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Safety and efficacy of e-cigarettes versus nicotine patches when used to help pregnant smokers quit. A randomised controlled trial.

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Abstract

Nicotine replacement therapy is commonly offered to pregnant women who smoke to help them quit, but it has limited efficacy in this group. E-cigarettes are also used by pregnant smokers, but their safety and efficacy in pregnancy are unknown. Here we report the results of comparing nicotine patches with refillable e-cigarettes in a randomised controlled trial involving 1,140 participants. In the unadjusted primary analysis, validated prolonged quit rates at the end of pregnancy in the two study arms were not significantly different, but some abstainers in the patch arm used e-cigarettes. In a pre-specified sensitivity analysis excluding abstainers using non-allocated products, e-cigarettes were markedly more effective than patches.Low birthweight (<2,500 g) was less frequent in the e-cigarette arm. Other adverse events and birth outcomes were similar in the two study arms. E-cigarettes may help pregnant smokers quit and their safety for use in pregnancy is at least on par with the safety of nicotine patches.

Introduction

Smoking in pregnancy increases the risk of adverse birth outcomes such as low birthweight, placental abruption, pre-term birth, miscarriage and neonatal or sudden infant death[5-8]. The need to identify stop-smoking interventions that help pregnant smokers is made even more urgent by the fact that the link between smoking and socio-economic disadvantage is particularly strong in pregnancy[9].

Two stop smoking medications have been tested with pregnant smokers so far. Nine placebo controlled trials evaluated the efficacy of nicotine replacement therapy (NRT)[10-18] and two trials evaluated bupropion[19,20], showing only limited effects for NRT and no effect for bupropion[1]. The results could be due to low treatment adherence, and in the case of NRT, also due to limited nicotine delivery. Pregnant smokers metabolise nicotine faster than smokers who are not pregnant and the standard NRT dosing may be too low[12,21-24].

Electronic-cigarettes (EC) are devices that deliver nicotine and flavourants in aerosol created by heating propylene glycol (PG) and vegetable glycerol (VG). EC can be seen as a form of NRT that has several potential advantages over traditional NRT products, as they allow smokers to titrate nicotine intake to their needs, select flavours they like, and retain a degree of enjoyment that they previously obtained from smoking[25-29]. EC are more popular among smokers trying to quit than traditional NRT products[30,31] and the first few trials comparing the two treatments in non-pregnant participants suggest that EC are more effective than NRT [32,33].

Use of EC as a quitting aid has increased also among pregnant smokers[3,4,34]. However, EC are a consumer rather than pharmaceutical product, and the efficacy and safety of such use is unknown.

Use of EC in pregnancy raises similar concerns about potential harmful effects of nicotine on the developing fetus as use of NRT. The use of NRT to help pregnant smokers quit is approved in a number of countries because while NRT contains nicotine, tobacco smoke contains this and many other toxins with documented teratogenic effects[2,35-39]. The evidence that nicotine is teratogenic is also only available from animal studies[36]. It is currently not clear whether nicotine affects pregnancy in doses used by human nicotine users. Two recent reviews concluded that existing data do not provide clear evidence on whether use of NRT during pregnancy is harmful to the fetus[1,40]. As the issue has not been definitely settled, and as EC aerosol also contains other chemicals in addition to nicotine[41], objective data on pregnancy outcomes in women who switch from smoking to EC use are urgently needed.

We aimed to compared the efficacy and safety of EC and nicotine patches when used to help pregnant smokers to attain prolonged abstinence from smoking in a randomised controlled trial.

Results

Figure 1 shows the flow of participants through the trial. We were able to establish self-reported smoking status at EOP, via direct contact or hospital records, in 531 (93%) and 516 (91%) participants in the EC and NRT arms, respectively.

Sample characteristics are shown in Table 1. The profiles of participants in the two study arms were similar.

Table 1 about here

Primary Outcome

Useable saliva samples were obtained from only 108 of 196 self-reported abstainers at EOP (55.1%) (66 in the EC arm and 42 in the NRT arm). Among those providing saliva samples, 13 also provided a CO reading, while 7 participants provided CO readings only.

Due to this, validated prolonged abstinence rates were low (6.8% vs 4.4% in the EC and NRT arms, respectively). They did not differ significantly between the two study arms (Table 2), Bayes factor=2.69.

'Per-protocol' and multiple-imputation analyses yielded similar results, but in the analysis excluding abstainers who regularly used non-allocated products, the difference between the two study arms (6.8% vs 3.6%) was significant (Table 2), Bayes factor=10.0.

Secondary Outcomes

Risk ratios favoured the EC arm to a similar extent across all abstinence outcomes (Table 2), but only reached statistical significance for abstinence at 4 weeks and for self-reported abstinence at EoP.

Among self-reported point-prevalence abstainers at EOP, 6 in the EC arm and 25 in the NRT arm were regularly using non-allocated products. When abstainers using non-allocated products were excluded, the differences between the two study arms were all significant, with RRs ranging from 1.79 to 2.03.

Table 2 about here

There was no difference between the study arms in the proportion of women with validated reduction of smoking at EOP by at least 50% compared to baseline. Self-reported smoking reduction was significantly more frequent in the EC arm (see Supplementary Table 1).

Table 3 shows treatment adherence in the two study arms. About 30% of participants did not set a TQD, with rates similar in the two study arms. The uptake of support phone calls was low in both study arms. Product use was initially also relatively low in both study arms, but higher in the EC arm. More participants used their products during pregnancy, with use again higher in the EC arm, where a third of the participants used EC at EOP.

Table 3 about here

Table 3 shows the products use among the full sample. Regarding current use of any nicotine product (allocated or unallocated) at EOP among self-reported point-prevalence abstainers from smoking, 58 (49.2%)of abstainers in the EC arm reported using a nicotine product (57 allocated and 1 non-allocated) while 15 (19.2%) in the NRT arm reported such use (5 allocated, 8 non-allocated and 2 both), (chi-square (1)=18.0, p<.001).

Regarding the type of products used, among 238 participants in the NRT arm who reported using NRT since the last support call, 236 (99.2%) used patches, including 16 who used a combination of patches with other NRT products; one used only inhaler and one used only mouth spray. Of 351 patch products dispensed by the study team, only 29 (8.3%) were for 10mg nicotine patches, while the rest was for the 15mg nicotine patches.

The 344 participants in the EC arm who used EC during at least one of the initial four weeks used almost exclusively refillable EC (94.2%) (see Supplementary Table 2). Most used e-liquids with a higher nicotine content (11-20 mg/mL) and with tobacco and fruit flavours . Looking at changes in 244 participants who provided information on their products at 4 weeks and at EOP, nicotine concentrations in their e-liquids decreased significantly over time (Bhapkar chi(2)=32.0, p<0.001).

Safety data were available from 1,110 women (97.4% of the sample; 97.4% in each arm). The total of 39 participants (20 in the EC and 19 in the NRT arm) delivered infants in non-study sites and no data were available on birthweight for 10 of them and on gestational age and birthweight for 29. Two women (one in each arm) had an elective termination and were excluded from the analyses. There were 1,097 singleton births and 13 pairs of twins (9 in the EC and 4 in the NRT arm).

Mean birthweight and rates of adverse birth outcomes were similar in the two study arms apart from the NRT arm having more infants with low birthweight (9.3% vs 14.3% in the EC and NRT arms, respectively, Table 4), Bayes factor=10.3. The analysis including twins did not change these results (see Supplementary Table 3).

Table 4 about here

Rates of other adverse events were also similar in the two groups (see Supplementary Table 4). Adverse reactions related to study products consisted primarily of skin irritation and nausea in the NRT arm, and cough and throat irritation in the EC arm (Supplementary Table 4).

The overall number of SAEs and AEs in the EC and NRT arm was 476 vs 479. The number of participants experiencing any SAEs or AEs in the two study arms was 285 vs 292 (RR=0.97, 0.87-1.09).

Discussion

The quit rates in the two study arms were not significantly different, but some abstainers in the patch arm used e-cigarettes. More participants in the e-cigarette arm continued to use their allocated product. Low birthweight (<2,500 g) was less frequent in the e-cigarette arm. Other adverse events and birth outcomes were similar in the two study arms.

In the primary analysis, EC were not significantly more effective than NRT. However, some participants who did not find their allocated product helpful switched to the alternative and this was much more common in the NRT arm. In the pre-specified sensitivity analysis excluding abstainers who regularly used non-allocated products, EC were significantly more effective than NRT. This sensitivity analysis may have over-estimated the treatment effect if some 'switchers' would have succeeded even if they did not use non-allocated products, but other approaches to controlling for unallocated product use pose larger problems, as discussed in the Methods section and Supplementary file 6.

