Study Protocol

A randomised controlled trial to examine the efficacy of e-cigarettes compared with nicotine replacement therapy, when used within the UK stop smoking service

Short title/Acronym:	Trial of EC (TEC)
Sponsor:	Queen Mary, University of London (QMUL)
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Site(s)	1. Tobacco Dependence Research Unit, Wolfson Institute of Preventive Medicine, QMUL 2. East Sussex Stop Smoking Service (Quit 51) 3. Leicester Stop Smoking Service
Investigators:	Dr Hayden McRobbie (Chief Investigator), QMUL; Professor Peter Hajek (Principal Investigator), QMUL; Dr Katie Myers Smith (co-investigator), QMUL; Professor Peter Sasieni (co-investigator), QMUL; Louise Ross (Principal Investigator), Leicester Stop Smoking Service, Emma Croghan (Principal Investigator), East Sussex Stop Smoking Service
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Clinical Trials Unit:	Barts CTU
Funder:	NIHR HTA

Chief Investigator Agreement Page

The clinical study as detailed within this research protocol (Version insert once finalised), or any subsequent amendments will be conducted in accordance with the Research Governance Framework for Health & Social Care (2005), the World Medical Association Declaration of Helsinki (1996) and the current applicable regulatory requirements and any subsequent amendments of the appropriate regulations.

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Signature and Date:

08.04.2015

STUDY SUMMARY/SYNOPSIS

TITLE	A randomised controlled trial to examine the efficacy of e-cigarettes (EC) compared with nicotine replacement therapy (NRT), when used within the UK stop smoking service.
SHORT TITLE	Trial of EC (TEC)
Protocol Version Number and Date	3.0, 08.04.2015
Methodology	Pragmatic randomised controlled trial (RCT)
Study Duration	33 months
Study Centre(s)	1. Tobacco Dependence Research Unit, Wolfson Institute of Preventive Medicine, QMUL 2. East Sussex Stop Smoking Service (Quit 51) 3. Leicester Stop Smoking Service
Objectives	***Primary:*** To determine the 12-month sustained biochemically validated abstinence rates in smokers using EC compared to smokers using standard NRT. ***Secondary:*** Abstinence rates at 4 weeks and 6 months, CO validated sustained abstinence rates between 6 and 12 months, effects of the two treatments on smoking reduction in participants who did not achieve full abstinence, changes in urges to smoke and other tobacco withdrawal symptoms at 1 and 4 weeks, ratings of the two treatment approaches by patients, rates of adverse reactions associated with the use of EC and NRT, cost-effectiveness of EC compared to NRT.
Number of Subjects/Patients	886 randomised participants
Main Inclusion/Exclusion Criteria	***Inclusion criteria:*** 18 years and older, current smoker accessing a stop smoking service, able to read/write/understand English. ***Exclusion criteria:*** Pregnant or breastfeeding, strong preference to use or not to use NRT or EC in the quit attempt, currently using NRT or EC, already enrolled in interventional research.
Statistical Methodology and Analysis	Abstinence rates and rates of those sustaining a 50% or greater reduction in baseline cigarette consumption and CO levels will be compared between the study arms using a Pearson Chi-squared test with logistic regression. Frequency of adverse reactions will be compared between arms. Time to relapse will be analysed using a Cox analysis. If no significant difference in abstinence rates is detected between the study arms then a non-inferiority analysis will be undertaken. Participants lost to follow-up or not providing biochemical validation will be included as non-abstainers.

GLOSSARY

AE	Adverse event
AR	Adverse reaction
CO	Carbon monoxide
CPD	Cigarettes per day
DMEC	Data Monitoring and Ethics Committee
EC	Electronic cigarette
EQ5D	European Quality of Life -5 Dimensions
FTND	Fagerstrom Test of Nicotine Dependence
JMRO	Joint Management Research Office
LOR	Letter of recommendation
MPSS	Mood and physical symptoms scale
NRT	Nicotine replacement therapy
QA	Quality assurance
QC	Quality control
RCT	Randomised controlled trial
SAE	Serious adverse event
SAR	Serious adverse reaction
SSC	Study Steering Committee
SSS	Stop Smoking Service
SUSAR	Suspected unexpected serious adverse reaction
TMG	Trial Management Committee
TQD	Target quit date
UC	Usual care

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1 Introduction

1.1 Background

Electronic cigarettes (EC) are battery-powered devices that provide inhaled doses of nicotine by delivering a vaporised liquid nicotine solution in propylene glycol or glycerol. No tobacco, smoke, or combustion is actually involved in their operation.

EC have largely been marketed as a 'lifestyle' product for smokers who want to reduce the risks of smoking. EC provide levels of nicotine similar to those provided by NRT, but they might have an advantage over existing NRT products because of their ability to provide more realistic sensorimotor and behavioural replacement for smoking.

Current smoking cessation treatments generally provide a combination of behavioural support and evidence-based medicines to target withdrawal discomfort, but sensorimotor factors are not well addressed. EC provide sensations similar to smoking a cigarette by emitting a smoke-like mist or vapour, and provide taste and throat sensations which are closer to smoking than those provided by oral NRT e.g. the nicotine inhalator. There is some evidence that these factors are important for smokers and that their inclusion enhances treatment efficacy [1].

