Supplementary Appendix

Contents

Previous randomised trials of e-cigarettes as an aid to smoking cessation

Considering e-cigarettes (EC) as a nicotine delivery product that might substitute for smoking, in short-term laboratory studies, first-generation cartridge-based EC provided nicotine delivery comparable to the licensed nicotine inhalator[1,2] while newer refillable EC had superior nicotine delivery[3] and both types of EC provided better replacement of the sensorimotor effects of smoking [1,4].Two randomized trials with long-term outcomes have evaluated the effects of the first-generation EC on smoking cessation compared with EC without nicotine[5,6]. One of them also included a study arm that used nicotine transdermal patches[5]. Two Cochrane reviews[7,8] concluded that there is some evidence that EC with nicotine are more effective than nicotine-free EC, but the trial that compared EC with nicotine patches found the same low efficacy for both treatments. Both trials used cartridge based EC with low nicotine delivery. The trial comparing EC and nicotine replacement treatment (NRT) was also conducted with minimal support for participants and no face-to-face contact, which may explain the low quit rates (7.3% and 5.8% at 6 months with EC and NRT, respectively).

A recent trial compared usual care among unselected smokers who were employees of a number of companies with the same intervention complemented by a cartridge-based EC provided free of charge; a choice of approved stop-smoking medications provided free of charge supplemented by the same EC if required; and medications/EC plus two types of financial incentives[9]. Treatments were offered on an ‘opt-out’ basis and their uptake was low. Abstinence rates were very low, which is reflective of the study design and the fact that the large majority of participants would not have been interested in quitting smoking. Regarding the EC arm vs

medications/EC arm comparison, six-month quit rates were non-significantly higher in the EC arm than in the medications/EC arm (1.0% vs 0.5%).

NRT supplies

At the time of the study, the London stop smoking service (SSS) provided NRT via a letter of recommendation that clients took to a pharmacy to exchange for NRT. They paid a prescription charge of £8.60 (US$11) per item, if applicable (some 50% of SSS clients are exempt from the charge). East Sussex and Leicester SSS provided NRT by direct supply at no charge.

While East Sussex and Leicester clients were able to receive their products at randomisation, we were concerned that if at the London site only NRT participants were asked to go to the local pharmacy and possibly pay the prescription charge while EC participants did not, this could generate a potential bias. To avoid this, the London participants selected their preferred NRT at their baseline session and were instructed to bring their NRT to their target quit date (TQD) session. After treatment allocation was revealed, participants allocated to NRT kept their NRT while those allocated to EC exchanged their NRT for the EC starter pack.

Biochemical validation of smoking abstinence

The UK National Health Service stop smoking services use end-expired carbon monoxide (CO) as their routine validation measure. The service target is to ensure CO validation of at least 85% of all claims of abstinence [10]. We included this measure because it is collected routinely anyway and because it is the standard

measure in studies evaluating nicotine containing products where measures of nicotine intake, such as levels of nicotine metabolite cotinine, are not suitable. Practically all trials of nicotine replacement treatments have used CO validation [11].

CO has a relatively short half-life and detects smoking only over the past 24 hours or so, which raises a possibility of false negatives. This, however, does not seem to pose major problems in practical use. Clients are normally not aware of the short CO half-life and smokers who take part in smoking cessation trials tend to smoke daily, which may explain the high concordance between CO results and results using cotinine concentrations. E.g. in a study comparing the two measures [12], 2/32 of self-reported abstainers who failed cotinine validation passed CO validation with cut-off point of 10ppm, but were detected with cut-off of 8ppm (used in our study) so there was full concordance. Another study that compared the two measures concluded that both sensitivity and specificity of cotinine and carbon monoxide validation were similar across 5 years [13]. Other validation measures are less well established. Anabasine has low specificity [14]; and carboxyhaemoglobin requires blood sampling and produces results that are practically identical to expired CO [15].