The biochemical validation of abstinence via posted saliva samples proved challenging. Validation results were only available from about half of self-reported abstainers. Asking women who are in late pregnancy or looking after a newborn infant to self-sample and post the samples back generated limited response. Some samples also had an insufficient volume for the analysis and some participants who were abstinent during pregnancy were reached only post-delivery when they had returned to smoking, and so validation could not be done. During the follow-up study period, the Covid-19 lockdown further reduced the samples return, although not significantly so. All this resulted in low validated quit rates, and reduced the power to detect a difference between the two study arms. Future studies may consider shorter follow-up windows and aim to collect validation samples in person.

Study results may have been affected by an external event that occurred during the trial. In 2019, there was an outbreak of a lung disease in young vapers in the USA. This was named 'E-cigarette or vaping product use-associated lung injury' (EVALI) and although it was eventually traced to vitamin E acetate added to local illicit marijuana products[54,55], it was widely reported internationally, including in the UK, as related to nicotine vaping. Anecdotal evidence from follow-up calls suggested that

the media warning about dangers of EC use led some participants to stop using EC and return to smoking.

Treatment adherence and overall abstinence rates were low, as in other studies of smoking cessation in pregnancy[10,13,15,17,18 56]. Compared to other smokers, women who wish to stop but are still smoking at 12 weeks gestation are likely to have higher nicotine dependence. Indeed, such smokers experience more severe withdrawal symptoms and cravings than other adults[57]. They may also have more uncertain motivation and/or competing priorities. Almost 30% of the sample did not set up a quit date, completion of support sessions was low and only 40% and 23% used their products for at least 4 weeks in the EC and NRT arm, respectively. A substantial proportion of participants may thus not have used the help on offer sufficiently enough to benefit from it.

Within the relatively low treatment uptake, use of EC was higher and of longer duration than use of NRT. This was despite cost to participants favouring NRT, as it was provided free of charge, while after the initial provision, EC arm participants had to pay for their own EC supplies. This advantage however could have been mitigated by participants needing a prescription for NRT, but not for EC. The finding of better use of EC tallies with EC being a more popular aid to stopping smoking than NRT among smokers at the population level[30]. It is worth noting that while the cost to participants was higher for EC, the cost to treatment providers was higher for NRT.

There are several other limitations to generalising the study findings. Participants may have had different expectations regarding the two study products, although their previous experience with EC and NRT was similar (about 50% have tried each product previously). We tried to mitigate this potential bias by only including participants who were willing to use either product and by avoiding any indication that one product may be superior to the other in information to participants, but despite this, more participants in the NRT arm never started product use. Engagement with treatment could also affect the response to follow-up calls. More participants in the NRT arm answered the follow-up calls only after delivery, though the difference did not reach significance and the time lapse between delivery and follow-up was shorter in the NRT arm (see Supplementary Table 5). Participants received several support calls. Although completion rates of the calls were low, the results may not generalise to settings where no support is provided. Regarding the blinding at follow-up calls, different teams conducted support and follow-up calls, but they occasionally covered for each other. A possibility of a re-contact cannot be ruled out, but in a trial with a large sample conducted over 2+ years, it would be unlikely that researchers would be able to recall participants' names or their allocation. Participants used almost exclusively refillable EC with a maximum of 20mg/ml nicotine, as higher nicotine concentrations are banned in the EU. The results may not generalise to modern 'pod' EC products with higher nicotine delivery. The NRT arm used almost exclusively nicotine patches. In non-pregnant smokers,

combinations of patches with other NRT products were shown more effective than single NRT[58].

Regarding safety outcomes, significantly more infants had low birthweight (<2500g) in the NRT arm. This could be a chance finding, but in a previous large study that compared nicotine and placebo patches, the nicotine arm had better birth and infant outcomes than the placebo arm over two years post-partum[59]. Both findings could be due to a larger reduction in smoking in the study arms with the more favourable safety outcomes. There were more congenital abnormalities in the EC arm, but the difference between the study arms was not significant. The overall incidence of adverse effects in the two study arms was similar. The findings do not suggest that EC use in pregnancy poses larger risks than use of NRT, despite the fact that EC was more likely to be used and was used for longer periods than NRT.

Adverse reactions linked to study products consisted primarily of skin irritation and nausea in the NRT arm and throat irritation and cough in the EC arm. EC seem more acceptable to pregnant smokers as more participants interrupted product use due to adverse reactions in the NRT arm.

Study data may contribute to our understanding of effects of nicotine on its own in later pregnancy. In animal studies, nicotine dosing in pregnancy generated a range of serious detrimental effects[60-62], but it is unclear whether this applies to the doses of nicotine and dosing schedules that are used by humans [63]. A recent report found a higher prevalence of low birth weight and preterm birth in EC users compared to non-users, but the sample of non-users comprised almost exclusively of never-smokers while most users are likely to have smoked during pregnancy[64]. Another cohort study that compared pregnant smokers who switched completely to EC use with both non-smokers and smokers found birthweight of infants of EC users matching that of infants of non-smokers and higher than in infants of smokers [66]. In this trial, birthweight was the same in both study arms, despite the higher use of nicotine products in the EC arm. Nicotine in late pregnancy did not seem to have contributed to restricted prenatal growth caused by smoking, but the finding does not encompass nicotine use in early pregnancy, as all participants were smoking in the first trimester. Nicotine may also pose other risks, and EC deliver other chemicals. A cross-sectional cohort study compared Neonatal Behavioural Assessment Scale (NBAS) scores in non-smokers, smokers, and smokers who switched to EC use and reported a greater number of abnormal reflexes in infants of both smokers and EC users compared to non-smokers[65]. This could be related to differences between smoking and non-smoking mothers, or to tobacco exposure in early pregnancy, but could be also due to nicotine exposure.

Given question marks that remain about potential risks of nicotine in pregnancy, stopping smoking without nicotine-containing aids is preferable to switching to such

products. Only where the choice is between using nicotine products such as NRT or EC or continuing to smoke, the nicotine product use would be the recommended option.

As noted above, the much higher post-smoking-cessation nicotine use in the EC arm did not seem to affect birth outcomes. As in previous studies[33,50], EC users were also reducing nicotine content of their EC over time. However, if EC use were to persist over long term, it is likely to carry some health risks [67], as well as maintaining nicotine dependence. In this scenario, EC would represent a harm reduction approach. It is also not known whether over an extended time period, EC use has positive or negative effects on the quality of life of ex-smokers and their rates of relapse. Longitudinal studies following up comparable cohorts of ex-smokers who do and do not use EC are needed to provide this information.

In summary, in the unadjusted primary analysis, there was insufficient evidence to confidently demonstrate that EC are more effective in helping pregnant smokers quit than NRT. EC effects appear to have been masked by EC use in the NRT arm. When abstainers using non-allocated products were excluded, EC were markedly more effective than patches in all abstinence outcomes. The safety data provide some reassurance that in pregnant smokers unable to quit unaided, EC do not seem to pose more risks to birth outcomes assessed in this study than nicotine patches and may reduce the incidence of low birth weight.

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Competing interests statement