1.2 Clinical Data

Our team has conducted a number of studies of EC [2–21] including some of the early research on EC showing that they could alleviate urges to smoke. At the time our first study was undertaken (2008-09) EC use was marginal, but it increased substantially over the following years. In the UK, current use in smokers increased from 2.7% in 2010 to 6.7% in 2012 [22].

Survey data consistently show that users report that EC help them to either quit or reduce smoking [12,13,22–24]. EC users are more likely to be current smokers than ex-smokers and use EC to quit or reduce risks of smoking [22,24]. They tend to be younger and better educated than other smokers [25,26].

Early pharmacokinetic studies showed that EC delivered low or no nicotine to the user [7,27,28]. However, these studies typically used short fixed puffing schedules and smokers without any experience in using EC. Some of the EC used were also of poor quality [7]. In later studies where users were able to familiarise themselves with the product and/or use it for longer periods, plasma nicotine delivery was comparable to that from oral NRT products (e.g. 4-5ng/ml) [29,30]. In experienced EC users increases of up to 13 ng/ml have been observed [9,31], which is similar to the changes seen after smoking a regular cigarette (e.g. 10-20 ng/ml [32]).

Several studies have now demonstrated that EC reduce urges to smoke after a period of abstinence [7,9,11,27–31].

Effects of EC on smoking

Several case studies have reported EC effectively helping people that have failed to quit with other methods [33–35]. Data from two prospective cohort studies and two RCTs give an indication of the potential for EC to help smokers reduce tobacco consumption and stop smoking.

Two reports [36,37], of the same study examined the effects of EC use in 40 highly dependent smokers unwilling to quit. Two years after enrolment, 28% had achieved a sustained ≥50% reduction from baseline cigarette consumption, and an additional 13% achieved at least 6 months of CO validated abstinence from conventional cigarettes. The second study using the same approach with 14 smokers with schizophrenia reported that at 1-year follow-up, half of the participants had achieved a ≥50% reduction of their baseline cigarette consumption for at least 30 days, and an additional 14% had achieved 30-day CO validated abstinence [38].

A double-blind trial of 300 smokers not intending to quit compared effects of EC containing 7.2mg or 5.4mg nicotine and a nicotine free EC provided for 12 weeks [39]. At one year, biochemically validated 6-month abstinence rates were 13%, 9% and 4% in the three groups. The difference between the three groups was not significant, but the two nicotine EC groups merged had a significantly higher quit rate than the non-nicotine group (11% vs. 4%, p=0.04). At one year, 27% of successful quitters (7/26) were still using EC, leaving the majority tobacco and nicotine free.

One RCT has evaluated the long-term effects of EC on smoking cessation in treatment-seeking smokers [6]. It compared nicotine-containing EC with 21 mg nicotine patches and with non-nicotine EC. In addition, participants were provided with a referral to a telephone Quitline but with no face-to-face contact. In this minimal support context, no significant differences across treatment arms was observed, with validated continuous abstinence at 6 months observed in 7.3% participants assigned to the nicotine EC, 5.8% assigned to the patch, and 4.1% assigned to the non-nicotine EC. Significantly higher self-reported smoking reduction and higher user endorsements were observed for the participants who received nicotine EC relative to those who received nicotine patch. The study was underpowered, used EC with low nicotine delivery, and the minimal support paradigm was not ideal for testing a new treatment. A commentary on the finding pointed out that because EC are more attractive than patches to many smokers, and can be accessed in most countries without the restrictions around medicines that apply to NRT or the costly involvement of health professionals, they have the potential to increase rates of smoking cessation and reduce costs to quitters and to health services [16].

EC safety

The most common side effects users reported were dryness or irritation of the throat and mouth [12,24,40,41]. Headache, cough, vertigo, nausea and palpitations were also reported.

None of the experimental [7,9–11,27,28,30,31] or prospective follow-up studies [36,38] reported serious adverse events (SAEs). Any AEs were largely mild to moderate and included symptoms such as mouth and throat irritation and dry cough, similar to those reported in user surveys. No significant difference in the frequency of AEs, between EC and control groups (non-nicotine EC or patch), were observed in the two randomised trials of EC [6,39].

Some commentators have expressed concern over the risk of nicotine poisoning with EC. These risks, however, are very low. We are aware of one report describing several suicide attempts, where adults drank up to 1,500 mg of nicotine in e-liquid (this is significantly greater than the often quoted lethal dose of 30-60 mg), which resulted in ‘voluminous vomiting’ and a full recovery within a few hours [42]. There is also a case report of an 18-month child who drank e-liquid and was admitted to

hospital with vomiting, ataxia, and lethargy, and was discharged after 24 hours of observation [43]. EC refill liquids now come in childproof bottles.

1.3 Rationale and Risks/Benefits

Data are urgently needed on whether EC match the efficacy of other existing treatments in helping smokers quit or reduce smoking. Several studies have suggested that EC have a substantial potential as a stop-smoking treatment but no study has compared EC to a standard intensive treatment so far.

Smokers now frequently ask the Stop Smoking Service (SSS) for advice on whether EC can help them quit smoking. In a survey of UK SSS managers, commissioners and advisers, the need for guidance on EC advice was the number one priority [22]. More recently the National Institute for Health and Clinical Excellence (NICE), in their guidance on Tobacco Harm Reduction, highlighted the critical need for outcome and safety research on novel nicotine-containing products, in particular EC [44].