Additional details of study measures and outcomes

The following measurements were collected at baseline: Demographic details, smoking and medical history, Fagerstrom Test of Cigarette Dependence (FTCD)[16], Mood and Physical Symptoms Scale (MPSS) (a measure of severity of tobacco withdrawal symptoms[17] that includes ratings of depression, irritability, restlessness, hunger and difficulty concentrating on scales from 1=not at all to 5=extremely; and frequency and intensity of urges to smoke on scales ranging from 1=not at all/no

urges to 6=all the time/extremely strong, expired-air carbon monoxide (CO), SSS and health service use, European Quality of Life-5 Dimensions-5 Levels (EQ5D5L) questionnaire[18]. The last two measures were part of a health economics analysis that accompanied the study and will be reported separately.

At further face-to-face contacts, the following were collected: adverse reactions and respiratory symptoms (using a checklist - see below); use of EC/NRT; rated helpfulness of the allocated product in refraining from smoking (1= not at all; 2 = slightly; 3 = somewhat; 4 = very; 5 = extremely) and how good it tastes and how satisfying it is compared to conventional cigarettes (1= much less; 2 = a little less; 3 = the same; 4 = a little more; 5 = much more); reasons for stopping product use; MPSS (to 4 weeks), expired air CO levels (to 4 weeks and at 12 month), SSS and health service use and EQ5D5L (at 6 and 12 months). In addition to this, serious adverse events (SAEs) since the last contact were recorded.

The adverse reactions (AR) checklist asked whether the participant had experienced nausea, sleep disturbance and throat/mouth irritation over the last week (at baseline) or since the last visit/contact (at follow ups) with answer options Yes or No. If Yes, the interviewer was to assess the level of severity by establishing whether 'Has the health problem stopped the participant doing things they would normally do? (tick ONE box)' with response option No, A little, A lot. The checklist also included a section that monitored respiratory symptoms by asking whether participants experienced shortness of breath, wheezing, cough, or phlegm (Yes or No) over the past week at baseline, and since the last contact at follow-ups.

Data were collected using a web-based application, which used the Oracle 11g database, set up by the Cancer Prevention Trials Unit (CPTU), QMUL.

Electronic CRFs were checked weekly and queries were raised and resolved with the relevant researcher/advisor. Source data verification was also carried out on a random 10% sample of paper questionnaires, comparing written entries with those on the database. There was a pre-specified quality target for discrepancies of ≤ 2%, which was met.

Regarding the primary outcome, details of the definition of abstinence are included in the enclosed Statistical Analysis Plan pages 16 – 17. As we initially set out to conduct Mantel-Haenszel tests as a first step in our analyses, we report the results of this analysis in Supplementary Table 12 for completeness. The results were the same in both analyses.

In the sensitivity analyses, each outcome was adjusted for baseline covariates selected using a stepwise regression approach, so that only significant covariates (p=0.1) were included in the final model.

To assess consistency of results across sites, we examined the treatment effect by SSS. Including an arm by SSS interaction did not improve the model fit compared to the model which included the main effects of arm and SSS only (likelihood ration test: chi(2)=1.85, p=.40). The 95% confidence intervals overlap in the range of RRs across the centres. Abstinence rates for the three SSS were: London (EC N=289 vs. NRT N=295): EC 18% (N=52) vs. NRT 9% (N=25); RR = 2.1, 95% CIs: 1.1 to 3.3; East Sussex (EC N=57 vs. NRT N=55): 11% (N=6) vs. 11% (N=6); RR = 1.0, 95% Cis: .3 to 2.8; Leicester (EC N=92 vs. NRT N=96): 23% (N=21) vs. 14% (N=13); RR = 1.7, 95% CIs: 0.9 to 3.2.

Secondary abstinence outcomes included sustained abstinence from 6 to 12 months, and at 4 and 26-week follow-up; proportion of 6-12 months non-abstainers

who reported reducing their cigarette consumption by ≥50% and showed a reduction in CO levels of ≥50% compared to baseline, and relapse rate and time to relapse. Time to relapse was assessed using a Cox analysis.

We also calculated 7-day self-reported abstinence rates at each time point. This is a less informative measure than sustained abstinence because not smoking for 7 days conveys little health benefits and is a weaker predictor of future smoking status than sustained abstinence, and it is also likely to reduce effects of treatment administered a year ago because it is influenced by proximate causes, but it was included to allow comparisons across trials.