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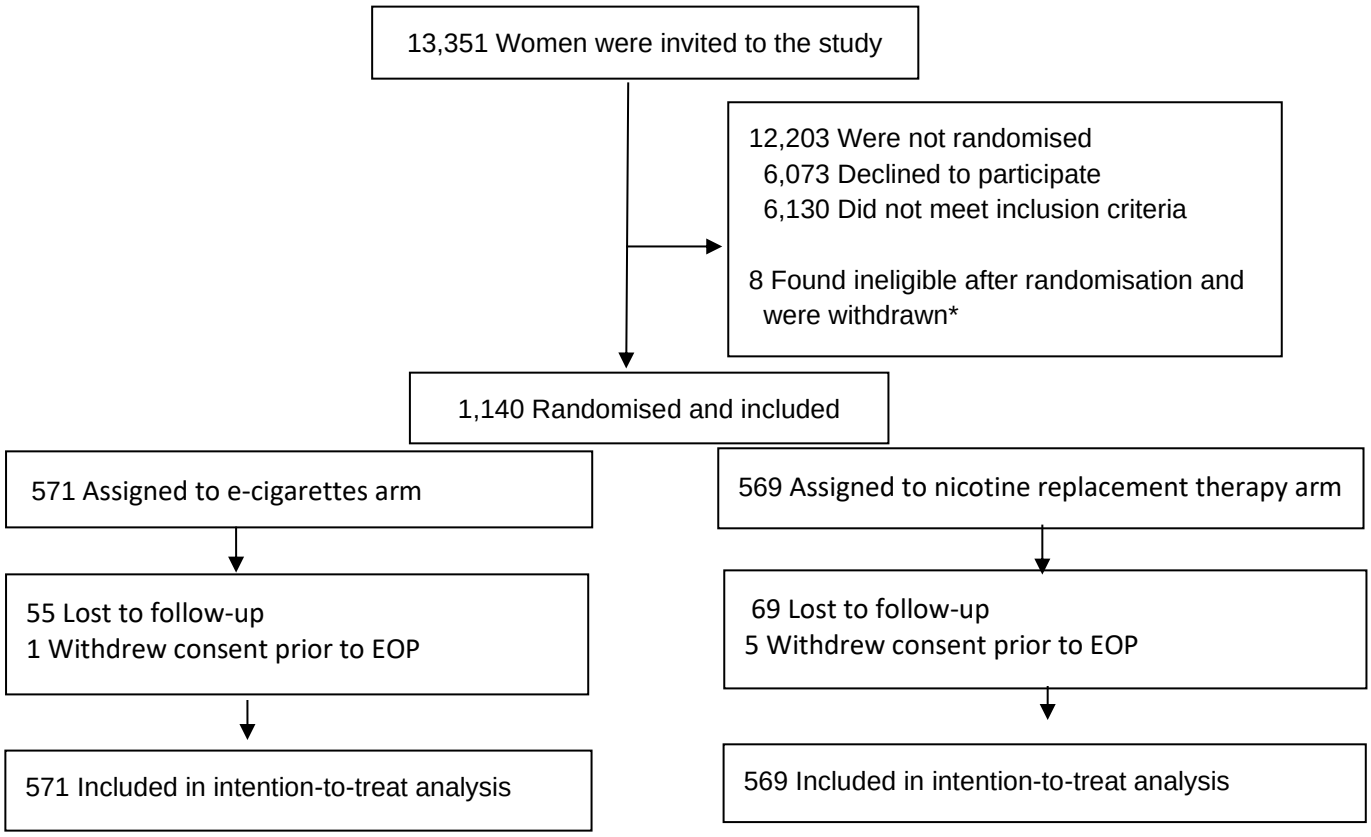
Figure 1



* 4 in each arm

Table 1. Baseline sample characteristics

	EC (N=571)	**NRT (N=569)**
Age median (IQR)	26.6 (22.5-30.9)	27.3 (23.6-31.1)
Education N (%)		
Primary and secondary school	229 (40.1)	234 (41.1)
Further education	288 (50.4)	273 (48.0)
Higher education	54 (9.5)	62 (10.9)
Employed N (%)	274 (48.0)	257 (45.2)
Ethnicity N (%)		
White British	513 (89.8)	495 (87.0)
Other	58 (10.2)	74 (13.0)
Cigarettes per day median (IQR)	10 (7- 15)	10 (7- 15)
FTCD mean (SD)	4.0 (2.1)	4.3 (2.1)
Cotinine levels ng/ml median (IQR) (EC=529, NRT=531)*	111 (75.8- 165)	118 (73.9- 176)
Lives with smoker N (%)	342 (59.9)	328 (57.6)
Past treatment[$] N (%)		

Champix	69 (12.1)	79 (13.9)
NRT	268 (46.9)	273 (48.0)
Zyban	7 (1.2)	5 (0.9)
None	272 (47.6)	267 (46.9)
Tried EC in the past N (%)	288 (50.4)	267 (46.9)

* Cotinine at baseline was missing for 80 (7.0%) participants, 53 due to insufficient samples and 27 lost at the hospital or in post

[$]More than one treatment could be selected

FTCD - Fagerstrom Test of Cigarette Dependence; NRT – nicotine replacement therapy

Table 2. Smoking cessation outcomes

	EC (N=571)	**NRT (N=569)**	**RR (95%CIs)**
Primary outcome			
Validated prolonged abstinence at EoP N (%)	39 (6.8)	25 (4.4)	1.55 (0.95- 2.53) p=0.08
Sensitivity analyses			
Per protocol (N=483 and 382) N (%)	39 (8.1)	23 (6.0)	1.34 (0.82- 2.21) p=0.25
Multiple imputation	(9.9)	(7.1)	1.39 (0.90- 2.14) p=0.13
Abstainers using non-allocated products excluded (N=571 and 564) N (%)	39 (6.8)	20 (3.6)	**1.93 (1.14- 3.26) p=0.02**
Secondary outcomes			
Self-reported abstinence at 4 weeks N (%)	89 (15.6)	61 (10.7)	**1.45 (1.07- 1.97) p=0.02**
Self-reported prolonged abstinence at EOP N (%)	63 (11.0)	44 (7.7)	**1.43 (0.99- 2.06) p=0.06**
Validated PP abstinence at EOP N (%)	58 (10.2)	40 (7.0)	**1.44 (0.98- 2.13) p=0.06**
Self-reported PP abstinence at EOP N (%)	118 (20.7)	78 (13.7)	**1.51 (1.16- 1.96) p=0.002**
Sensitivity analyses with abstainers using non-allocated products excluded			
Self-reported abstinence at 4 weeks N=570 and N=556	88 (15.4)	48 (8.6)	**1.79 (1.28-2.49) p=0.001**
Self-reported prolonged abstinence at EOP N=569 and N=556	61 (10.7)	31 (5.6)	**1.92 (1.27-2.92) p=0.002**
Validated PP abstinence at EOP N=569 and N=558	56 (9.8)	29 (5.2)	**1.89 (1.23-2.92) p=0.004**
Self-reported PP abstinence at EOP N=565 and N=544	112 (19.8)	53 (9.7)	**2.03 (1.50-2.76) p< 0.001**

EOP – end of pregnancy; PP – point prevalence

Table 3. Treatment adherence

	EC (N=571)	**NRT (N=569)**	**RR (95%CI)**
TQD set N (%)	418 (73.2)	394 (69.2)	1.06 (0.98-1.14) p=0.14
Support sessions completed Median (IQR)	1 (0-3)	1 (0-2)	0 (-0.31 to +31)* p=1.00
Allocated product use N (%)			
Did not use allocated product at all	88 (15.4)	184 (32.3)	**0.48 (0.38-0.60) p<0.001**
Request after initial 2-week supply	315 (55.2)	207 (36.4)	**1.52 (1.33-1.73) p<0.001**
Current use at 4 weeks	228 (39.9)	128 (22.5)	**1.78 (1.48-2.13) p<0.001**
Regular use during study **	438 (76.7)	292 (51.3)	**1.49 (1.36-1.64) p<0.001**
Current use at EOP	193 (33.8)	32 (5.6)	**6.01 (4.21-8.58) p<0.001**
Non-allocated product use N (%)			
Current use at 4 weeks	11 (1.9)	56 (9.8)	**0.20 (0.10-0.37) p<0.001**
Regular use during study **	16 (2.8)	101 (17.8)	**0.16 (0.09-0.26) p<0.001**
Current use at EOP	4 (0.7)	49 (8.6)	**0.08 (0.03-0.22) p<0.001**

* Median difference (95%CI)

** Used for 5+ days during the first 4 weeks or at EOP using currently or have used regularly for at least 1 week or occasionally for at least 3 weeks.

EOP – end of pregnancy; TQD – target quit date

Table 4: Birth outcomes in the two study arms

	EC (N=546)*^	NRT (N=549)*^	RR (95% CI)
Miscarriage N (%)	2 (0.4)	3 (0.6)	0.67 (0.11 - 4.00) p=0.66
Stillbirth N (%)	2 (0.4)	0 (0)	N/C
Neonatal death N (%)	2 (0.4)	3 (0.6)	0.67 (0.11 - 4.00) p=0.66
Post-neonatal death N (%)	0	3 (0.6)	N/C$
Maternal death N (%)	0	0	N/C$
Preterm birth N (%)	46 (8.4)	63 (11.5)	0.73 (0.51 - 1.05) p=0.09
Low birthweight N (%) (N = 541- 541)	52 (9.6)	80 (14.8)	**0.65 (0.47 - 0.90) p=0.01**
NICU admission N (%)	51 (9.3)	46 (8.4)	1.11 (0.76 - 1.63) p=0.58
Congenital abnormalities N (%) #	25 (4.6)	15 (2.7)	1.68 (0.89 - 3.14) p=0.11
Terminations N (%) -Due to congenital abnormalities -Due to premature rupture of membranes	 1 (0.2) 2 (0.4)	 2 (0.4) 0	 1.51 (0.25–9.00) p=0.65 N/C$
Number of women with adverse birth outcomes N (%)	112 (20.5)	119 (21.7)	0.95 (0.75-1.19) p=0.64
Delivery by caesarean section N (%)	131 (24.0)	148 (27.0)	0.89 (0.73- 1.09) p=0.26
Gestational age – weeks Mean (SD) N: 545 vs. 547	38.4 (3.0)	38.2 (3.1)	0.23 (-0.14-+0.59)** p=0.22
Birthweight in kg Mean (SD) N: 541 vs. 541	3.1 (0.60)	3.1(0.62)	0.03 (-0.04 to +0.10)** p=0.45

* Participants are included more than once if they had more than one event.

