoraria for speaking at a research meeting and received benefits in kind and travel support from a manufacturer of smoking cessation medications; JW has provided consultancy to the manufacturers of smoking cessation medications; (3) their spouses, partners, or children have no financial relationships that may be relevant to the submitted work; and (4) all authors have no non-financial interests that may be relevant to the submitted work.

Background

Since their launch in 2004, electronic cigarettes ('e cigarettes', hereafter 'ECs'), a diverse range of battery operated devices that vapourise nicotine for inhalation, have been purchased by millions of people. Many smokers use ECs to help quit (27% of those making a quit attempt in the United Kingdom, in May 2013[1]), and sales are increasing so rapidly some analysts predict they will surpass cigarette sales within a decade.[2]

The place of ECs in tobacco control is controversial,[3,4] and there is a paucity of reliable data to inform debate. Such research as exists points to ECs potential to assist smokers to quit or reduce smoking: surveys indicate many try ECs for these reasons,[5, 6] and studies show ECs are capable of delivering nicotine into the bloodstream, and attenuating tobacco withdrawal as effectively as nicotine replacement therapy (NRT).[7,8] EC use also simulates behavioural and sensory dimensions of smoking. A recent trial in 300 smokers unwilling to quit found low rates of cessation at 12 months for nicotine EC and placebo ECs (See Panel: Research in context).[9] ECs also have potential to harm: studies have detected toxins in EC fluid and vapour,[10] but at similar levels to NRT, lower than in cigarette smoke,[11] and a recent review considered ECs very unlikely to pose additional risks to smokers.[12]

Aim

This trial aimed to assess if ECs with cartridges containing nicotine ('nicotine ECs') were more effective for smoking cessation than nicotine patches, and in a blind comparison, than ECs with cartridges containing no nicotine ('placebo ECs'). We also hypothesised nicotine ECs would be more effective than patches and placebo ECs on smoking reduction, tobacco dependence, withdrawal symptom relief, and have no greater risk of adverse events.

Methods

Study design and participants

This was a three arm parallel group, randomised controlled trial conducted in Auckland, New Zealand (NZ), with first randomisation on 6th September 2011 and last follow up on 5th July 2013. The published protocol describes procedures in detail.[13] In brief, people were eligible if aged ≥18 years, smoked ≥ ten cigarettes per day for the past year, wanted to stop smoking, and could provide consent. We recruited via community newspapers, inviting people to call the study centre for eligibility pre-screening undertaken by research assistants (RAs), who also performed follow up assessments. Participants were mailed study information, and consent forms to sign and return. We excluded pregnant and breastfeeding women, people using cessation medications or in an existing cessation programme, reporting heart attack, stroke, or severe angina two weeks prior, having poorly controlled medical conditions, allergies, or other chemical dependence. The Northern X Regional Ethics Committee approved the study (Number NTX/10/11/111); the Standing Committee on Therapeutic Trials approved nicotine EC use as they are not allowed for sale in NZ, but may be imported for personal use or for research.

Randomisation and masking

Callers who met the inclusion criteria and gave demographic details and information about nicotine dependence (Fagerström Test for Nicotine Dependence [FTND][14]) were randomised to nicotine ECs, patches, or placebo ECs, with computerised stratified block randomisation (stratification factors: ethnicity [Māori or non-Māori], sex [male or female] and level of nicotine dependence [> 5 or ≤ 5 FTND]). It was not feasible to mask participants to allocation to patch or EC. RAs undertaking outcome assessments used a list generated by the trial database giving no indication of product allocation.

Study products

Elusion™ ECs are among the EC market leaders in Australasia; in NZ, Elusion™ zero nicotine cartridges are readily available for sale and identical in appearance to nicotine cartridges. We commissioned analyses of these ECs: the liquid was free of diethylene glycol (a toxin detected in one brand of EC fluid[10]); nicotine cartridges (labeled '16 mg') contained 10 to 16 mg nicotine/ml, and placebo cartridges contained no nicotine; vapour analyses undertaken midway in the trial (using Goniewicz et al's methodology[15]) showed 300 puffs of the nicotine ECs delivered 3 to 6 mg nicotine, equivalent to smoking one to five cigarettes. Plasma levels in four experienced nicotine EC users peaked at 10 minutes at 3·4 ng/ml, a median increase from baseline of 2·1 ng/ml. We chose nicotine patches (21mg/24 hours) for comparison with ECs as they are the most popular NRT product, have proven effectiveness, and few known adverse events.