To explore some of the possible mediators of any treatment effects, we compared the two study arms in early tobacco withdrawal symptoms and in mean ratings of product helpfulness, taste and satisfaction, using t-tests (or non-parametric tests where normality could not be assumed) with adjustments where needed for normal distribution.

Regarding adverse reactions, the frequency of participants reporting nausea, sleep disturbance and throat/mouth irritation at least once, and overall incidence of adverse reactions, were compared between study arms using Chi^2 test.

We also monitored changes in respiratory symptoms because if EC use has any detrimental effects in the medium term, this might be most evident in the respiratory tract. The changes in the four listed respiratory symptoms (shortness of breath, wheezing, cough and phlegm production) from baseline to 1-year follow up in the two study arms were compared using logistic regression with symptoms at 1-year regressed onto study arm while adjusting for baseline scores and study centre.

At suggestions from reviewers, we conducted two additional analyses. We compared smokers who were screened but did not progress to randomisation with those who did in baseline characteristics (see Supplementary Table 13); and compared abstainers in the two study arms (see Supplementary Table 14).

NRT and EC product use and contamination across time

As noted in the main text, 88% of NRT arm participants used NRT combinations. This comprised mostly patch plus one of the oral products. Based on products that participants started to use on their TQD, nicotine patch was used by 84% of participants, followed by nicotine inhalator (37%), mouth spray (28%), mouth strips (15%), lozenge (9%), chewing gum (8%), microtabs (8%), and nasal spray (0.5%). Switching to different NRT products during the first four weeks of treatment was common (59% of participants).

Regarding product use in the EC arm, very few participants were using first-generation cartridge-based EC products (0% to 3% at different time-points, see Supplementary Table 4). Most participants started to purchase their own e-liquids from the first week onwards, with only 7% requesting the second bottle. Flavours of e-liquids that participants purchased varied over time, with fruit flavours the most popular, followed by tobacco, mint and candy flavours. The nicotine content of e-liquid that participants used at each time point reduced over time (see Supplementary Table 4). We conducted an exploratory analysis including 162 EC arm participants who provided information on nicotine strength of their e-liquid at all time points. The mean nicotine content was 18mg/ml, 12mg/ml and 8mg/ml at 4, 26 and 52 weeks, respectively (Friedman test=255.6, $p<.001$).

Over time, NRT arm participants were more likely to try EC than the other way round, but the initial level of cross-contamination was low. The pre-specified acceptable level of initial cross-contamination (defined as using non-allocated product on five or more consecutive days in the first four weeks of treatment) was 15%, the observed level was under 3%.

At 12 months follow-up, 5.7% of EC arm participants reported using non-allocated NRT for at least five consecutive days in the past six months and 22.2% of NRT arm participants reported using non-allocated EC (see Supplementary Table 5).

Use of other stop-smoking medications (varenicline and bupropion) was rare (3%-4%) and did not differ between the study arms (see Supplementary Table 5).

Quit rates in the trial and in routine service

The one year quit rate for smokers treated individually by specialist advisors in nine SSS who were using the same approach that was used in this trial and that had above average short-term quit rates compared to national service average was 10.4% in 2013-2014, using the same abstinence criteria that we used[19]. However, 46% of these clients were treated with varenicline and varenicline was associated with 1.7 times higher quit rate than NRT (corresponding with the results of a recent large RCT[20]), which indicates the quit rate with NRT of about 7.5%. The quit rate of 9.8% in our NRT group is comparable and does not suggest that allocation to NRT arm resulted in reduced effort to quit.

Effects of EC use on respiratory system

Previous data on this issue were contradictory. Cell and animal studies suggested that EC use may lead to respiratory infections[21-24], but in a large online survey of EC users, two thirds reported that their switch to EC use was accompanied by a reduced incidence of respiratory infections[25]. Two case studies described non-smokers with chronic throat and nose infections that resolved after they started to vape[26,27]. It was hypothesised that this could be due to known antibacterial effects of propylene glycol and glycerine[28,29].