EC are cheaper than a standard 12-week treatment course of NRT (and other prescription non-nicotine smoking cessation medicines), and hold greater appeal to smokers [6,7]. There are few other smoking cessation treatment improvements on the horizon and EC are the most promising current development awaiting objective scrutiny. In order to inform their practice, health care commissioners need to know if they are as effective as licensed nicotine smoking cessation medicines when used with the support routinely provided by the UK stop-smoking service. This proposal aims to provide this information.

EC use does not involve tobacco combustion, which is the primary source of the many thousands of dangerous chemicals to which smokers of conventional cigarettes are exposed. Studies on EC users have identified little or none of the known toxins associated with tobacco smoking [45], and while they may not be entirely safe, no serious health risks have been identified. There is little doubt they are substantially safer than conventional cigarettes, and they have the potential benefit of reducing urges to smoke and boosting rates of smoking cessation.

Electronic cigarettes have a potential to increase the reach and reduce the costs of the UK SSS. The aim of this trial is to determine if EC are more effective than standard NRT products when used with face-to-face behavioural support as provided by the SSS.

2 Trial Objectives and Design

2.1 Trial Objectives

Primary Objective - To determine the 12-month sustained, biochemically validated abstinence rates in smokers using EC compared to smokers using standard NRT.

Secondary Objectives -

1. Abstinence rates at 4 weeks and 6 months.
2. Abstinence rates between 6 and 12 months
3. Effects of the two treatments on smoking reduction in participants who did not achieve full abstinence.

4. changes in urges to smoke and other tobacco withdrawal symptoms at 1 and 4 weeks.
5. Ratings of the two treatment approaches by patients.
6. Rates of adverse reactions associated with the use of EC compared to standard NRT.
7. Cost-effectiveness of EC compared to standard NRT.

2.2 Trial Design

This is a pragmatic RCT where smokers who want help to quit smoking will be individually randomised to receive usual care (UC; a choice of NRT combined with usual care behavioural support provided by the SSS) or EC with the same behavioural support.

3 Subject Selection

3.1 Number of Subjects and Subject Selection

886 participants would be recruited from SSS. Participants would present to the clinics either in response to advertisements in local newspapers, through GP practices or following routine referrals.

3.2 Inclusion Criteria

- Aged 18 or over
- Current smoker accessing the SSS
- Able to read/write/understand English

3.3 Exclusion Criteria

- Pregnant or breastfeeding
- Strong preference to use or not to use NRT or EC in their quit attempt
- Enrolled in other interventional research
- Currently using NRT or EC

4 Study Procedures

4.1 Informed Consent Procedures

Potential participants will be informed of the study by SSS and research staff who will discuss the study, and if interested/eligible potential participants will be provided with written information, along with the standard SSS client registration form, prior to their first session. At the baseline session, study details would be discussed with clients interested in taking part and informed consent obtained by good clinical practice (GCP) trained members of the study team, who are delegated to do so on the delegation log.

4.2 Screening Procedures

Potential participants would be screened for eligibility during the baseline session.

4.3 Randomisation Procedures

Randomisation (1:1 in permuted blocks) will be undertaken using a web-based application, set up by the Barts Clinical Trials Unit (Barts CTU), and will be stratified by study site. Participants who are eligible and consent to take part will be randomly allocated to the experimental or control interventions at the target quit day (TQD) session. The TQD is being used as the point of randomisation to limit any differential drop-out. The staff randomising the patient will access the web-based application when the patient is with them, entering their participant ID number, date of birth and initials into the program. There are no stratification factors. The allocation will immediately be provided by the program. In the event that a site has no web access they will be able to fax the relevant CRFs to the CTU for a telephone randomisation during standard working hours.

4.4 Schedule of Treatment for each visit

Identical multi-session behavioural support will be provided to both groups. The exact procedures differ slightly between the different study sites, but usual care for smoking cessation involves face-to-face support sessions (Withdrawal Oriented Treatment [46]), which usually begin 1-2 weeks prior to the TQD. Clients attend weekly for several weeks after the TQD. Study data will be collected face-to-face at the first (baseline) session, the TQD, and for the first 4 weeks post-TQD.

Participants would also be contacted by telephone at 24 and 52 weeks post TQD to obtain smoking status and assess EC/NRT/other product use and adverse reactions; those who report abstinence or a reduction in smoking by at least 50% would be asked to provide a CO reading at 52 weeks.

Participants would be compensated £20 for their travel and time at the 52-week visit.

Control Group

Participants will be informed about the range of NRT products available at the baseline session. The supply of NRT differs slightly between the different study sites. For example, the Tower Hamlets SSS provides NRT via a letter of recommendation (LOR) to supply on a fortnightly basis for the first 4 weeks, which clients take to a pharmacist to exchange for NRT paying a prescription charge of £8.05, if applicable (some 50% of SSS clients are normally exempt from the charge) whereas East Sussex SSS provide NRT by direct supply at no charge. For those sites giving LORs, participants will be given an LOR at their baseline session (as per standard practice) and instructed to collect the NRT and bring it to their TQD session. At the TQD those randomised to the NRT condition will keep their NRT and have their first use during the session. For sites that provide NRT on direct supply, participants randomised to the NRT condition will be provided with their NRT during the TQD session. For all sites, detailed instructions on use and information on common side effects will be provided as part of the behavioural support. At the completion of the study treatment period participants can request further supplies of NRT in line with the SSS standard practice (for example, at the Tower Hamlets service, patients can request further 2 week LOR supplies of NRT up to a total of 12 weeks).