Methods

Procedures

Participants allocated to patches were sent exchange cards in the mail redeemable for patches from community pharmacies, with instructions to use patches daily, one week before until 12 weeks after their chosen quit day (QD), consistent with smoking cessation guidelines.[16] We also supplied vouchers to these participants to cover dispensing costs. Participants in both EC arms were couriered an EC, spare battery and charger, and cartridges (with labels masked to nicotine content), plus simple instructions to use them *ad libitum* from one week before until 12 weeks after QD. All randomised participants were referred to the NZ Quitline for behavioural support (involving at least one proactive telephone support session). Following randomisation, additional baseline data were collected: education, smoking and quitting history, quitting self-efficacy, medication, withdrawal symptoms and stage of addiction (Autonomy Over Smoking Scale, AUTOS),[17] and behavioural dependence (Glover-Nilsson Smoking Behavioural Questionnaire, GN-SBQ).[18] The primary outcome was continuous smoking abstinence (self-reported abstinence over the whole follow-up period allowing ≤ five cigarettes in total [Russell Standard definition[19]]), six months after QD, verified at that point in time by exhaled breath carbon monoxide (CO) measurement (< ten ppm) using Bedfont Micro+™ Smokerlyzers® (Bedfont Scientific Ltd, UK). Secondary outcomes assessed at one, three, and six months post QD were: continuous abstinence, seven day point prevalence abstinence (proportion reporting no smoking, not a puff, in the past week), number of cigarettes smoked per day, proportions reducing smoking, time to relapse to regular smoking, number of patches or cartridges used; use of other cessation treatments; withdrawal symptoms, stage of addiction[17] and smoking latency,[20] and adverse events. Data collection continued as scheduled if participants discontinued study treatments.

Statistical analysis
A sample size of 657 (292 in the nicotine EC and patches groups, 73 in the placebo EC group) conferred 80% power, two-sided P=0·05, to detect an absolute difference of 10% in quit rates between nicotine EC and patches groups (1:1 ratio), and 15% between nicotine EC and placebo EC groups (4:1 ratio), with expected quit rates of 15% in the placebo EC group and 20% in the patches group (based on meta-analyses of NRT trials).[21] Analyses used SAS version 9·3 (SAS Institute Inc., Cary, NC, USA). The primary analyses used the ITT approach (participants with unknown smoking status considered as smoking). Quit rates, relative risks (RR) and absolute risks for nicotine ECs *vs* patches, and *vs* placebo ECs. Treatment groups were compared using chi-squared tests, with multivariate regression adjusting for other variables as appropriate. Proportions with significantly reduced smoking consumption of at least 25% and 50% were calculated similarly. Change from baseline in each of the repeated AUTOS measures and cigarettes smoked per day (in non abstainers) was analysed using mixed models with a compound symmetry covariance structure including baseline values. Per protocol analyses were performed for the primary outcome, whereby participants with major protocol violations (e.g. cross-over treatments, withdrawals and loss to follow-up) were excluded. We assessed consistency of effects for pre specified subgroups (male/female, ethnicity [Maori versus non-Maori]) using tests for heterogeneity. Secondary analyses were conducted with overall cessation rates corrected for discordance between reported and verified cessation. Time to relapse analysis used Kaplan Meier curves, and the Log rank test. Adverse events were defined according to international guidelines, categorised by CB (blind to intervention product) as related or unrelated to the intervention, and analysed as serious or non-serious, by treatment group and association with study treatment, in line with recommended best practice.[22]

Role of the funding source
The study sponsor had no role in design, data collection, analysis, interpretation, or writing of the report. CB had full access to all study data and final responsibility for the decision to submit for publication.

Results
Figure 1 shows the flow of participants. Overall, loss to follow up was 22%: 17%, 27% and 22% in the nicotine EC, patches and placebo EC groups respectively. Participants' baseline characteristics were evenly balanced between treatment groups (table 1).

Figure 1 here
Figure 1. Flow of participants.

Table 1. Baseline characteristics of participants.

Tables 2 and 3 show verified continuous abstinence rates at six months after QD in each group were highest for nicotine ECs (7·3%), followed by patches (5·8%) and placebo ECs (4·1%), but with insufficient statistical power to conclude superiority of nicotine ECs to patches or to placebo ECs. Seven day point prevalence abstinence was closer to our estimates of 20%, and the RR indicated a difference in favour of nicotine ECs, but was not statistically significant at six months. Repeated measures analyses also showed a benefit of nicotine ECs over patches; but both these measures used self reported cessation. Subgroup analyses stratified by sex or ethnicity found no statistically significant differences in primary outcome.

Table 2. Continuous smoking abstinence and seven day point prevalence, nicotine e cigarette (EC) *vs* patches.

Table 3. Continuous abstinence and seven day point prevalence, nicotine e cigarette (EC) *vs* placebo EC.

Quit rates were initially high then declined in all groups. Most participants relapsed within 50 days. Among those who relapsed, the nicotine EC group took a median of 35 days, more than twice as long as the patches group (14 days, P=0·0001) or placebo EC groups (12 days, P=0·09) (figure 2). Cigarette consumption fell by two cigarettes/day on average in the nicotine EC group, 57% of whom had reduced daily cigarettes by at least half at six months (P=0·005), a significantly greater proportion than in the patches group (41%, P=0·002) (table 4).