Regarding SAEs summarized in Table 8, there were six pulmonary events altogether, five in the EC arm and one in the NRT arm (not counting a hospitalization concerning a lung mass in the NRT arm). Although none of these SAEs were thought likely to be caused by EC or NRT use, the difference in frequency of these events between arms is notable. The two participants that were hospitalized with pneumonia were both smoking at the time (one was also vaping). The participant in the EC arm who was hospitalized with asthma had recently stopped vaping and relapsed to smoking. One of the COPD exacerbation cases was smoking and vaping at the time, EC use was not ascertained in the remaining case. This study was not designed to examine the safety of vaping and the difference in occurrence of acute pulmonary SAEs in the EC and NRT arms (1.1% vs. 0.2%) is likely to be a chance finding. However, future trials should be designed to enable a more accurate assessment of any potential pulmonary risk of EC use.

Regarding the elicited respiratory symptoms, the two study arms did not differ in changes in shortness of breath and wheezing, but there were significant differences in cough and phlegm production, symptoms that typically accompany respiratory infections. Both study arms improved in these compared to baseline, but the EC arm

recorded an improvement that was significantly larger; and the difference persisted when smoking status was controlled for.

To explore this finding further, we run an additional analysis that was not pre-planned and that included all participants who reported EC use between 6-12 months regardless of study arm. EC users were less likely to experience cough (RR=.69, 95%CI [.55, .86]) and phlegm production (RR=.74, 95%CI [.58, .94]) than participants not using EC. Controlling for smoking status did not change the result (RR=.71, 95%CI [.6, .9] for cough and RR=.76, 95%CI [.6, .97] for phlegm).

Participants were not asked if they noticed an improvement (which could lead to providing answers considered desirable) but reported the actual symptom occurrence. Nevertheless, the finding could still be due to some kind of reporting bias or chance and it needs to be interpreted with caution, especially as there could be detrimental effects of EC use that we did not assess. Future studies should include objective measures of respiratory health to clarify this issue.

Supplementary table 1: Additional sample characteristics

	EC N=438	NRT N=446	Total N=884
Marital status – N (%)			
Single	224 (51.1)	249 (55.8)	473 (53.5)
Separated or divorced	89 (20.1)	86 (19.3)	174 (19.6)
Married	116 (26.5)	105 (23.5)	221 (24.9)
Widowed	10 (2.3)	6 (1.4)	16 (1.8)
Educational qualification – N (%)			
Primary school	19 (4.3)	22 (4.9)	41 (4.6)
Secondary school	141 (32.2)	130 (29.2)	271 (30.7)
Further education/diploma	117 (26.7)	127 (28.5)	244 (27.6)
Higher education	161 (36.7)	167 (37.5)	328 (37.1)
Past use of stop smoking aids – N (%) Nicotine replacement therapy Varenicline Bupropion Electronic cigarettes Did not try NRT, V or B	 328 (74.9) 149 (34.1) 34 (7.8) 186 (42.5) 84 (19.2)	 334 (74.9) 151 (33.8) 35 (7.9) 181 (40.6) 92 (20.6)	 662 (74.9) 300 (33.9) 69 (7.8) 367 (41.5) 176 (19.9)
Age started smoking – Median (IQR)	16 (14-18)	16 (14-18)	16 (14-18)
Spouse or partner smokes – N (%)	167 (38.1)	178 (39.1)	345 (39.1)
Study Site – N (%)			
London	289 (66.0)	295 (66.2)	584 (66.1)
Leicester	92 (21.0)	96 (21.5)	188 (21.3)
East Sussex	57 (13.0)	55 (12.3)	112 (12.7)

*Fagerstrom Test for Cigarette Dependence

Note: The main baseline characteristics are presented in the paper

Supplementary Table 2: Sensitivity analyses for difference between EC and NRT arms in sustained validated abstinence at one year

Sensitivity analyses [a]	Risk Ratio	95% CI	p-value
Participants who attended at least one treatment session	1.79	1.27-2.52	.001
Excludes participants who used non-allocated products for at least 5 days (N=411 vs 345)	1.84	1.27-2.66	.001
Participants with complete outcome at 52 weeks (N = 356 vs. 342)	1.75	1.25-1.45	.001
Impute missing information using multiple-imputation by chained equations (N=438 vs 446)	1.85	1.32-2.60	<0.001