Intervention Group
Participants in the intervention group who are attending a site using LORs will also be given an LOR at their baseline session and will be asked to collect the NRT and bring it to their TQD session. Participants who are then randomised to the EC condition at the TQD will return their NRT in exchange for an EC starter kit (18mg/ml nicotine), which will include a two week supply of e-liquid and information on where to purchase more themselves. Participants in the EC condition will have an option to request a further 2-week supply of the liquid at 2 weeks post-TQD if they are using the supplied product and have not managed to buy their own e-liquids by this point. They will be provided with both verbal and written instructions on how to operate the EC. Participants will be advised on how to obtain further supplies themselves. They will be free to try other brands and at every contact point we will monitor which EC product is being used as well as the frequency and length of use.

At the TQD all participants will be asked to sign a commitment form stating that they will commit to using their allocated treatment, and will not use the non-allocated treatment, for at least the initial four weeks post-TQD.

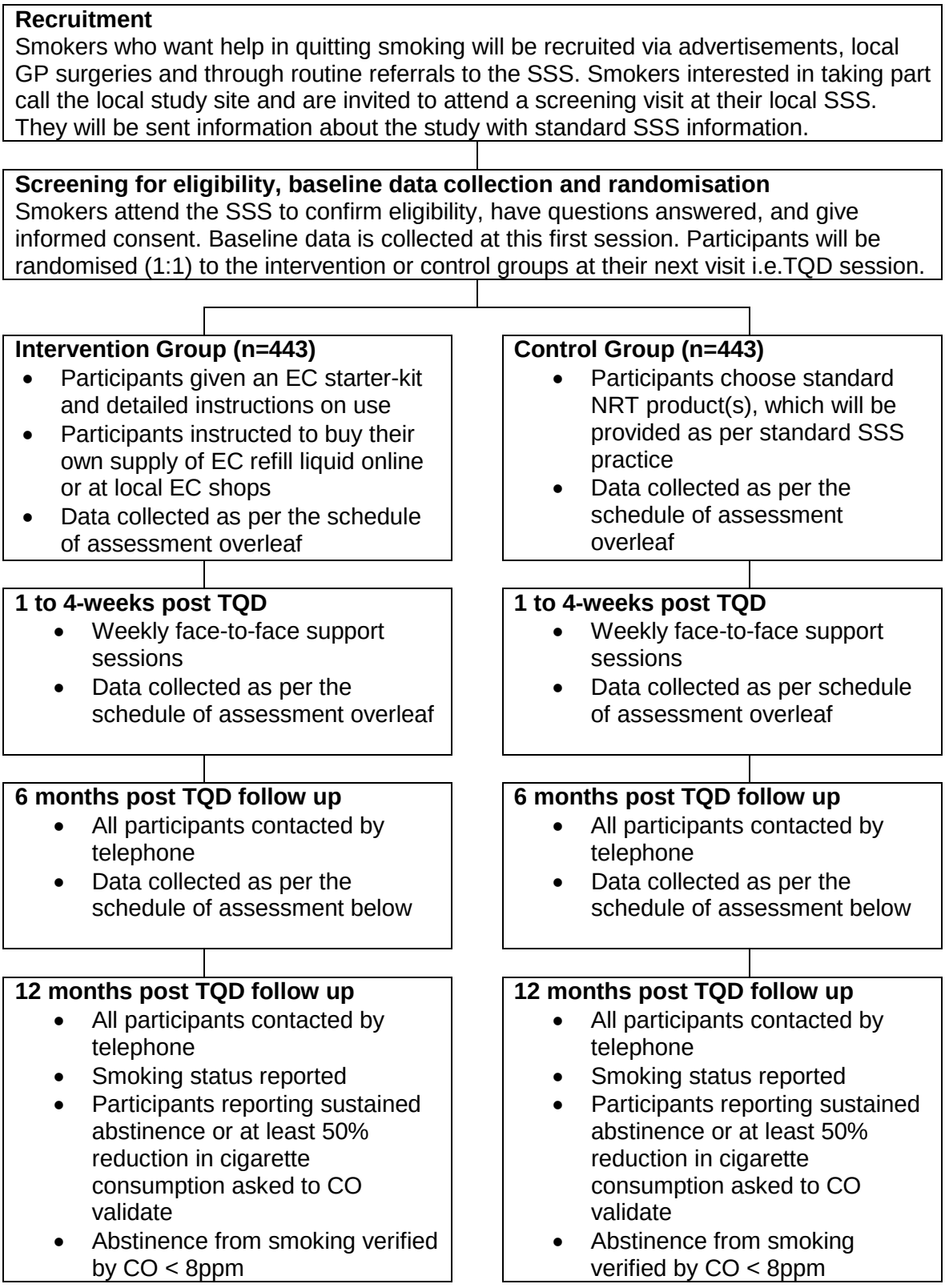
4.5 Measures

- Demographic details, smoking and medical history
- Fagerstrom Test of Cigarette Dependence (FTND) [47]
- Mood and Physical Symptoms Scale (MPSS): Measure of severity of urges to smoke and other tobacco withdrawal symptoms [48]
- Self-reported smoking status
- End-expired carbon monoxide reading: Collected using a calibrated CO monitor. A reading of <8ppm would be used as a cut-off for abstinence
- Adverse reactions
- Use of EC/NRT and ratings of helpfulness to refrain from smoking and satisfaction in comparison to usual cigarettes. Participants who stop using EC will also be asked their reasons for doing so.
- European Quality of Life-5 Dimensions (EQ5D) questionnaire at baseline and at 6 and 12 months [49]
- Smoking cessation service and health service use at baseline and at 6 and 12 months

4.6 Study product (E-cigarette)

We will use a second generation EC with e-liquid containing 18mg/ml nicotine (the most commonly used nicotine content [45]). The EC will have a CE mark. Participants will then be directed to select and purchase their own refill e-liquid. They will also be able to purchase another EC brand on their own. This will (a) ensure that people use a refill e-liquid they like; (b) reflect what happens in ‘real life’; and (c) avoid giving the EC arm an advantage of free treatment when some people in the UC arm will have to pay a prescription charge.