Table 4. Change in cigarette consumption over follow up period, nicotine e-cigarette (EC) and patches.

Figure 2. Kaplan Meier curve for time to relapse to regular smoking (days).

Over six months AUTOS scores in the EC groups halved from baseline compared to a decline of one third in the patches group (data not shown). The difference between nicotine EC and patches groups in total AUTOS score reduction from baseline to six months was significant (1·12, P=0·05), but between nicotine EC and placebo EC groups changes were not statistically significant (P=0·14). Behavioural dependence at baseline was balanced, with 37% in both nicotine EC and patches groups and 42% in the placebo group scoring ‘strong’ or ‘very strong’, but there was no association of score with outcome.

Table 5 shows a higher number and proportion of adverse events in the nicotine EC than in the patches group; we found no evidence of a relationship with study product, and the event rate was not significantly different (incidence rate ratio [IRR] for nicotine EC *vs* patches=1·05, 95% CI 0·82 to 1·34, P=0·7).

Table 5. Adverse events by type (serious or non-serious), relationship to study treatment and event rate, by study treatment.

Adherence to study treatments was significantly higher in the nicotine EC group compared to patches group (P<0·0001 at each follow up assessment), and to the placebo EC group (P<0·0001 at each follow up assessment): at one month post QD, 78% in the nicotine EC group and 82% in the placebo EC group were using the allocated product, compared to 46% allocated to patches. However, by three months, 51% of nicotine EC and 53% placebo EC groups were still using allocated treatments, but only 18% in the patches group; at six months, 30% of nicotine EC group and 35% in the placebo EC groups persisted with EC use, with only 8% in the patches group still using patches. Among those in the nicotine EC group verified as abstinent, 38% still used ECs at six months; among non-quitters, 28% still used ECs (whether nicotine ECs or placebo ECs is unclear). As average daily use was low, some could have used cartridges allocated at randomisation; others may have purchased cartridges online. Participants using nicotine ECs reported an average of 1·3,1·1 and 0·7 cartridges and in the placebo EC group 1·1,1·2 and 0.7 cartridges, at one, three and six months respectively. Nicotine patches were used as instructed (an average of one daily). Few used other cessation products: at six months, seven participants in the nicotine EC group and seven in the patches groups reported using bupropion (n=2) or varenicline (n=5) in the past month; in the placebo EC group, three reported using varenicline.

Quitline support was accessed by fewer than half of participants: 42%, 39% and 38% in nicotine EC, patches, and placebo EC groups, respectively, but *post hoc* analysis found no benefit of using support on the primary outcome for participants in the nicotine EC group (P=0·67), nor patches group (P=0·16).

There was sustained enthusiasm for ECs: at one month, 89%, 92% and 56% in the nicotine EC, placebo EC, and patches group, respectively, stated they would recommend their allocated product to a friend wanting to quit; at six months the figures were barely changed: 85%, 88%, and 50%. Among participants allocated to ECs, 40% liked their tactile, cigarette like qualities, sensory familiarity, health benefits, taste, lack of cigarette odor and ease of use.

Discussion

In this, the largest randomised controlled trial of ECs on smoking cessation yet undertaken, and the first to compare ECs with a NRT product, we found nicotine EC use for 13 weeks gave six month abstinence rates that were modest but approximately 25% and 75% higher than those in the patches and placebo EC groups, respectively. These differences did not, however, reach statistical significance, but were nevertheless consistent across a range of analyses, and the 95% CIs indicate an advantage cannot be excluded. In *post hoc* analyses using a 5% non-inferiority limit for the risk difference (based on a margin used in our non-inferiority smoking cessation trial of cytisine[23]), nicotine ECs were at least as effective as patches (the absolute risk difference for the main primary outcome was 1·51 [95% CI -2·49 to 5·51]; - 0·49 is within the margin of -5). Thus we conclude nicotine ECs may well be more effective than patches for cessation, among smokers wanting to quit, but we cannot be fully confident this is the case; at the least they are likely to be as effective as patches, on cessation at six months.

Strengths of our study include use of a conservative primary outcome measure, and rigorous trial conduct to mitigate risk of bias.We used a pragmatic design because we consider an assessment of 'real world' effectiveness of ECs to be a priority for policy development though it could be argued a trial of a novel intervention should be more explanatory rather than pragmatic in design. There were a number of limitations. First, the effect size and baseline quit rate estimates on which the study sample size was calculated were optimistic; hence, statistical power to detect differences was limited. Second, participants assigned to patches had a higher loss to follow up and withdrawal rate. It is likely some took part just to try ECs but lost interest when randomised to patches. Those who reported previously trying to quit with patches or other forms of NRT (about 20% in the past year in each group) may have disadvantaged patches; however, at one month the difference between the ITT and per protocol analysis results was minimal suggesting this was not a major issue.