[a] adjusted for study centre

Supplementary Table 3: 7-day abstinence from smoking at different time-points

	EC (n=446)	NRT (n=438)	Unadjusted Relative Risk (95% CI)	Adjusted Relative Risk(95% CI)
7-day point prevalence at 4 weeks post TQD, N (%)	195 (44.4)	136 (30.4)	1.46 (1.23 – 1.74)	1.43 (1.20 to 1.70) [a]
7-day point prevalence at 26 weeks post TQD, N (%)	158 (36.0)	115 (25.7)	1.39 (1.14 – 1.70)	1.36 (1.12 to 1.66) [b]
7-day point prevalence at 1-year post TQD, N (%)	146 (33.3)	98 (21.9)	1.52 (1.23 – 1.90)	1.52 (1.22 to 1.89) [c]

[a]adjusted for study centre, age, FTCD, age started smoking, ethnicity
[b] adjusted for study centre, age, FTCD, age started smoking, marital status, ethnicity
[c] adjusted for study centre and partner smoking

Supplementary Table 4: EC products used in EC arm

N (%) of EC users that used refillable EC 1 week post quit (N=384)* 4 weeks post quit (N=343)* 26 weeks post quit (N=270)* 52 weeks post quit (N=235)*	 383 (99.7%) 343 (100%) 265 (98.2%) 227 (96.6%)
Nicotine strength of e-liquid in mg/ml – median (IQR) 4 weeks post quit (N=340) 26 weeks post quit (N=267) 52 weeks post quit (N=232)	 18 (16-18) 12 (6-18) 11 (5-18)
Requested additional e-liquid at 2 weeks post-TQD, N (% of full sample)	30 (7%)

Flavours used ** N (%)	**1 week** (N=155)	**4 weeks** (N=156)	**26 weeks** (N=516)	**52 weeks** (N=511)
Tobacco	15 (10)	44 (28)	163 (32)	127 (25)
Fruit	70 (45)	51 (33)	150 (30)	169 (33)
Menthol/Mint	31 (20)	20 (13)	75 (15)	81 (16)
Tobacco menthol	5 (3.2)	7 (4.5)	13 (2.5)	12 (2.3)
Vanilla	5 (3.2)	1 (0.6)	11 (2.1)	14 (2.7)
Chocolate, dessert, sweet or candy	17 (11)	18 (12)	62 (12)	72 (14)
No flavour	0	0	0	2 (0.4)
Coffee	2 (1.3)	1 (0.6)	6 (1.2)	8 (1.6)
Alcoholic drink	2 (1.3)	2 (1.3)	7 (1.4)	3 (0.6)
Energy drink or soft drink	6 (3.9)	10 (6.4)	17 (3.3)	13 (2.5)
Other	2 (1.3)	2 (1.3)	12 (2.3)	10 (2.0)

* N providing information from which % was calculated

** Some participants used multiple flavours; the N and % are based on the overall number of entries

Supplementary Table 5: Use of non-allocated products

	EC N=438	**NRT** N=446
Use of non-allocated product within the initial 4 weeks		
Used for 5 or more consecutive days, N (%)	3 (0.7)	11 (2.5)
Use of non-allocated products at 6M (excludes initial 4 weeks)		
Used for 5 or more consecutive days since week 4: N (%)	16 (3.6)	57 (12.8)
Length of non-allocated product use in weeks among users since previous assessment (0-20): Median (IQR)	3 (1-9)	8 (1-20)
Use of non-allocated products at 12M (excludes initial 4 weeks)		
Used for 5 or more consecutive days since week 26: N (%)	14 (3.2)	77 (17.3)
Length of non-allocated product use in weeks among users since previous assessment (0-24): Median (IQR)	6.5 (0-12)	20 (6-24)
Use of other non-study stop-smoking medications (including single use)		
Varenicline: N (%)	15 (3.4)	13 (2.9)
Bupropion: N (%)	0 (0)	0 (0)

Supplementary Table 6: Ratings of products' helpfulness, taste and satisfaction compared to conventional cigarettes