4.7 Flow Chart of Study Procedures



• Data collected as per the schedule of assessment below • Participants lost to follow-up considered to be smoking • **Analysis (n=443)**	• Data collected as per the schedule of assessment below • Participants lost to follow-up considered to be smoking • **Analysis (n=443)**

4.8 Schedule of Assessment

	Study session							
Measures/ Procedures	**Baseline**	**TQD**	**TQD+1 week**	**TQD+2 weeks**	**TQD+3 weeks**	**TQD+4 weeks**	**TQD+24 weeks**	**TQD+52 weeks**
Informed consent	X							
Baseline questionnaire	X							
Current Illness	X		X	X	X	X	X	X
Current medication	X		X	X	X	X	X	X
Randomisation		X						
Commitment form		X						
CO validation	X	X	X	X	X	X		X (if report abstinence or at least 50% reduction)
MPSS	X	X	X			X		
Smoking status/CPD	X	X	X	X	X	X	X	X
Adverse reactions			X	X	X	X	X	X
EC/NRT ratings			X			X		
Quantity/dose of EC/NRT used and helpfulness		X	X	X	X	X	X	X
EC dispensed, demonstration on first use		X		X				
NRT* dispensed, demonstration on first use		X		X		X		
EQ5D questionnaire	X						X	X
Smoking cessation service and health service use	X						X	X

* Dispensing sessions may differ slightly between sites depending on local SSS practices

4.9 End of Study Definition

The study would be completed and the REC informed after the final attempt to collect 12 month follow-up data from the last randomised participant.

4.10 Subject Withdrawal

Participants will be able to withdraw from the study at any time. This will not put at risk their usual medical care. Unless withdrawn participants request otherwise, data collected up to the point of their withdrawal will be used in the study analysis. Participants will be withdrawn if they withdraw their consent to participate. We do not foresee any other reasons to withdraw participants.

4.11 Data Collection and Follow up for Withdrawn Subjects

Participants that withdraw from the study would be followed up at weeks 4, 24 and 52, unless they did not wish to be contacted.

5 Adverse event/reaction reporting

5.1 General Definitions

5.1.1 Adverse Event (AE) and Adverse Reaction (AR)

An AE is any untoward medical occurrence in a subject to whom the study product has been administered, including occurrences which are not necessarily caused by or related to that product. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporarily associated with the use of the study product.

All AEs judged by either the reporting investigator or the Sponsor as having a reasonable causal relationship to the study treatment qualify as an AR.

5.1.2 Serious Adverse Event (SAE) and Serious Adverse Reaction (SAR)

An SAE/SAR fulfils at least one of the following criteria:

- Is fatal – results in death
- Is life-threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

5.2 Investigators Assessment

5.2.1 Seriousness

Adverse events/reactions will be assessed for seriousness according to the definitions given in section 5.1.2.

5.2.2 Causality

The causality of all serious adverse events/reactions will be assessed in relation to the trial treatment by the local PI and the CI. The following ARs are

deemed potentially related to the study treatment: nausea, throat irritation and sleep disturbance.

5.2.3 Severity

The severity of the event/reaction will be assessed according to the following terms and assessments. The intensity of an event should not be confused with the term “serious” which is a regulatory definition based on patient/event outcome criteria.

Mild: Some discomfort noted but without disruption of daily life
Moderate: Discomfort enough to affect/reduce normal activity
Severe: Complete inability to perform daily activities and lead a normal life

5.3 Notification and reporting Adverse Events or Reactions

Data on ARs, SARs and SAEs will be collected. If the AR is **not** defined as SERIOUS, the AR will be recorded in the CRF and the participant will be followed up by the research team. All ARs will be documented in the CRF.

5.4 Notification and Reporting of Serious Adverse Events/Reactions

All SAEs including SARs will be recorded in the subjects’ notes, the CRF, the sponsor SAE form and reported to the co-ordinating site. **Related and unexpected SAE’s should be reported to the sponsor** at research.safety@bartshealth.nhs.uk or by fax on: 0207 882 7276) within 24 hours of PI or co-investigators becoming aware of the event. Nominated co-investigators can be authorised to sign the SAE forms in the absence of the CI at the co-ordinating site or the PI at the participating sites. The original and any subsequent follow up of SAE Forms together with the fax confirmation sheet must be kept with the investigator site file at the study site.

Additionally related and unexpected SAE’s will be reported to the Ethics committee within 15 days.