Third, the modest abstinence rate for nicotine ECs is similar to quit rates found in studies of NRT products used without behavioural support.[24] Adding more intensive support may well have improved quit rates, but it would also have misrepresented the typically low support environment in which most EC users attempt to quit. The modest rates may have been compounded by inadequate nicotine replacement: as noted, the cartridges contained less nicotine than labeled, and delivery was inefficient (not uncommon in other earlier ECs[15, 25]). Furthermore, users consumed on average just over one cartridge per day, delivering around only 20% of the nicotine obtained from cigarette smoking.[26] While trials of early ECs on withdrawal relief found low levels of nicotine delivery attenuated withdrawal symptoms,[7, 8] improved nicotine delivery by newer models of ECs may provide greater withdrawal relief, enhancing cessation effectiveness. Trials of such 'second generation' ECs are needed.

We included the placebo EC arm to explore the role of behavioural replacement by ECs, independent of nicotine delivery in cessation.[27] However, our study was underpowered to detect a small effect and the GN-SBQ instrument, which purports to measure behavioural dependence, may have been inadequate for this purpose.

One third of those allocated to the EC groups reported ongoing product use at six months suggesting they may have become long term EC users. Some quitters still required ongoing nicotine, and obtained it from ECs. Those who had relapsed to smoking but continued EC use (so called "dual use") at six months reduced cigarette consumption. Research has found higher cessation rates in people using NRT while still smoking;[28] if ECs act in the same way this would be a positive feature. Further research is needed to explore this area.

Finally, our trial provides for the first time adverse events information on 362 people randomly allocated to ECs or to patches. The finding of no significant differences in adverse events occurrence between groups over the duration of a standard NRT treatment course, and the further three months' monitoring, suggests such short term EC use is of low risk. However, longer term use requires more research.

In conclusion, we report new findings from a pioneering trial of one brand of ECs on smoking cessation, withdrawal, dependence, smoking reduction, and adverse events, over six months, compared to nicotine patches. At the least our study has established benchmarks for EC performance relative to NRT and placebo ECs, with which to design future, more adequately powered trials. Our findings point to potential for ECs in regard to cessation effectiveness beyond that noted in the present study. Further, because they have far greater reach and higher acceptability among smokers than NRT, and appear to have no greater risk of adverse effects, ECs also have potential for improving population health.

Panel: Research in context

Systematic Review

Our systematic review of ECs for smoking cessation, searching Medline, PsycINFO, CINAHL, EMBASE, and Cochrane using the terms e-cig$ OR elect$ cigar$ OR electronic nicotine, retrieved 186 articles and identified only one randomised, placebo controlled trial with a cessation endpoint measured at six months or more.[9] Risk of bias assessment used the Cochrane methodology. This trial, conducted between 2011 and 2012, recruited 300 adult Italian smokers unwilling to quit, with 100 randomised to each of three arms: 7·2 mg nicotine cartridges for 12 weeks, 6-weeks 7·2 mg cartridges followed by 6-weeks 5·4 mg cartridges, and 0 mg nicotine cartridges for 12 weeks). No behavioural support was provided but nine follow up visits occurred, with CO measures at each. The primary outcome was not clearly pre specified nor power calculations undertaken to estimate power. Analysis was by ITT. At 12 months 39% had been lost to follow up, a potential source of bias. Of those assessed, 9% had quit (13%, 9% and 4% in the two nicotine EC and placebo EC groups respectively) and reduction occurred in 10%, 9% and 12%; none of the comparisons were statistically significant. The reliability of ECs was problematic. These results are similar to those reported in previous trials of unsupported pharmacotherapy with patches[29] and comparable with our trial findings.

Interpretation

The study ECs, with or without nicotine, were modestly effective at helping smokers to quit. Nicotine ECs may be more effective or of similar effectiveness to patches but studies to date have lacked sufficient statistical power to draw more definitive conclusions. EC use was associated with few adverse events, similar to patches, but longer term data are needed. Uncertainty exists about the place of ECs in tobacco control, and more research is urgently needed to more clearly establish their overall benefits and harms at both individual and population levels.

Competing interests

The ECs and cartridges were Elusion™ brand products provided by PGM International Ltd, NZ. PGM International Ltd had no role in the study design, data collection, data analysis, data interpretation, or writing of this publication. All authors declare that (1) no authors have received support from any companies for the submitted work; (2) ML, via his company HealthNZ, previously undertook research funded by Ruyan (an EC manufacturer). CB and HM have undertaken research on Ruyan ECs funded by HealthNZ, independently of Ruyan. HM has received honoraria for speaking at research symposia and received benefits in kind and travel support from, and has provided consultancy to the

manufacturers of smoking cessation medications. NW has provided consultancy to the manufacturers of smoking cessation medications, received honoraria for speaking at a research meeting and received benefits in kind and travel support from a manufacturer of smoking cessation medications; JW has provided consultancy to the manufacturers of smoking cessation medications; (3) their spouses, partners, or children have no financial relationships that may be relevant to the submitted work; and (4) all authors have no non-financial interests that may be relevant to the submitted work.