Rating	EC (n=324)**	NRT * (n=228)**	Mean difference (95% CI)
Helpfulness[a], mean (SD)			
1 week post quit	4.3 (0.9)	3.6 (0.9)	0.7 (0.5 to 0.9)
4 weeks post quit	4.3 (0.9)	3.7 (0.9)	0.6 (0.4 to 0.7)
Taste compared to cigarettes[b], mean (SD)			
1 week post quit	3.0 (1.4)	2.7 (1.6)	0.3 (0.1 to 0.6)
4 weeks post quit	3.5 (1.3)	3.1 (1.5)	0.4 (0.2 to 0.6)
Satisfaction compared to cigarettes[b], mean (SD)			
1 week post quit	2.4 (1.0)	2.0 (1.2)	0.4 (0.2 to 0.6)
4 weeks post quit	2.7 (1.1)	2.3 (1.2)	0.5 (0.3 to 0.6)

* Where 2 NRT products were used, the average rating of the two was taken.

** Only cases with complete data across measures are included.

[a] Helpfulness in refraining from smoking was rated from 1=not at all helpful to 5=extremely helpful

[b] How good the product tastes and how satisfying it is compared to conventional cigarettes was rated as Much less than normal cigarettes=1, A little less=2, The same=3, A little more=4, Much more than normal cigarettes=5

Supplementary Table 7: Change in withdrawal symptoms from baseline in abstainers

Week 1 post-TQD	**EC (n=158)**	**NRT (n=131)**	**Mean difference (95% CI)**
Depressed – mean (SD)	0.05 (0.7)	0.08 (.8)	-0.03 (-0.20 to 0.15)
Irritable – mean (SD)	0.27 (1.2)	0.78 (0.12)	-0.51 (-0.81 to -0.22)
Restless – mean (SD)	0.13 (1.1)	0.43 (1.5)	-0.30 (-0.61 to 0.01)
Hungry – mean (SD)	0.33 (1.1)	0.59 (1.3)	-0.26 (-0.53 to 0.01)
Poor concentration – mean (SD)	-0.06 (0.8)	0.25 (1.2)	-0.31 (-0.54 to -0.08)
Composite MPSS score – mean (SD)	0.14 (0.58)	0.43 (0.75)	-0.28 (-0.44 to -0.13)
Week 4 post-TQD	**EC (n=191)**	**NRT (n=134)**	
Depressed – mean (SD)	-0.02 (0.8)	-0.04 (0.9)	-0.02 (-0.06 to 0.11)
Irritable – mean (SD)	-0.01 (0.1)	020 (1.1)	-0.21 (-0.44 to 0.03)
Restless – mean (SD)	-0.13 (1.1)	-0.08 (1.3)	-0.04 (-0.31 to -.22)
Hungry – mean (SD)	0.19 (1.2)	0.31 (1.4)	-0.11 (-0.39 to 0.17)
Poor concentration – mean (SD)	-0.15 (0.9)	-0.04 (1.0)	-0.11 (-0.32 to 0.10)
Composite MPSS score – mean (SD)	-0.01 (0.6)	0.08 (0.8)	-0.10 (-0.25 to 0.05)

Supplementary Table 8: List of serious adverse events by study arm

EC arm	NRT arm
Death from acute myocardial infarction	Death from spinal cord injury
Femoral fracture	Pulmonary and ovarian mass
Colon cancer	Diverticulitis
Ovarian cyst ruptured	Ovarian abscess
Renal stone removal	Transient ischaemic attack
Depression	Nephrolithiasis
Fibromyalgia	Bacterial sepsis
Infective exacerbation of chronic obstructive airways disease (x2)	Asthmatic attack
Tonsillar bleeding	Acute myocardial infarction
Intervertebral disc disorder	Coronary artery bypass
Ovarian cystectomy	Diverticulitis
Pneumonia (x2)	Intervertebral disc disorders
Cholecystitis	Neoplasm of unspecified nature
Ear infection bacterial	Cervical vertebral fracture
Knee surgery NOS	Tendinitis NOS
Hospitalisation, reason not disclosed	Acute pancreatitis unspecified
Urinary tract infection bacterial	Hernia of abdominal cavity
Allergic reaction	Pyelonephritis
Eye infection intraocular	Other knee injury
Hospitalisation, reason not disclosed	Acute pancreatitis unspecified
Acute myocardial infarction	Headaches
Suicidal ideation	Cholecystitis acute
Abdominal sepsis	
Malignant neoplasm of oropharynx NOS	
Asthmatic attack	