6 Statistical Considerations

6.1 Primary Endpoint

CO validated sustained abstinence rates at 52 weeks post–TQD

6.2 Secondary Endpoints

- CO validated sustained abstinence rates at 4 and 24 weeks post–TQD
- CO validated sustained abstinence rates between 24 and 52 weeks
- 7-day point prevalence abstinence at 4, 24 and 52 weeks
- Smoking reduction in participants who did not achieve full abstinence
- Treatment ratings (e.g. satisfaction, helpfulness)

- Changes in urges to smoke and other tobacco withdrawal symptoms at 1 and 4 weeks.
- Adverse reactions
- Cost-efficacy of the interventions.

Abstinence at 4 weeks after TQD would be defined as a self-report of no smoking of conventional cigarettes (not a puff) for the previous 2 weeks, validated by a CO reading of <8ppm. Participants who do not provide a CO reading at Week 4 will be considered to be smoking. 24 and 52 week sustained abstinence will be calculated in accordance with the Russell Standard [50] as a self-report of smoking no more than 5 cigarettes since 2 weeks post-TQD. This self-report will be validated by CO readings as above for the 52 week follow-up. Participants lost to follow-up or not providing biochemical validation will be included as non-abstainers.

6.3 Sample Size

From extensive past experience, the 12-month validated abstinence rate (Primary outcome) associated with UC in our setting is 14% [51]. Our projection of a feasible rate with the EC is based on our work and two published studies. Our recent work [52] suggests that EC delivers nicotine quickly, with Tmax occurring within 5 minutes. This is similar to nicotine nasal spray. In a comparative study of the nasal spray + patch versus patch alone, 1-year abstinence rates were 27% vs. 11%, RR= 2.45 [53]. More relevant, in a recent cohort study a second generation EC achieved 36% CO validated abstinence at 6-months [54]. Assuming 25% relapse between 6 and 12 months [55], this would translate to a 1-year rate of 27%. Relative to our assumed UC rate, this would give RR = 1.9. However, in deciding an appropriate sample size for this study we have been more conservative. We wish to detect a RR of 1.7 (EC rate = 24%) with 0.95 power, but also have reasonable power (say, 0.75) if the RR should be as low as 1.5 (EC rate = 21%). This latter figure would still represent a clinically significant difference. To achieve these levels of power (2-sided, alpha = 0.05, continuity correction), a total of 886 participants (443 in each group) are required.

If we find no significant difference in abstinence rates between the study arms then we will undertake a non-inferiority analysis. Our sample size of 886 will provide 90% power to exclude a difference in favour of the standard group of more than 5%.

6.4 Statistical Analysis

Analyses will be undertaken after the last participant has completed the 12-month follow-up and the database has been locked.

For the primary analysis the proportion of people remaining abstinent at a year will be compared between the study arms using Chi-squared test with a secondary logistic regression adjusted for study site, sex, age, education, marital status, occupation, entitlement to free prescriptions, ethnicity, daily cigarette consumption, FTCD, age started smoking, partner smoking status, previous smoking cessation medicines used.

For the secondary analyses, we will examine the differences between study arms in the proportions of participants with sustained abstinence at 4, 24 and 52 week follow-up, and sustaining a 50% or greater reduction in baseline cigarette consumption and CO levels at 52 weeks, using Chi-squared test/logistic regression. The frequency of

adverse reactions will also be compared between arms. Between-group differences in urges to smoke and other tobacco withdrawal symptoms will be examined using ANOVA, controlling for baseline ratings. We will also examine time to relapse in a secondary analysis using a Cox analysis with model adequacy assessed by cumulative martingale residuals. An intention to treat analysis will be used with participants lost to follow-up or not providing biochemical validation included as non-abstainers [50]. A sensitivity analysis will be conducted with only participants who attended at least one treatment session from the TQD included.

Economic analyses

The trial will include an incremental cost-effectiveness analysis of EC over and above UC. Intervention and UC costs will be estimated using local costs of staff time, overheads and smoking cessation aids used in each trial arm. Patients will be asked to complete a questionnaire to record their utilisation of smoking cessation materials and services. This will enable a distribution of patient costs to be constructed and secondary analysis of the relationship between patient cost and outcome. The EQ-5D [49] will be completed by patients at baseline, 6 and 12 months with population values attributed to estimate Quality Adjusted Life Years (QALYs). The QALY change will be calculated using the area under the curve method [56]. Patient costs will be combined with QALY changes to estimate the incremental cost per QALY of EC over and above usual care at follow up. The health economic analysis will use existing models to estimate the potential long-term health care cost savings from smokers quitting smoking as a result of the intervention. These will be combined with longer term health utilities from published studies according to smoking status. The combination of trial data and health utility data will provide inputs to a longer term health economic model to estimate the longer term QALYs and cost per QALY gained.

We will construct cost-acceptability curves [56] to demonstrate the probability that EC is more cost-effective than usual care at a range of threshold values for a QALY.

7 Data Handling & Record Keeping

7.1 Confidentiality

Only study personnel will have access to study data. We will not request any patient identifiable data or medical information about participants from their other doctors (hospital or general practitioner, GP).

The Participants' GPs will be advised of their participation in the study, providing the participant gives consent to this. If the participant does not wish their GP to be informed, this will not prevent them from taking part in the study.

All information will be kept confidential, as per normal practice for patients attending the SSS. Copies of all documents regarding the study will be kept in the trial master file (TMF) and/or relevant site file. Participants will be assigned a trial ID number.