** Mean difference (95%CIs)

^ Singleton births only

$ Not calculated

2 infants in the EC arm and 1 in the NRT arm had 2 congenital abnormalities

NICU – Neonatal Intensive Care Unit;

Methods

Trial Design

A randomised controlled trial with 1:1 randomisation to EC or nicotine patch.

Participants

Participants were pregnant daily smokers (12-24 weeks gestation) who wanted help with stopping smoking, had no strong preference for NRT or EC, and agreed to only use the product allocated to them (and not the non-allocated product) for at least the first four weeks.

Exclusion criteria included age <18 years old, allergy to nicotine skin patches, current daily use of NRT or EC, and serious medical problems or high-risk pregnancy.

Participants were recruited from 23 hospital sites across England, and one NHS Stop Smoking Service (SSS) in Scotland. Recruitment was managed by research midwives in England and by the SSS in Scotland. Participants were identified from patient records and sent study information and invitation letters (alongside ultrasound scan appointment letters if appropriate) or invited via telephone, email or text; approached in person when attending antenatal hospital appointments; referred by community midwives or stop-smoking advisors; or self-referred via posters advertising the study at the sites' antenatal clinics.

Recruitment took place between January 2018 and November 2019.

Procedures

Potential participants were provided with study details that treated the two study arms in identical ways (see Supplementary file 1). Those interested in the trial were invited to the baseline visit. There, research midwives checked participants' eligibility and collected informed consent. Participants then completed a baseline questionnaire, provided a saliva sample, and were randomised to one of the two study arms. The relevant product was shown and its use explained, and the date and time for the first support call was set up, typically in one week's time. Participants were advised that the product would be posted to them in time for the first call. The site principal investigator then reviewed the participant's documentation and confirmed eligibility.

The study products were posted centrally from the Health and Lifestyle Research Unit (HAL). HAL stop-smoking advisors and researchers also delivered up to six initial support calls (see 'Behavioural support' section below) and collected the end of pregnancy and post-pregnancy follow-up data over the phone or via online/postal questionnaires. If HAL staff could not reach participants, their smoking status at

delivery was obtained from study sites, where available. Study sites also reported on pregnancy outcomes.

The first follow-up was conducted towards the end of pregnancy (EOP). As the majority of pregnant smokers who abstain during pregnancy return to smoking after delivery[42,43], EOP follow-up calls were made at 35 weeks gestation. Following an example from a recent trial[44], to increase the chance of reaching participants, a period for data collection was from 35 weeks gestation to 10 weeks post-estimated delivery date. The effort put into collecting follow-up data was stadardised (see Supplementary File 2).

At EOP, participants reporting abstinence from smoking, dual use of cigarettes and EC or NRT or a reduction of cigarette consumption of 50% or more were asked to provide a saliva sample. Sampling kits were posted to them with a self-addressed envelope on the day their smoking status was established. Once the returned samples were received, participants were sent £20 for their time and effort. During the last 14 months of the study, we also asked self-reported abstainers using nicotine containing products to attend local study sites to provide a carbon monoxide (CO) reading.

An additional follow-up call was conducted at 3 months post-partum to establish smoking status at EOP if this was not available from previous attempts at contact and to collect self-reports any new or worsening of old health problems in the mother and infant. If any of these health problems met the definition of a serious adverse event, further information was retrieved from hospital records. Follow up calls took place between April 2018 to Sept 2020.

The study was approved by the National Research Ethics Service Committee London –South East (ref: 17/LO/0962) and the MHRA via the CTIMP Notification Scheme. A Data Monitoring and Ethics Committee and a Trial Steering Committee supervised the study (see Supplementary file 3). The study was pre-registered on ISRCTN, ref: ISRCTN62025374. The full protocol is at https://fundingawards.nihr.ac.uk/award/15/57/85. A summary of protocol amendments following study initiation can be found in Supplementary file 4.

Study arms

E-cigarette: Participants were posted an EU Tobacco Product Directive-compliant refillable EC starter kit (One Kit by the UK E-cig Store), together with two 10ml bottles of tobacco flavoured e-liquid (18% nicotine; 70% PG and 30% VG), a pack of five replacement coils, and an instructional leaflet (See Supplementary file 5). Further supplies of e-liquid were posted on request for up to 8 weeks. A lower strength e-liquid (11%) and e-liquid with fruit flavour were available as alternatives. Participants were encouraged to source for themselves e-liquids of strength and flavour they liked as well as different EC devices, and arrange their own supplies

after 8 weeks, if needed. The cost of the kit provided by the study was £22.75 and the cost of e-liquid was up to £24 for eight-weeks supply.

Nicotine replacement treatment: Participants were posted an initial two-week supply of Nicorette Invisi 15mg/16hr nicotine patches with manufacturer instruction leaflets and instructed to apply patches every day upon waking, and remove them before bedtime. Further supplies were posted on request for up to 8 weeks. A lower strength patch (10mg/16hr) was available as an alternative. Participants were encouraged to access themselves further supplies via their GP or local stop smoking service (SSS). This could be patches and/or other NRT products such as nicotine chewing gum, inhalator or mouth spray, to use in addition to patch alone if needed. In the UK, pregant smokers receive NRT free of charge. The cost of patches provided by the study was up to £93.58 for eight-weeks supply.

Behavioural support that accompanied both study arms: Participants received six phone calls from stop-smoking advisors that followed the practice of the UK SSS[45]. The first call explained their product use and helped to prepare for their Target Quit Date (TQD). The second call, conducted on or near the TQD, checked on any product issues and provided tips and strategies for quitting. The further weekly calls checked on participants' progress, product use and supplies, and offered guidance on maintaining abstinence/stopping smoking. The final call took place four weeks post-TQD. The first call took up to 20 minutes, the other calls took on average 10 minutes.

Measures

At baseline, demographic details and smoking history were collected, including age in years, education (primary and secondary school only; further training but not university courses; higher (university) education); whether in paid employment; ethnicity (White British, White other, Asian Bangladeshi, Asian Indian, Asian Pakistani, Black African, Black Caribbean, Mixed, Other, don't wish to answer); number of cigarettes smoke per day; Fagerstrom Test of Cigarette Dependence (FTCD, score range 0-10[46]); whether living with another smoker; whether used NRT, varenicline and bupropion in the past; and whether tried EC in the past Participants also provided saliva samples for assessment of their cotinine levels.

At phone calls at weeks 1-4 post-TQD and at EOP, participants reported on their smoking status and on allocated and non-allocated product use.

At EOP, saliva samples and CO readings were collected as described above.

At each contact, including the call at 3 months post partum, participants were asked about any health problems since the last call and reports were classified as serious adverse events (SAE), adverse events (AE) or adverse reactions (AR). Sites were contacted when needed to check medical notes for clarifications. Participants not

using allocated products were asked for reasons and if these included physical symptoms, these were also recorded. Research midwives collected birth and maternal outcomes via hospital records and reported any birth-related SAE's and AE's.

Outcomes

The primary endpoint was prolonged abstinence from smoking from 2 weeks after the TQD until EOP, defined as per Russell Standard[47] (up to five lapses allowed with no smoking at all during the previous week at the time of final follow-up); validated by salivary cotinine (<10 ng/ml)[48] for those not reporting using any nicotine product, or by salivary anabasine (<1 ng/m)[49] or CO level <8ppm for those reporting current use of EC or NRT (ref). Where there was a discrepancy between anabasine and CO values, the CO result was used. Bedfont Pico CO monitor was used at all study sites. Participants with missing validation as well as those lost to follow-up were included as non-abstainers.

Secondary endpoints included self-reported prolonged abstinence from smoking at EOP, self-reported point prevalence abstinence (no smoking for at least the past 7 days) at 4-weeks and at EOP, validated point prevalence abstinence at EOP, and proportion of non-abstinent participants reducing their cigarette consumption by at least 50%. Participants who were only reached post-delivery and who reported that they had now returned to smoking, but had been abstinent at delivery, were included as self-reported EOP abstainers, but as non-abstainers in the validated outcomes.