Authors' contributions

CB, NW, HM and ML conceived the original idea for the trial, sought and obtained funding CB, NW, HM, ML, CH, VP and JW wrote the study protocol. CH managed the day to day running of the trial, including all participant follow-up. VP undertook the data analyses. This paper was written by CB with input from all co-authors. CB is guarantor for this paper. All authors read and approved the final manuscript.

The trial randomised the first participant on 6th September 2011 and finished the last follow-up on 5th July 2013.

Acknowledgements

We gratefully acknowledge the participants, research assistants, our colleagues, the Health Research Council of NZ, PGM International, and NZ Quitline.

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Figure 1. Flow of participants.

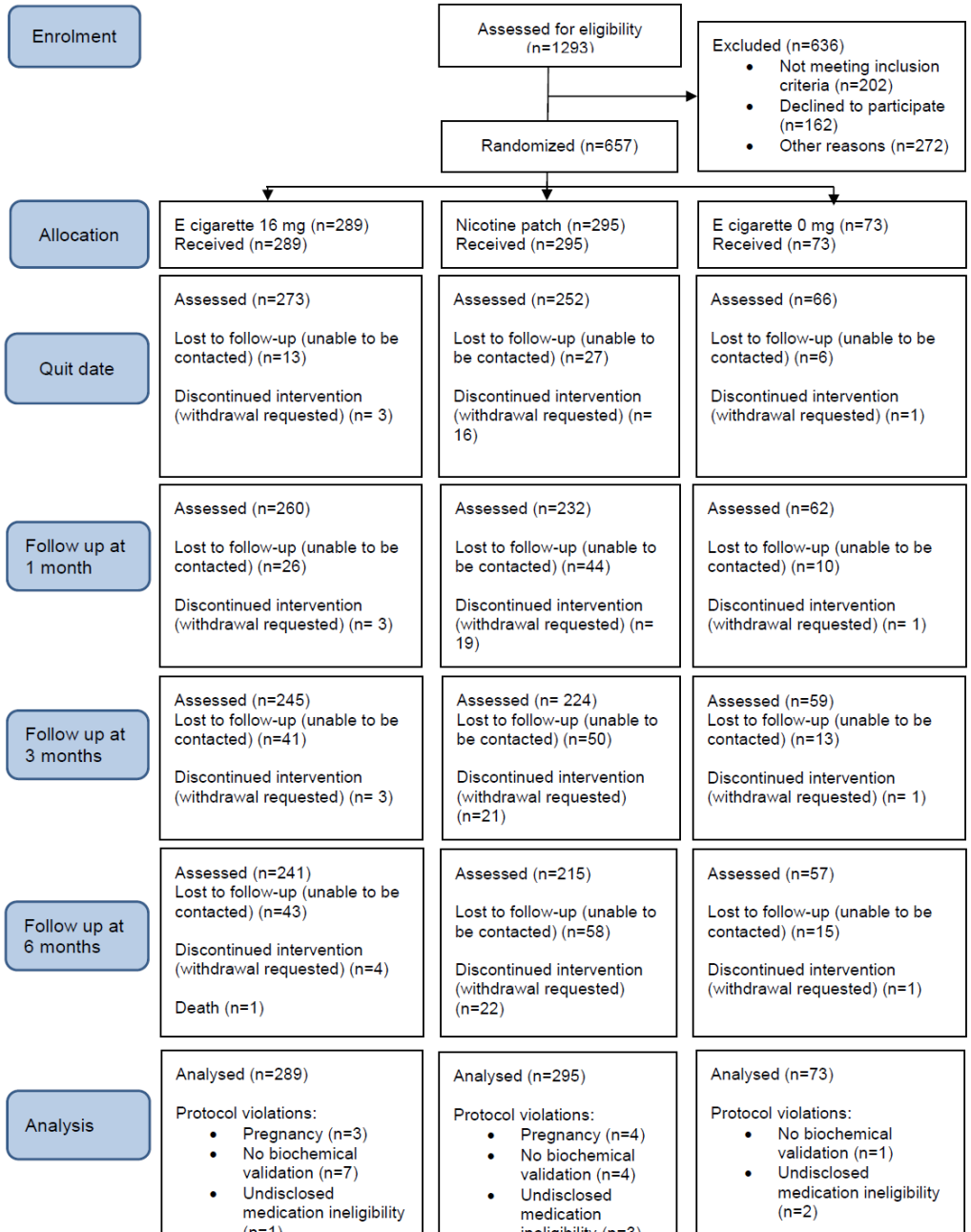
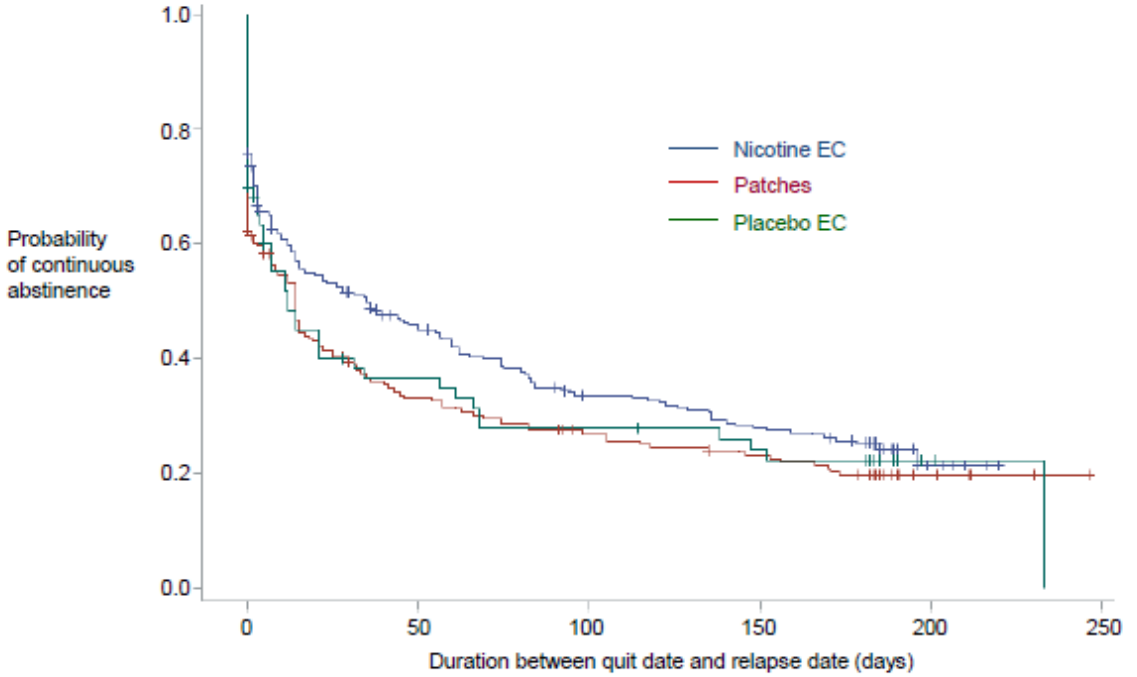