NOS = not otherwise specified

Supplementary Table 9: Adverse reactions reported at least once, N (%)

	EC (N=438)	NRT (N=446)	Relative risk (95% CI)**
Nausea	137 (31)	169 (38)	0.83 (0.69 to 0.99)
Sleep disturbances	279 (64)	303 (68)	0.94 (0.986to 1.04)
Throat/mouth irritation*	286 (65)	221 (51)	1.27 (1.13 to 1.43)

* Participants who never tried other NRT product than patches were excluded (N=432)
** Logistic regression with symptoms reported at least once (between 1 and 52 weeks) regressed onto study arm while adjusting for study centre

Supplementary Table 10: Participants rating the adverse reactions as severe, N (%)

	EC (N=438)	NRT (N=446)	Relative risk (95% CI)**
Nausea	29 (6.6)	29 (6.5)	1.02 (0.62 to 1.67)
Sleep disturbances	57 (13)	58 (13)	1.0 (0.71 to 1.4)
Throat/mouth irritation*	26 (5.9)	17 (3.8)	1.51 (0.84 to 2.74)

* Participants who never tried other NRT product than patches were excluded (N=432)
** Logistic regression with symptoms reported at least once (between 1 and 52 weeks) regressed onto study arm while adjusting for study centre

Supplementary Table 11: Reasons for ineligibility in 463 out of 2,045 potential participants that were screened

Reason for ineligibility	N (%)
Does not want EC	56 (12.1)
Does not want NRT	46 (9.9)
Does not want randomisation (preference for or dislike of one of the products, detail not recorded)	63 (13.6)
Not happy with another part of the study (wants varenicline 68, wants group treatment 13, commuting 6, waiting time 5, wants home visits 4, does not want nicotine 4, could not attend appointment 2, wants both products 1, wants neither product 1)	104 (22.5)
Using EC	11 (2.4)
Using NRT	10 (2.2)
Using EC or NRT (detail not recorded)	63 (13.6)
Not smoking any more	45 (9.7)
Pregnant/breastfeeding	14 (3.0)
Under 18	1 (0.2)
Taking part in another trial	4 (0.9)
Does not speak English	1 (0.2)
Already enrolled	6 (1.3)
Using varenicline	2 (0.4)
Information missing	37 (8.0)
Total ineligible	463

Supplementary Table 12: Mantel-Haenszel test to compare quit rates between study arms

	EC (N=438)	NRT (N=446)	OR (95%CIs)
Primary outcome			
Abstinence at 52 weeks N (%)[a]	79 (18.1)	44 (9.9)	2.02 (1.36 to 3.01)
Secondary Outcomes			
Abstinence between weeks 26 and 52, N (%)[a]	93 (21.2)	53 (11.9)	12.01 (1.39 to 2.92)
4 weeks post TQD, N (%)[a]	192 (43.7)	134 (30.0)	1.83 (1.38 to 2.42)
26 weeks post TQD, N (%)[a]	155 (35.3)	112 (25.1)	1.62 (1.21 to 2.18)
CO validated reduction ≥ 50% in non-abstainers (N=738) [a]	44 (12.8)	29 (7.4)	1.85 (1.13 to 3.03)
7-day point prevalence at 4 weeks, N (%)[a]	195 (44.4)	136 (30.4)	1.84 (1.39 to 2.44)
7-day point prevalence at 26 weeks, N (%)[a]	158 (36.0)	115 (25.7)	1.61 (1.21 to 2.16)
7-day point prevalence at 52 weeks, N (%)[a]	146 (33.3)	98 (21.9)	1.78 (1.31 to 2.40)

[a] all analyses stratified by study centre. The assumption of homogeneity across centres is met for all outcomes

Supplementary Table 13. Baseline characteristics of smokers who were randomised and those who were not