Regarding safety outcomes, we monitored SAEs, AEs and ARs and specifically the following: termination, miscarriage (non-live birth prior to 24 weeks gestation), stillbirth (non-live birth at 24 weeks gestation or later), neonatal death (from live birth to 28 days), post-neonatal death (from 29 days), preterm birth (<37 weeks gestation), low birthweight (<2,500g), neonatal intensive care admissions (NICU), congenital abnormalities, caesarian-section delivery, birthweight and gestational age.

Sample size

We estimated from previous trials the quit rate at delivery in the NRT arm of 8%[17] and in the EC arm of 14%[50] (odds ratio 1.87; RR = 1.75). To have 90% power (alpha=0.05, two-tailed test) to detect this difference, 1,140 participants (570 in each condition) were needed.

Randomisation and blinding

An independent statistician developed the randomisation sequence using permuted block randomisation with block size of at least six and a maximum of 12. The randomisation list was only accessible to the independent statistician, on a secure server. Researchers conducting randomisation, informed participants of the study

arm they had been allocated to by the database application. Researchers conducting follow-up calls were blind to treatment allocation until the follow-up contact was made. Once contact was made and the trial application was opened, condition-specific questions were visible on the computer screen. The trial statistician was blind to participant allocation until the analysis of the primary and secondary outcomes was complete. This was achieved by only extracting and importing into Stata baseline characteristics, study arm and smoking status variables in the first stage of the analysis. Variables coding treatment adherence and product use were only extracted once primary and secondary outcome analyses were completed.

Statistical methods

The analysis plan was pre-registered on the Open Science Framework (https://osf.io/dvh4a). We report mean and standard deviation for continuous measures that are approximately symmetric; median and quartiles if the distribution is skewed. Binary outcomes were analysed using a binomial regression with a logarithmic link, which allows estimating risk ratios (RR), calculated with NRT arm as the reference. If the model were not to converge, we would use a Poisson regression model with robust standard errors. All tests were 2-sided.

For the primary outcome, we conducted three pre-specified sensitivity analyses: a per-protocol analysis that excluded participants who did not start product use or never established contact with the study team, an analysis where we estimated missing data using multiple imputation (MI) by chained equation, and an analysis where we excluded abstainers who used non-allocated products (i.e. EC in NRT arm and NRT in EC arm) for at least 5 consecutive days during the 4 weeks post-TQD or who reported at EOP current use or regular use for at least 1 week or occasional use for at least 3 weeks.

Regarding use of non-allocated products, as different rates of product switching was expected in the two study arms (with a higher rate in the NRT arm), excluding all non-allocated product users would be likely to result in overestimation of cessation rate in the arm allocated to the less effective treatment and underestimate the difference between groups. Further details are provided in Supplementary file 6. Excluding abstainers who used non-allocated products was considered to provide an estimate in both groups where the non-allocated treatment could not have contributed to abstinence.

Regarding multiple imputation, its use in smoking cessation trials is problematic because missingness is not random[51], but as it is often reported, we included it for completeness. Using multiple imputation by chained equation, we imputed missing data on self-reported sustained smoking status (i.e. smoker vs. abstainer), biochemical validation results, and current nicotine use (yes vs. no) to derive validated sustained abstinence (i.e. the primary outcome). Imputing was done separately by randomised group and we generated 50 completed datasets[52,53]. The

following auxiliary variables were included in the MI model, as they were associated with either self-reported abstinence or the results of saliva assays or their missingness: FTCD, living with a smoker, number of cigarette per day, education, occupation status, daily use of allocated products on all 4 intervention weeks, and point abstinence at week 4.

For the secondary outcomes as for the primary outcome, sensitivity analyses were conducted excluding abstainers who used non-allocated products. We also conducted an exploratory analysis where these participants were classified as non-abstainers (see Supplementary file 6).

Differences between the two study arms in AEs, SAEs and ARs, coded as present vs. absent, were assessed using binomial regression with logarithmic link. The primary analysis was of singleton births. A sensitivity analyses that included multiple births estimated standard errors allowing for intragroup correlation and estimated 95% confidence intervals. To account for clustering at the mother level, a clustered sandwich estimator of the variance was applied.

When no adverse birth outcome was recorded, we assumed that none had occurred. For the safety analyses, the denominator excluded participants who withdrew from the study prior to delivery (N=6).

For key outcomes, we calculated Bayes Factor (BF, See Supplementary file 6). This was not pre-specified, but was included to clarify whether the data support the null hypothesis or are insensitive.

Supplementary Files

Supplementary file 1: Patient Information Sheet

INVITATION TO PARTICIPATE IN A RESEARCH PROJECT

Helping Pregnant Smokers Quit: A Multi-Centre RCT of Electronic Cigarette and Nicotine Patches

Barts and The London School of Medicine and Dentistry, Queen Mary, University of London

(REC ref: 17/LO/0962; IRAS ID:220190)

We would like to invite you to take part in a research study. The information which follows tells you about it. It is important that you understand what is in this leaflet. Please ask any questions you want to about the research and we will try our best to answer them.

The Study

In this study we want to find out whether weekly phone calls, together with an e-cigarette (EC) *or* a nicotine patch are effective in helping pregnant women stop smoking. If you decide to take part in the study, a computer will decide at random (by chance) which of these treatments you will receive.

What are E-cigarettes and nicotine patches?

Nicotine patches are placed on the body and provide nicotine throughout the day so smokers don't feel the urge to smoke as much. Patches are put on in the morning and taken off before going to bed. E-cigarettes (EC) are battery-operated devices that provide nicotine in a vapour that looks like smoke. They can be used throughout the day to reduce the need to smoke. Both products are considered safe when used temporarily to help with stopping smoking.

What will happen if you take part?

You will be asked to attend one session with research staff which can happen at the same time as your ultrasound or other routine appointments. After this, your first supply of patches or EC will be posted to you and a stop smoking advisor will call you on a weekly basis for 6 weeks to check on your progress and provide advice and support.

The study will last between 7 to 10 months (including the final follow-up) depending on what stage in your pregnancy you join the study. The table below provides details of what will happen throughout the study.

Session 1	You will ***see the research midwife/nurse/stop smoking advisor*** and they will describe the study and answer any questions. Your consent to take part in the study and information about your smoking will be collected. They will also take a saliva sample to measure the amount of nicotine you are getting from your cigarettes. You will then be allocated to one of the two treatment groups: EC or Patches. This is decided at random by a computer. The research staff will explain how to use your allocated product and will set a date and time for the stop smoking advisor to call you. A two-week supply of your study product (EC/patch) will be posted to you in the next week.
Phone call 1 (before your quit day)	***A stop smoking advisor will give you a call*** on your agreed day and time. They will check that you have received your study product and answer any questions you may have on how to use it. They will then help you set a quit day and advise on preparing for it.
Phone calls 2-6 (on your quit day and 1-4 weeks after quitting)	During these ***weekly phone calls***, the advisor will provide support and guidance on quitting, and check on your progress. You will also be asked some questions about your product use and how you have been feeling. You will be posted further supplies of your product as needed.
Phone call 7 (end of pregnancy)	***You will receive a phone call*** to complete a short questionnaire about your smoking, product use and health. If you have stopped smoking or reduced your smoking by over 50%, you will be sent a saliva sample kit and asked to return it back to us in the post**.** If you are required to do a saliva sample, we will send you a saliva kit with £10 and then once you return the sample and the site receive it you will be sent a further £10 for your time. If you are not smoking but still using a nicotine product, we will also ask you to attend an appointment to give a carbon monoxide reading. If you attend for this, you will be given £20 for your time.
Phone call 8 (3 months after having your baby)	***You will receive a phone call to*** find out about your smoking and you and your baby's health.

Who can take part?

You will be able to take part if you are:

- Aged 18 years or over
- 12-24 weeks pregnant
- A daily smoker wanting to quit
- Willing to use either EC or nicotine patches, with no strong preference for one or the other
- Willing to receive weekly and follow-up phone calls
- Able to speak English

You will **not** be able to take part if you:

- Have a known allergic reaction to nicotine skin patches (a contraindication for patch use)
- Are currently using NRT or EC daily
- Are taking part in another interventional trial (as per Good Clinical Practice)
- Have a serious medical problem or high-risk pregnancy

Benefits and Risks

We do not expect there to be any risks from using EC or nicotine patches to stop smoking. Nicotine patches are used routinely in pregnancy by the UK Stop Smoking Services. The most common side effect that people report experiencing when using patches is skin irritation.