Figure 2.



	No. of subjects	Event	Censored	Median relapse duration (95% CI)
Nicotine EC	289	197 (68%)	92 (32%)	35 (15, 56)
Patches	295	200 (68%)	95 (32%)	14 (8, 18)
Placebo EC	73	51 (70%)	22 (30%)	12 (5, 34)

Table 1. Participants' baseline characteristics.

Variables	16 mg EC (n=289)		Patch (n=295)		0 mg EC (n=73)		Total (n=657)	
Age (mean years ±SD)	43·6,	12·7	40·4,	13·0	43·2,	12·4	42·1,	12·9
Female (No., [%])	178	(62%)	182	(62%)	45	(62%)	405	(62%)
Ethnicity[1]								
NZ Maori (No., [%])	95	(33%)	95	(32%)	23	(32%)	213	(32%)
Non-Maori (No., [%])	233	(67%)	241	(68%)	59	(68%)	533	(68%)
Education below Year 12 (6th form) or no qualification (No., [%])	150	(52%)	123	(42%)	38	(52%)	311	(47%)
Average number of cigarettes (including RYO) smoked per day (mean ±SD)	18·4,	7·2	17·6,	6·0	17·7,	5.6	18·0,	6·5
Age started smoking (years, mean ±SD)	15·6,	4·7	15·2,	3·8	15·7,	5·1	15·5,	4·4
Number of years smoking continuously (mean ±SD)	25·9,	13·1	23·.5,	12·9	24·8,	13·7	24·7,	13·1
Type of tobacco usually smoked (No.,[%])	167	(58%)	167	(57%)	47	(64%)	381	(58%)
Factory made only	92	(32%)	92	(31%)	21	(29%)	205	(31%)
RYO only	30	(10%)	35	(12%)	5	(7%)	70	(11%)
Both								
Lives with other smokers (No., [%])	151	(52%)	149	(51%)	42	(58%)	342	(52%)
At least 1 quit attempt in last 12 months	158	(55%)	169	(57%)	39	(53%)	366	(56%)
FTND score (mean ±SD)	5·6,	2.0	5·5,	2.0	5·5,	2.0	5·5	2.0
FTND > 5 (high dependence) (No., [%])	157	(54%)	162	(55%)	40	(55%)	359	(55%)
GN-SBQ score (mean ±SD)	20·1,	7·9	20·1,	8·4	21·4	8·6	20·2	8·2
Self-efficacy to quit (mean ±SD)[2]	3·7,	1.0	3·7,	0·9	3·6,	1.0	3·7,	1.0
AUTOS total score (mean ±SD)	22·6	7.2	23·1	7.6	23·4	7·3	22·9	7·4

Legend:
SD: standard deviation; RYO: roll your own (loose tobacco) cigarettes; FTND: Fagerstrom test of Nicotine Dependence; GN-SBQ: Glover Nilsson Smoking Behavioural Questionnaire; AUTOS: Autonomy Over Smoking Scale. Higher scores indicate greater dependence.
[1]All non-Maori ethnicity categories aggregated as 'Non-Maori'.
[2]Self-efficacy to quit: belief in ability to quit this time, measured on scale of 1 to 5, 1=very low, 5=very high.