	Randomised (N = 886)	Not randomised (N = 145) *
Age (years) – median (IQR)	41 (33-52)	36 (29-45)
Female – N (%)	425 (48)	64 (44)
Marital status – N (%)		
Single	474 (54)	85 (59)
Separated or divorced	175 (20)	23 (16)
Married	221 (25)	32 (22)
Widowed	16 (2)	4 (3)
Missing information	0	1 (1)
Educational qualification – n (%)		
Primary school	41 (5)	9 (6)
Secondary school	271 (31)	47 (33)
Further education/diploma	246 (28)	34 (24)
Higher education	328 (37)	53 (37)
Missing information	0	2 (1)
Employment status – n (%)		
In paid employment	615 (69)	108 (75)
Entitled to free prescriptions– n (%)	362 (41)	43 (30)
Smoking and quitting history		
Cigarettes smoked per day – Median (IQR)	15 (10-20)	15 (10-20)
Baseline CO – Median (IQR)	20 (13-28)	21 (12-30)
FTCD * – Mean (SD)	4.5 (2.5)	4.5 (2.4)

Past use of stop smoking aids – n (%)		
Nicotine replacement therapy	663 (75)	89 (62)
Varenicline	300 (34)	34 (24)
Bupropion	69 (8)	10 (7)
Electronic cigarettes	368 (42)	59 (41)
Did not try NRT, V or B	177 (20)	47 (32)
Age started smoking – Median (IQR)	16 (14-18)	16 (14-18)
Spouse or partner smokes – N (%)	347 (39)	62 (43)
Study Site – n (%)		
London	586 (66)	129 (89)
Leicester	188 (21)	8 (6)
East Sussex	112 (13)	8 (6)

* There were 147 persons in this group but data from 2 are missing

Supplementary Table 14. Characteristics of 4-week abstainers in the two study arms

	EC (N = 192)	NRT (N = 134)
Age (years) – median (IQR)	41 (32-51)	44 (35-54)
Female – N (%)	97 (51)	49 (37)
Marital status – N (%)		
Single	89 (46)	74 (55)
Separated or divorced	43 (22)	24 (18)
Married	56 (29)	34 (25)
Widowed	4 (2)	2 (2)
Educational qualification – n (%)		
Primary school	9 (5)	7 (5)
Secondary school	57 (30)	38 (28)
Further education/diploma	53 (28)	40 (30)
Higher education	73 (38)	49 (37)
Employment status – n (%)		
In paid employment	311 (68)	90 (67)
Entitled to free prescriptions– n (%)	79 (41)	54 (40)
Smoking and quitting history		
Cigarettes smoked per day – Median (IQR)	15 (10-20)	18 (10-20)
Baseline CO – Median (IQR)	20 (13-28)	20 (13-29)
FTCD – Mean (SD)	4.2 (2.5)	4.5 (2.4)
Past use of stop smoking aids – n (%) Nicotine replacement therapy Varenicline Bupropion Electronic cigarettes Did not try NRT, V or B	 140 (73) 68 (36) 15 (8) 80 (42) 40 (21)	 103 (77) 36 (27) 11 (8) 50 (37) 27 (20)

Age started smoking – Median (IQR)	16 (14-18)	16 (14-18)
Spouse or partner smokes – N (%)	76 (40)	49 (37)
Study Site – n (%)		
London	130 (68)	81 (61)
Leicester	44 (23)	38 (28)
East Sussex	19 (10)	15 (11)

Supplementary Table 15: Members of the trial committees

Name	**Role**	**Committee**
Professor Ian Roberts	Chair (independent)	TSC
Professor Sarah Lewis	Member (independent)	TSC
Professor Linda Bauld	Member (independent)	TSC
Professor Michael Ussher	Member (independent)	TSC
MrDarush Attar-Zadeh	Member (independent)	TSC
Mr Brian Eastwood	Lay member (independent)	TSC
Mr Benjamin Roberts	Lay member	TSC
Professor Tim Peto	Chair (independent)	DMEC
Dr Angela Crook	Member (independent)	DMEC
Dr Lion Shahab	Member (independent)	DMEC

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