EC do not contain tobacco, and therefore do not deliver the many harmful substances found in normal cigarettes. The vapour from EC contains propylene glycol which is approved for use in pregnancy (e.g. in asthma inhalers) and vegetable glycerol, which has no known adverse effects. Some flavourings may over time affect the user's lungs, but to a much smaller extent than smoking, and to our knowledge, no chemicals other than nicotine (which you would inhale anyway if you continued to smoke) have been identified in EC vapour that would be expected to affect the health of the baby. The most common side effects that people report experiencing when using EC are mouth/throat irritation. EC are not currently licensed as a medicine, but they are currently regulated as a consumer product.

The benefit of taking part in the study is that you will receive free, specialist stop-smoking treatment, which if successful, would not only improve your health but also that of your baby.

What if new information becomes available?

In the event of new information becoming available, you will be informed of this and will have the opportunity to withdraw from the study.

Data Protection

Queen Mary University of London is the sponsor for this study based in the United Kingdom. We will be using information from you in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. Queen Mary University of London will keep identifiable information about you for 20 years after the study has finished.

Your rights to access change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

You can find out more about how we use your information at http://www.jrmo.org.uk/

The study team will collect information from you for this research study in accordance with our instructions.

Queen Mary University will use your name and contact details to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Individuals from Barts Health NHS Trust and

regulatory organisations may look at your medical and research records to check the accuracy of the research study. Queen Mary University will pass these details to Barts Health NHS Trust along with the information collected from you. The only people in Barts Health NHS Trust who will have access to information that identifies you will be people who need to contact you for the purpose of the study or audit the data collection process. The people who analyse the information will not be able to identify you and will not be able to find out your name, or contact details.

You will be allocated a unique participant number by our database. Personal information will be stored on an electronic database created and held on a separate server to the anonymised participant data. Medical records will be accessed by research staff in order to collect safety data and your birth and maternal outcomes, but this data will be kept anonymised like the other data. We will inform your GP, with your consent, that you are taking part in this study. If you agree to it, we may use information held by the NHS and NHS Digital to keep in touch with you should we need to do longer-term follow-ups for safety outcomes. The results of this study may be presented to other individuals working in the field of smoking cessation or may be published in journals. However, all data will be anonymised and there will be no information included which could identify you.

What will happen to the samples I give?

The saliva samples you give will be anonymised like the rest of your data, and they will be sent via recorded delivery to the research unit (2 Stayner's Road, London E1 4AH), where they will be stored securely in a freezer for up to 3 years. At the end of the study, they will be sent to a laboratory (ABS Labs Ltd.) to be analysed. When the analysis is finished, the samples will be destroyed.

How have patients and the public been involved in this study?

We discussed e-cigarettes with our panel of smokers and with 4 women receiving treatment at our pregnancy stop-smoking service, and they influenced our decision to do this study. A panel of EC testers also tested EC and liquids for the study, and recommended which EC we should use. We plan to continue to involve patients and the public in the study by including at least 2 lay people in our Trial Steering Committee.

Your Rights

Your participation in this study is entirely voluntary, and you are free to drop out of the study at any time. Your records will be kept strictly confidential and your ordinary medical care will not be put at risk if you decide not to take part or drop out.

What happens if you are concerned or have any questions?

You will be able to contact Dr Katie Myers-Smith or Dr Dunja Przulj on 0207 882 8230 or via health-research@qmul.ac.uk if you are worried about anything or have any questions. The Chief Investigator of this study is Christopher Griffiths, Professor of Primary Care, Institute of Population Health Sciences, Yvonne Carter Building, 58 turner Street, London, E1 2AB, , Tel: 020 7882 2501.

A summary of the results of this study will be available upon request.

We believe that this study is safe and do not expect you to suffer any harm or injury because of your participation in it. However, Queen Mary University of London has agreed that if you are harmed as a result of your participation in the study, you will be compensated, provided that, on the balance of probabilities, an injury was caused as a direct result of the intervention or procedures you received during the course of the study. These special compensation arrangements apply where an injury is caused to you that would not have occurred if you were not in the trial. These arrangements do not affect your right to pursue a claim through legal action.

If you wish to raise a complaint or would like to seek independent advice outside the study team, you can call the local patient advice and liaison service (PALS) on 0203 594 2040/2050 or you can email them at pals@bartshealth.nhs.uk.

This study has been reviewed by the NRES Committee London South East.

This study is funded by the National Institute for Health Research Health Technology Assessment Programme (NIHR HTA Project 15/57/85).

We would like to thank you for your interest in this study.

NHS
National Institute for Health Research

Supplementary file 2

Schedule of follow-up calls

Text reminders were sent to participants the day before their follow up call was due. Participants were asked to text back if they did not wish to be called. Participants were also able to text back their smoking status if a call was not convenient. The follow-up efforts at EOP used the following protocol: 2 calls and text in the first week; 2 calls and text in second week; 1 call in week 3 followed by posting a questionnaire, emailing it and a text; no contact during weeks 4-5 to allow return of questionnaires; 2 calls in week 6; 1 text in week 7; 2 calls in week 8; 1 text in week 9; 1 call in week 10; 1 text in week 11 followed by an email; 1 call in week 12; 1 text in week 13; 1 call in week 14 and a final text in week 15. The follow-up efforts at 3 months PP: 2 calls and text in the first week; 1 call in second week followed by posting and emailing of questionnaire and a text; no contact during weeks 3-4 to allow return of questionnaires; 1 call and 1 text in week 5; final call in week 6.

Supplementary file 3: Study committees

DMEC	**Paul Aveyard (Chair)**
	Dominic Stringer (Statistician)
	Anne Greenough (Neonatologist)
TSC	**Jamie Brown (Chair)**
	Eleni Vangeli (expert in tobacco research)
	Leoni Brose (expert in tobacco research)
	Maryjane Winston (lay member)

Supplementary file 4: Summary of Protocol Amendments

Approved version*	Date	Summary
3.4	30/6/2017	Ethics committee recommended that age eligibility criteria be included in protocol (missed in error)
4.0	3/1/2018	Change in Sponsor representative; change to storage of paper forms
5.0	28/2/2019	Amendment to named statistician and change of name and address for CTU, data collection to include carbon monoxide measurement to verify abstinence in those using a nicotine product, replacement of participants randomised but later found ineligible, addition of new questions on respiratory health; addition of online survey method for follow up data collection; addition of collection of smoking status from hospital records at delivery
6.0	14/8/2019	Professor Christopher Griffiths added as new CI; update to saliva payments.
7.0	3/2/2020	Updates to protocol to reflect finalised SAP

*Versions prior to this were drafts before ethical and regulatory approvals.

Supplementary file 5: Leaflet with instructions on EC use

Queen Mary University of London

Helping Pregnant Smokers Quit: A Multi-Centre RCT of Electronic Cigarette and Nicotine Patches

[insert site logo]

How to use your electronic cigarette (EC)

Charging your EC: Unscrew the battery (5) from the tank (2).

Twist the swivel cover (6) and connect the charger (7) to the port under the cover. The charger connects to a USB computer port, or to an adaptor so EC can be charged from a wall plug.

The EC needs about 30 minutes to charge. A red light on the charger will turn green when the battery is fully charged.

EC will need to be charged about once a day.

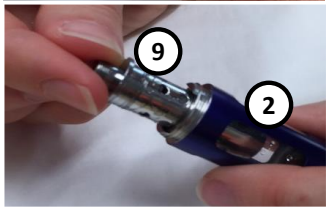
When your EC is charged, the button on the battery (4) glows green when pressed.

Filling your EC: Unscrew tank (2) from the battery (4), keep it facing up, and unscrew the mouthpiece (1). Place the mouthpiece on a piece of tissue.

Caps on e-liquid bottles (8) need to be pushed down before unscrewing them.

Insert the nozzle of the bottle into the tank aiming it at the side of the tank. Avoid getting any liquid into the central tube. Squeeze the bottle to fill the tank until it is almost full. Do not overfill.

Screw the mouthpiece and the tank back, do not overtighten the connections. EC will need refilling when the liquid has almost run out. When the coil is brand new, the liquid needs to soak into the coil for a few minutes.



Replacing the coil: The tank (2) contains the coil (9) which is attached to the connector (3). The coil needs to be replaced about every 2 weeks. If the vapour starts to taste different it may be a sign that the coil needs changing.

With the tank empty and the battery unscrewed, unscrew the connector (3) and pull out the coil (9). You can wash the tank with hot water. When dry, insert a new coil making sure it aligns with the tank and then screw on the connector and battery.

General tips: * When using your EC for the first time, press the button (4) three times quickly to unlock it. (It will flash). To lock it, press it three times quickly again. (It will flash green when locked). * If you get e-liquid on your skin, wipe and wash the area. * Any condensation can be cleaned with a cotton bud, dirt in connections can be removed with a tooth pick. * As you hold down the button to vape, a little crackling sound is normal.