7.2 Study Documents

- A signed protocol and any subsequent amendments
- Current/Superseded Patient Information Sheets (as applicable)
- Current/Superseded Consent Forms (as applicable)
- Indemnity documentation from sponsor
- Conditions of Sponsorship from sponsor
- Conditional/Final R&D Approval
- Ethics submissions/approvals/correspondence
- CVs of CI and site staff
- GCP certificates of study and site staff
- Delegation log
- Patient identification log
- Screening log
- Enrolment log
- Correspondence relating to the trial

7.3 Case Report Form

Appropriately trained staff will be responsible for ensuring the correct sections are completed at the relevant time-points throughout the study. All completed CRFs will be reviewed and signed off by the PI.

7.4 Record Retention and Archiving

All information relevant to the study will be archived and retained for 20 years at the Barts Health NHS Trust facility in Prescot Street. Local site files will be archived according to local procedures, for a minimum of 20 years. Electronic data (which will not include participants' personal data) will be kept on a Barts' CTU secure online database for 20 years, following the CTUs SOP on electronic archiving. Sponsor will be informed in writing when and where all data is archived.

7.5 Compliance

The CI and Site PIs will ensure that the trial is conducted in compliance with the principles of the Declaration of Helsinki (1996), and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework, sponsor's policies and procedures and any subsequent amendments.

7.6 Clinical Governance Issues

7.6.1 Ethical Considerations

This protocol and any subsequent amendments, along with any accompanying material provided to the patient in addition to any advertising material will be submitted by the Chief Investigator to a Research Ethics Committee.

7.7 Quality Control and Quality Assurance

7.7.1 Summary Monitoring Plan

This study will be subject to the Quality Control (QC)/Quality Assurance (QA) system of the Joint BH/QMUL Research Management Office (JRMO).

Monitoring will be proportional to the objective, scope, design, size, complexity and risks of the project. The JRMO will risk assess the trial in line with the JRMO risk assessment standard operating procedure. The trial's risk assessment will assist the JRMO in the trial's final monitoring design format and schedule. The monitoring design will be detailed in the final monitoring plan and signed by the CI. A Copy of the plan will be kept in the TMF. The CI will ensure that this agreement/wording is not altered without written authorisation (email confirmation) from the JRMO; all new versions will be signed. The study manager will monitor the host sites using the same monitoring design and frequency as for the main site.

CI/study team will notify the GCP team once the first patient has been consented onto the trial at each site. The JRMO will update the monitoring schedule with the date the first monitoring event is due.

7.8 Audit and inspection

The investigator will permit study-related monitoring, audits, and inspections by the Ethics Committee, the sponsor, Barts CTU, government regulatory bodies of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.).

7.9 Reporting of Serious breaches in GCP or trial protocol

All breaches and potential breaches in GCP or trial protocol will be logged by the coordinating office and reported to the Sponsor and Barts CTU within 24 hours. Any breach deemed serious by the sponsor will be reported to the REC within 7 days as per the REC procedure.

7.10 Trial Committees

A Study Steering Committee (SSC) and Data Monitoring and Ethics Committee (DMEC) will be convened. A trial management committee (TMC) will also be convened. The TMC will consist of Dr Hayden McRobbie (chief investigator), Dr Katherine Myers Smith (study manager), Anna Phillips (researcher), Professor Peter Hajek (co-investigator) and an appropriate member of the Barts CTU.

7.11 Publication Policy

Study results will be written up for submission to international conferences and peer-reviewed journals. No participant will be identifiable from any publication or report.

8. Indemnity

The JRMO has arranged for suitable indemnity concerning negligent harm to be in place for this study. Indemnity will be provided by Queen Mary, University of London.

The insurance that Queen Mary, University of London has in place provides "No Fault Compensation" for participants which provides an indemnity to participants for non-negligent harm.

9. References

1 Walker N, Howe C, Bullen C, *et al.* The combined effect of very low nicotine content cigarettes, used as an adjunct to usual Quitline care (nicotine replacement therapy and behavioural support), on smoking cessation: a randomized controlled trial. *Addict Abingdon Engl* 2012;**107**:1857–67. doi:10.1111/j.1360-0443.2012.03906.x

2 Goniewicz ML, Knysak J, Gawron M, *et al.* Levels of selected carcinogens and toxicants in vapour from electronic cigarettes. *Tob Control* 2014;**23**:133–9.

3 Goniewicz ML, Kuma T, Gawron M, *et al.* Nicotine levels in electronic cigarettes. *Nicotine Tob Res* 2013;**15**:158–66.

4 Goniewicz M, Hajek P, McRobbie H, *et al.* Do electronic cigarettes need accurate labelling of nicotine content? 2013.

5 Benowitz NL, Goniewicz ML. The regulatory challenge of electronic cigarettes. *JAMA* 2013;**310**:685–6.

6 Bullen C, Howe C, Laugesen M, *et al.* Electronic cigarettes for smoking cessation: a randomised controlled trial. *Lancet* 2013;**382**:1629–37. doi:10.1016/S0140-6736(13)61842-5

7 Bullen C, McRobbie H, Thornley S, *et al.* Effect of an electronic nicotine delivery device (e cigarette) on desire to smoke and withdrawal, user preferences and nicotine delivery: randomised cross-over trial. *Tob Control* 2010;**19**:98–103. doi:10.1136/tc.2009.031567

8 Bullen C, Williman J, Howe C, *et al.* Study protocol for a randomised controlled trial of electronic cigarettes versus nicotine patch for smoking cessation. *BMC Public Health* 2013;**13**:210.