Table 2. Continuous smoking abstinence and seven day point prevalence, nicotine e-cigarette (EC) versus patches.

Number abstinent[1]	**Nicotine EC N=289 (%)**		**Patches N=295 (%)**		**Difference Chi-square P-value**	**Relative risk (RR) (95% CI)**	**Risk difference (RD) (95% CI)**
Continuous abstinence							
One month	66	(22•8)	46	(15•6)	0•003	1•46 (1•04-2•06)	7.25 (0•.88-13•62)
Three months	37	(12•8)	26	(8•8)	0•12	1•45 (0•90-2•33)	3•99 (-1•04-9•02)
Six months (primary outcome)	21	(7•3)	17	(5•8)	0•46	1•26 (0•68-2•34)	1•51 (-2•49-5•51)
Sensitivity analyses for six months continuous abstinence data							
Complete case analysis[2]	21/241	(8•7)	17/215	(7•9)	0•76	1•10 (0•60-2•03)	0•80 (-4•27-5•87)
Per protocol analysis 1[3a]	21/231	(9•1)	15/207	(7•3)	0•48	1•25 (0•66-2•37)	1•84 (-3•28 -6•96)
Per protocol analysis 2[3b]	20/211	(9•5)	13/151	(8•6)	0•78	1•10 (0•57-2•14)	0•87 (-5•10-6•84)
Per protocol analysis 3[3c]	12/147	(8•2)	12/138	(8•7)	0•87	0•94 (0•44-2•02)	-0•54 (-7•00-5•92)
Not biochemically verified[4]	29	(10•0)	21	(7•1)	0•21	1•41 (0•82-2•41)	2•91 (-1•63-7•45)
Repeated measures analysis[5]							
Overall treatment effect	-	-	-	-	0•05	1•61 (1•00-2•57)	-
One month effect	-	-	-	-	0•004	1•87 (1•23-2•85)	-
Three months effect	-	-	-	-	0•12	1•52 (0•89-2•58)	-
Six months effect	-	-	-	-	0•21	1•46 (0•81-2•62)	-
Seven day point prevalence abstinence							
One month	69	(23•9)	51	(17•3)	0•05	1•38 (1•00-1•91)	6•59 (0•05-13•13)
Three months	62	(21•5)	50	(17•0)	0•17	1•27 (0•91-1•77)	4•50 (-1•88-10•88)
Six months	61	(21•1)	46	(15•6)	0•09	1•35 (0•96-1•91)	5•52 (-0•75-11•79)

[1]All analyses are ITT unless otherwise stated (assumes participants with missing smoking status were smoking).
[2]Complete case analysis: excludes 128 participants with missing six month visits (withdrawn/lost to follow-up): (48 in nicotine EC group and 80 in patches group), and include 456 (241 in nicotine EC group and 215 in patches group).
[3a]Per protocol analysis 1: excludes protocol violations: pregnancy, death, quitters who did not have biochemical verification, undisclosed medication ineligibility, withdrew, and lost to follow up at six months.
[3b]Per protocol analysis 2: excludes protocol violations from Per protocol analysis 1 plus: Cross overs, Other/combined NRT product use, and non-NRT use (e.g. varenicline).
[3c]Per protocol analysis 3: excludes protocol violations from Per protocol analysis 2 plus: Participants still using product to which they were randomised, at six months.
[4]Continuous abstinence not biochemically verified: 6 in nicotine EC group: 1 moved, 2 refused, 3 did not attend appointment, 1 Adverse Event (birth) did not want to attend; 4 in patches group: 1 moved, 3 refused.
[5]Not biochemically verified; Output is difference in least squares means, not RR.

Table 3. Continuous abstinence and seven day point prevalence, nicotine e-cigarette (EC) versus placebo EC.