If you encounter any problems, call us on 0207 882 8230. *PREP EC instructions V3.1 27 April 2017*

Supplementary file 6: Sensitivity analyses and Bayes factor

In addition to the pre-specified sensitivity analysis that excluded abstainers using non-allocated products, we also conducted an exploratory sensitivity analysis that assumed that abstainers using non-allocated products would not succeed in stopping smoking without such use, and reclassified them as non-abstainers. This approach maintains randomisation, allows the inclusion of the whole sample and maintains statistical power.

Sensitivity analyses of abstinence outcomes counting abstinence only if not accompanied by regular use of non-allocated product

	EC (N=571)	**NRT (N=569)**	**RR (95%CIs)**
Validated prolonged abstinence at EoP	39 (6.8)	20 (3.5)	1.94 (1.15- 3.29)
Self-reported prolonged abstinence at EoP	61 (10.7)	31 (5.5)	1.96 (1.29-2.97)
Validated point-prevalence abstinence at EoP	56 (9.8)	29 (5.1)	1.92 (1.25-2.97)
Self-reported point-prevalence abstinence at EoP	112 (19.6)	53 (9.3)	2.11 (1.55-2.86)
Self-reported abstinence at 4 weeks	88 (15.4)	48 (8.4)	1.83 (1.31-2.55)

Rationale for using the sensitivity analysis that excludes abstainers using non-allocated products

Regarding use of non-allocated products, a statistical adjustment could not be used because non-allocated products were different in the two study arms. The pre-specified sensitivity analysis excluded abstainers using non-allocated products rather than all such users. The latter is the usual approach to control for contamination, but in this case, the efficacy of the two ‘contaminators’ was expected to be different, and the contamination rates were markedly different in the two study arms. To illustrate the effect of this, let us assume that the true quit rate is 10% with treatment A and 20% with treatment B and that the intervention is tested in a sample 100 participants in each study arm. There will be 10 successful quitters in A and 20 in B. If all who fail with A (N=90) try B and 20% succeed (N=18) while half of those who fail with B try A (N=40) and 10% succeed (N=4), quit rates will be 28% ((10+18)/100) and 24% ((20+4)/100) in the A and B arms, respectively, masking the real 10% vs 20% treatment difference. To try to control for the bias by excluding all users of non-allocated products (‘switchers’) changes this to an even less accurate success rates of 100% (10/(100-90)) vs 33% (20/(100-40)). Excluding only abstinent switchers results in quit rates of 12% (10/(100-18)) vs 21% (20/(100-4)), the closest value to the true treatment effect. The additional exploratory sensitivity analysis shown above that includes only abstinence that was achieved without regular use of non-allocated

product would result in the hypothetical example in quit rates of 10% vs 20%, the same as the true treatment effects.

Bayes factor calculations

Bayes Factor (BF) indicates whether there is evidence for no effect or the data are insensitive in case of a non-significant result[68]. We specified a half-normal distribution (i.e. top half of a normal distribution with mode=0) with the standard deviation set to the expected effect size (i.e. log risk ratio). The expected effect size was based on our previous EC vs NRT study for smoking cessation[50] and on a study comparing nicotine and placebo patches for effects of nicotine on birth weight[17].

For the primary outcome, the data were found to be insensitive (BF=2.7). For the outcome excluding abstainers using non-allocated products and for the difference between the two study arms in the incidence of low birthweight, the effects were strong (BF=10.0 and BF=10.3, respectively).

The Table below shows regular use of non-allocated products (NRT in the EC arm and EC in the NRT arm) overall and in validated and self-reported abstainers.

Use of non-allocated products in the two study arms

	EC (571)	**NRT (569)**
Use of non-allocated product, N (%)	16 (2.8%)	101 (17.8%)
Users of non-allocated product among validated abstainers at EOP, N (% of abstainers)	0 (0%)	5 (20.0%)
Users of non-allocated product among self-reported sustained abstainers at EOP, N (% of abstainers)	2 (3.2%)	13 (29.5%)
Users of non-allocated product among self-reported 7-day abstainers at EOP, N (% of abstainers)	6 (5.1%)	25 (32.1%)

Supplementary tables

Supplementary Table 1. Smoking reduction in non-abstainers

	EC (N=453)	**NRT (N=491)**	**RR (95%CIs)**
Validated* 50% reduction at EOP	12 (2.7)	12 (2.4)	1.08 (0.49-2.39) P = 0.84
Sensitivity analysis			
Reducers using non-allocated product excluded (N=453 and N=489)	12 (2.7)	10 (2.0)	1.30 (0.57-2.97) p = 0.54
Self-reported 50% reduction at EoP	192 (42.4)	166 (33.8)	**1.25 (1.06- 1.48) p = 0.007**
Sensitivity analysis			
Reducers using non-allocated product excluded (N=448 and N=450)	187 (41.7)	125 (27.8)	**1.50 (1.25-1.81) p < 0.001**

* 50+% reduction in cotinine levels compared to baseline.

Supplementary Table 2:. Product use

Product use monitoring

Product use was indexed by the number of days per week products were used since the previous contact at weeks 1-4, and at EOP, the total number of weeks that the product was used regularly (five or more days per week) and occasionally (less than 5 days a week).

EC use in the EC arm

Products used during the initial 4 weeks (n=344)* N (%)	Refillable EC	324 (94.2)
	Cig-a-like	1 (0.3)
	Cartridge/Pod	1 (0.3)
	Information missing	18 (5.2)
Nicotine strength N (%)	0 mg/mL	7 (2.0)
	1-10mg/mL	47 (13.7)
	11-20mg/mL	199 (57.9)
	Information missing	91 (26.5)
Flavour N (%)	Fruit	180 (52.3)
	Tobacco	24 (7.0)
	Mint/menthol	22 (6.4)
	Chocolate, dessert, candy	11 (3.2)
	Other	21 (6.1)
	Information missing	86 (25.0)
Products used since last contact at EOP (N=371) N (%)	Refillable EC	330 (89.0)
	Cig-a-like	0 (0)
	Cartridge/Pod	2 (0.5)
	Information missing	39 (10.5)
Nicotine strength N (%)	0 mg/ml	8 (2.2)
	1-10mg/ml	77 (20.8)
	11-20mg/ml	61 (16.4)
	Information missing	225 (60.7)
Flavour N (%)	Fruit	97 (26.2)
	Mint/menthol	38 (10.2)
	Chocolate, dessert, candy	19 (5.1)
	Tobacco	17 (4.6)
	Other	24 (6.5)
	Information missing	176 (47.4)

* If several products were used, only the last product used is listed

Supplementary Table 3 . Birth outcomes by study arms, including twin births (9 EC vs. 4 NRT)

	EC (N=564)^	NRT (N=557)^	RR (95% CI)
Miscarriage N (%)	3 (0.5)	3 (0.5)	0.99 (0.20-4.87) p=0.99
Stillbirth N (%)	2 (0.4)	0 (0)	N/C
Neonatal death N (%)	2 (0.4)	3 (0.5)	0.66 (0.11–3.93) p=0.65
Post-neonatal death N (%)	0	3 (0.5)	N/C[$]
Maternal death N (%)	0	0	N/C[$]
Preterm birth N (%)	56 (9.9)	69 (12.4)	0.80 (0.56-1.14) p=0.22
Low birthweight N (%) N: 558 vs. 549	63 (11.3)	86 (15.7)	**0.72 (0.53-0.99) p=0.04**
NICU admission N (%)	58 (10.3)	46 (8.3)	1.25 (0.85-1.81) p=0.25
Congenital abnormalities N (%) [#]	26 (4.6)	15 (2.7)	1.71 (0.92-3.20) p=0.09
Terminations N (%) -Due to congenital abnormalities	1 (0.2)	2 (0.4)	1.48 (0.25–8.84) p=0.67
-Due to premature rupture of membranes	2 (0.4)	0	N/C[$]
Total number of adverse birth outcomes	213	227	
Number of women with adverse birth outcomes N (%) (N=555 vs 553)	120 (21.6)	122 (22.1)	0.98 (0.78-1.22) p=0.86
Delivery by cesarean section N (%)	145 (25.7)	152 (27.2)	0.94 (0.77-1.15) p=0.56
Gestational age – weeks Mean (SD) N: 562 vs. 555	38.3 (3.1)	38.2 (3.1)	0.12 (-0.25-0.49)* p=0.52
Birthweight in kg Mean (SD) N: 558 vs. 549	3.1(0.63)	3.1 (0.63)	0.01 (-0.07-0.08)* p=0.86

^ Number of babies
# 2 infants in the EC arm and 1 in the NRT arm had 2 congenital abnormalities
$ Not calculated

* Mean difference (95%CIs)

Supplementary Table 4: Other serious adverse events (SAEs), adverse events (AEs) and adverse reactions (ARs)

Event	EC	NRT
Other SAEs mother		
Premature rupture of the membranes	5	5
Pre-eclamspia	3	3
Threatened labour	3	3
Vaginal haemorrhage	2	4
Genitourinary tract infection	0	4
Haemorrhage in pregnancy	2	2
Abdominal pain	2	1
Migraine	1	2
Premature labour	1	2
Other (see list)	18	21
Other SAEs baby		
Newborn Respiratory Disorders	9	7
Jaundice	3	2
Vomiting	2	2
Meconium aspiration syndrome	3	1
Drug withdrawal syndrome	3	1
Sepsis neonatal	4	0
Hypoglycaemia neonatal	3	0
Tonsillitis	2	1
Foetal growth restriction	1	2
Other (see list)	20	20
AEs mother		
Nasopharyngitis	25	17
Lower respiratory tract infection	15	9
Nausea	12	11
Headache	11	9
Cough	8	8
Gestational diabetes	6	11
Influenza like illness	7	6
Migraine	2	7
Urinary tract infection	3	5
Abortion induced	4	2
Perinatal depression	4	2
Vaginal hemorrhage	4	2
Asthma	2	3
Oropharyngeal pain	1	4
Vomiting	3	2
Hypertension	0	4
Viral infection	2	2
Abdominal pain upper	3	1
Depression	1	2
Dyspepsia	1	2
Hypotension	1	2
Other	48	35
AEs baby		

Foetal Growth Restrictions Other	1 4	2 8
Total number of other mother/infant SAEs and AEs N (%)	255	239
Number of participants with other SAEs and AEs N (%)	181	162
ARs potentially related to treatment		
Application site irritation, hypoaesthesia ,rash, pain, or pruritus Nausea Cough Oropharyngeal pain or irritation Rash Headache Dizziness Chest pain or discomfort Vomiting Dyspnea Migraine Myalgia Other (see list)	0 17 42 39 0 4 1 11 1 3 1 0 7	81 36 0 0 14 9 8 0 3 0 2 3 6
Total number of ARs	126	162
Number of participants with ARs *	108	148
*Action following ARs***		
Study drug discontinuation/interruption following AR	36	111
Study drug dose change following AR	41	12

* RR=0.86, 95%CI: 0.74-1.01

** $Chi^2_{(1)}$=46.0, p<.001

Note: Cases of conditions that led to hospitalization are listed under SAEs while those that did not are considered AEs. The same condition (e.g. foetal growth restriction) may thus appear under different headings.

SAE and AE that occurred only once or twice

SAE baby

EC (N=20): Neonatal seizure (2), Viral infection (2), Hypothermia neonatal (1), Abdominal distension (1), Infantile apnoea (1), Asthma (1), Bradycardia (1), Foetal cardiac arrest (1), Beta haemolytic streptococcal infection (1), Hospitalisation for further diagnosis (1), Hypoxic-ischaemic encephalopathy (1), Immune thrombocytopenia (1), Neonatal infection (1), Low birthweight baby (1), Necrotising enterocolitis neonatal (1), Skin discolouration (1), Spinal cord neoplasm (1), Foetal hypokinesia (1)

NRT (N=20): Poor feeding infant (2), Hypothermia neonatal (1), Infantile apnoea (1), Benign Neonatal Sleep Myoclonus (1), Bronchiolitis (1), Bronchitis (1), Cardiac arrest neonatal (1), Skull fracture (1), Cholecystectomy (1), Haematoma (1), Hypertonia neonatal (1), Neonatal infection (1), Intraventricular haemorrhage neonatal (1), Low birthweight baby (1), Neonatal pneumothorax (1), Poor weight gain neonatal (1), Shoulder dystocia (1), Perinatal stroke (1), Foetal hypokinesia (1)

SAE mother

EC (N=18): Abdominal pain upper (1), Acute myocardial infarction (1), Alcoholism (1), Cerebral haemorrhage (1), Dehydration (1), Epilepsy (1), Influenza (1), Kidney infection (1), Mastitis (1),

Nephrolithiasis (1), Pneumonia (1), Postpartum haemorrhage (1), Puerperal pyrexia (1), Renal pain (1), Sciatica (1), Sepsis (1), Ureteric injury (1), Wound infection (1)
NRT (N=21): Cellulitis (1), Cervix inflammation (1), Diarrhoea (1), Eclampsia (1), Endometritis decidual (1), Epilepsy (1), Gastritis (1), Gestational diabetes (1), Haemoglobin decreased (1), Hyperemesis gravidarum (1), Influenza (1), Lower respiratory tract infection (1), Pneumonia (1), Premature separation of placenta (1), Preterm premature rupture of membranes (1), Pulmonary thrombosis (1), Pyelonephritis acute (1), Retained products of conception (1), Sepsis (1), Tooth infection (1), Upper respiratory tract infection (1)

AE baby
EC (N=4): Acid Reflux (1), Foetal hypokinesia (1), Viral infection (1), bronchitis (1)
NRT (N=8): Bronchitis (1), Chesty Cough (1), Difficulty breathing (1), Infection (1), Respiratory distress (1), Viral infection (1), Bilateral ventriculomegaly (1), Cyst, NOS (1)

AE mother
EC (N=48): Anaemia of pregnancy (2), Application site irritation (2), Kidney infection (2), Mouth ulceration (2), Placenta praevia (2), Abdominal discomfort (1), Acne (1), Acute sinusitis (1), Anxiety (1), Back pain (1), Bartholin's abscess (1), Chest discomfort (1), Chest pain (1), Cholestasis (1), Constipation (1), Deep vein thrombosis (1), Dermatitis allergic (1), Diarrhoea (1), Dizziness (1), Dyspnoea (1), Ear infection (1), Eczema (1), Fatigue (1), Fluid retention (1), Food poisoning (1), Iron deficiency (1), Ligament injury (1), Mastitis (1), Neck pain (1), Oedema peripheral (1), Oligohydramnios (1), Otitis media acute (1), Panic attack (1), Pelvic pain (1), Pre-eclampsia (1), Pulmonary embolism (1), Pyrexia (1), Road traffic accident (1), Seasonal allergy (1), Subcutaneous abscess (1), Thrombosis (1), Tooth extraction (1), Wheezing (1)
NRT (N=35): Abdominal pain (2), Anxiety (1), Back pain (1), Bile output increased (1), Bronchitis (1), Candida infection (1), Chest discomfort (1), Cholestasis (1), Constipation (1), Crohn's disease (1), Decreased appetite (1), Depressed mood (1), Dizziness (1), Dyspnoea (1), Gastroenteritis (1), Haemorrhage urinary tract (1), Ligament pain (1), Mental disorder (1), Mood swings (1), Muscle spasms (1), Pain (1), Palpitations (1), Panic attack (1), Peripheral swelling (1), Post procedural complication (1), Premature rupture of membranes (1), Rash (1), Rhesus antibodies (1), Sinusitis (1), Suicidal ideation (1), Symphysiolysis (1), Tonsillitis (1), Tooth fracture (1), Abdominal pain lower (1)

AR
EC (N=7): Asthma (2), Dyspepsia (2), Lip swelling (1), Stomatitis (1), Wheezing (1)
NRT (N= 6): Arthralgia (1), Eczema (1), Functional gastrointestinal disorder (1), Hyperhidrosis (1), Muscle swelling (1), Nightmare (1)

Supplementary Table 5. Median time to follow-up in the two study arms

	EC N=505	NRT N=490	Wilcoxon rank sum
Follow-up completed pre-delivery	-23 days (IQR=-31 to -14; N=318)	-23 days (IQR=-31 to -16; N=282)	z=-0.4, p=0.68.
Follow-up completed post-delivery	16 days (IQR=0 to +66; N=187)	10 days (IQR= 0 to +36; N=208)	z=2.0, p=0.04

Note: 17 participants had no date of delivery recorded and 2 had the date of follow-up missing

There were 395 women who answered the follow-up calls only after delivery, 187 (37%) of the EC arm vs 208 (42%) of the NRT arm (chi(1)=3.1, p=0.08). Of these women, 12 (6.4%) vs 9 (4.3%) were self-reported abstainers (chi(1)=0.85, p=0.36). Among these, 5 (41.7%) vs 3 (33.3%) reported relapsing back to smoking since delivery (chi(1)=0.15, p=0.70).