Number abstinent[1]	**Nicotine EC N=289 (%)**		**Placebo EC N=73 (%)**		**Difference Fishers Exact P-value**	**Relative risk (RR) (95% CI)**	**Risk difference (RD) (95% CI)**
Continuous abstinence							
One month	66	(24•8)	11	(15•1)	0•15	1•52 (0•84-2•72)	7·77 (-1·76-17·30)
Three months	37	(12•8)	5	(6•9)	0•16	1•87 (0•76-4•59)	5•95 (-1•01-12•91)
Six months (primary outcome)	21	(7•3)	3	(4•1)	0•44	1•77 (0•54-5•77)	3•16 (-2•29-8•61)
Sensitivity analyses for six months continuous abstinence data							
Complete case analysis[2]	21/241	(8•7)	3/57	(5•3)	0•59	1•66 (0•51-5•36)	3•45 (-3•35-10•25)
Per protocol analysis 1[3a]	21/231	(9•1)	3/54	(5•6)	0•40	1•64 (0•51-5•29)	3•53 (-3•62-10•68)
Per protocol analysis 2[3b]	20/211	(9•5)	2/46	(4•4)	0•26	2•18 (0•53-9•00)	5•13 (-1•97-12•23)
Per protocol analysis 3[3c]	12/147	(8•2)	1/30	(3•3)	0•36	2•45 (0•33-18•13)	4•83 (-2•97-12•63)
Not biochemically verified[4]	29	(10•0)	4	(5•5)	0•26	1•83 (0•66-5•05)	4•55 (-1•72-10•82)
Repeated measures analysis[5]							
Overall treatment effect	-	-	-	-	0•13	1•91 (0•83-4•37)	-
One month effect	-	-	-	-	0•09	1•80 (0•90-3•61)	-
Three months effect	-	-	-	-	0•16	2•00 (0•76-5•28)	-
Six months effect	-	-	-	-	0•23	1•92 (0•65-5•66)	-
Seven day point prevalence abstinence							
One month	69	(23•9)	12	(16•4)	0•17	1•45 (0•83-2•53)	7•44 (-2•38-17•26)
Three months	62	(21•5)	12	(16•4)	0•34	1•31 (0•74-2•29)	5•01 (-4•72-14•74)
Six months	61	(21•1)	16	(21•9)	0•88	0•96 (0•59-1•57)	-0•81 (-11•40-9•78)

[1]All analyses are ITT unless otherwise stated (assumes all participants with missing smoking status were smoking).
[2]Complete case analysis: excludes 64 participants with missing six month visits (withdrawn/Lost to follow-up), (48 in nicotine EC group and 16 in placebo EC group) and includes 298 (241 in nicotine EC group and 57 in placebo EC group).
[3a]Per protocol analysis 1: excludes protocol violations: pregnancy, death, quitters that did not have biochemical verification at six months, undisclosed medication ineligibility, withdrew, and lost to follow up at six months.
[3b]Per protocol analysis 2: excludes protocol violations from Per protocol analysis 1 plus: Cross overs, Other/combined NRT product use, and Non NRT use.
[3c]Per protocol analysis 3: excludes protocol violations from Per protocol analysis 2 plus: Participants still using product to which they were randomised, at six months.
[4]Continuous abstinence not biochemically verified: 7 in nicotine EC group who reported quitting did not attend for biochemical verification.
[5]Not biochemically verified; output is difference in least squares means (not RR).

Table 4. Change in cigarette consumption over follow up period, nicotine e-cigarette (EC) and patches.

Treatment effect results for CPD[1] (change from baseline)	Nicotine ECs		Patches		Difference (Nicotine ECs - Patches)		
	Mean	SE	mean	SE	Mean	SE	P-value
Overall	11·1	0·4	9·1	0·4	2·0	0·5	<0·0001
One month	12·9	0·4	10·5	0·4	2·4	0·6	<0·0001
Three months	10·8	0·4	9·1	0·4	1·7	0·6	0·006
Six months	9·7	0·4	7·7	0·4	1·9	0·6	0·0017

SE= Standard error; CPD=cigarettes per day.
[1]For those reporting smoking at least one cigarette in last seven days.

Table 5. Adverse events by type (serious or non-serious) and relationship to study treatment.

Adverse events	Nicotine ECs		Patches		Placebo ECs	
	N	%	N	%	N	%
Total	137		119		36	
Event type						
Serious[1]	27	19·7	14	11·8	5	13·9
Any non-serious event	110	80·3	105	88·2	31	86·1
Relationship to study treatment						
Definitely	·	·	1	0·8	·	·
Probably	1	0·7	1	0·8	1	2·8
Possibly	5	3·6	4	3·4	1	2·8
Unrelated	131	95·6	113	95·0	34	94·4
Event rates[2]	·	0·08	·	0·08	·	0·09

[1]Serious adverse event' by convention includes: Death (n=1, in Nicotine EC group), Life threatening illness (n=1, in nicotine EC group), Hospitalisation or prolongation of hospitalisation (12%, 8%, 11% of all events, in nicotine ECs, patches, and placebo ECs, respectively), Persistent or significant disability/incapacity, Congenital abnormality, Medically important (6%, 4%, 0% of all events, in nicotine ECs, patches and placebo ECs, respectively). No serious adverse events in the EC groups were related to product use.
[2]Event rate = number of events per total person time (duration in months from baseline to last visit completed), expressed as adverse events per person months. The difference between the rates in the nicotine EC and patches were not statistically significant (IRR 1·05, 95%CI 0·82-1·34, P=0·7)