9 Dawkins L, Corcoran O. Acute electronic cigarette use: nicotine delivery and subjective effects in regular users. *Psychopharmacology (Berl)* 2014;**231**:401–7.

10 Dawkins L, Turner J, Crowe E. Nicotine derived from the electronic cigarette improves time-based prospective memory in abstinent smokers. *Psychopharmacol Berl* 2013;**227**:377–84. doi:10.1007/s00213-013-2983-2

11 Dawkins L, Turner J, Hasna S, *et al.* The electronic-cigarette: effects on desire to smoke, withdrawal symptoms and cognition. *Addict Behav* 2012;**37**:970–3.

12 Dawkins L, Turner J, Roberts A, *et al.* 'Vaping' profiles and preferences: an online survey of electronic cigarette users. *Addiction* 2013;**108**:1115–25. doi:10.1111/add.12150

13 Goniewicz Maciej L, Lingas Elena O, Hajek Peter. Patterns of electronic cigarette use and user beliefs about their safety and benefits: An Internet survey. [References]. *Drug Alcohol Rev* 2013;**32**:133–40.

14 Goniewicz ML, Zielinska-Danch W. Electronic cigarette use among teenagers and young adults in Poland. *Pediatrics* 2012;**130**:e879–85.

15 Hajek Peter. Commentary on Wagener et al. (2012): E-cigarettes: A vulnerable promise. *Addict Abingdon Engl* 2012;**107**:1549.

16 Hajek P. Electronic cigarettes for smoking cessation. *Lancet* 2013;**382**:1614–6.

17 Hajek P, Foulds J, Le Houezec J, *et al.* Should e-cigarettes be regulated as a medicinal device? *Lancet Respir Med* 2013;**1**:429–31.

18 Kosmider L, Knysak J, Goniewicz ML, *et al.* [Electronic cigarette--a safe substitute for tobacco cigarette or a new threat?]. *Przegl Lek* 2012;**69**:1084–9.

19 Kralikova E, Kubatova S, Truneckova K, *et al.* The electronic cigarette: what proportion of smokers have tried it and how many use it regularly? *Addiction* 2012;**107**:1528–9. doi:10.1111/j.1360-0443.2012.03916.x

20 Kralikova E, Novak J, West O, *et al.* Do e-cigarettes have the potential to compete with conventional cigarettes? A survey of conventional cigarette smokers' experiences with e-cigarettes. *Chest* 2013;**44**:1609–14. doi:10.1378/chest.12-2842

21 McRobbie H, Bullen C, Hartmann-Boyce J, *et al.* Electronic cigarettes for smoking cessation and reduction. *Cochrane Database Syst Rev* 2014;**12**:CD010216. doi:10.1002/14651858.CD010216.pub2

22 Dockrell M, Morison R, Bauld L, *et al.* E-Cigarettes: Prevalence and Attitudes in Great Britain. *Nicotine Tob Res* 2013;**15**:1737–44. doi:10.1093/ntr/ntt057

23 Siegel MB, Tanwar KL, Wood KS. Electronic Cigarettes As a Smoking-Cessation Tool. *Am J Prev Med* 2011;**40**:472–5. doi:10.1016/j.amepre.2010.12.006

24 Etter J-F. Electronic cigarettes: a survey of users. *BMC Public Health* 2010;**10**:231.

25 Li J, Bullen C, Newcombe R, *et al.* The use and acceptability of electronic cigarettes among New Zealand smokers. *N Z Med J* 2013;**126**:48–57.

26 McMillen R, Maduka J, Winickoff J. Use of emerging tobacco products in the United States. *J Environ Public Health* 2012;**2012**:989474.

27 Eissenberg T. Electronic nicotine delivery devices: ineffective nicotine delivery and craving suppression after acute administration. *Tob Control* 2010;**19**:87–8. doi:10.1136/tc.2009.033498

28 Vansickel AR, Cobb CO, Weaver MF, *et al.* A clinical laboratory model for evaluating the acute effects of electronic 'cigarettes': nicotine delivery profile and cardiovascular and subjective effects. *Cancer Epidemiol Biomarkers Prev* 2010;**19**:1945–53. doi:10.1158/1055-9965.EPI-10-0288

29 Nides MA, Leischow SJ, Bhatter M, *et al.* Nicotine blood levels and short-term smoking reduction with an electronic nicotine delivery system. *Am J Health Behav* 2014;**38**:265–74.

30 Vansickel AR, Weaver MF, Eissenberg T. Clinical laboratory assessment of the abuse liability of an electronic cigarette. *Addiction* 2012;**107**:1493–500. doi:10.1111/j.1360-0443.2012.03791.x

31 Vansickel AR, Eissenberg T. Electronic Cigarettes: Effective Nicotine Delivery After Acute Administration. *Nicotine Tob Res* 2012;**15**:267–70. doi:10.1093/ntr/ntr316

32 Benowitz NL, Jacob P 3rd, Herrera B. Nicotine intake and dose response when smoking reduced-nicotine content cigarettes. *Clin Pharmacol Ther* 2006;**80**:703–14. doi:10.1016/j.clpt.2006.09.007

33 Caponnetto P, Polosa R, Russo C, *et al.* Successful smoking cessation with electronic cigarettes in smokers with a documented history of recurring relapses: a case series. *J Med Case Rep* 2011;**5**:585. doi:10.1186/1752-1947-5-585

34 Farsalinos KE, Romagna G. Chronic idiopathic neutrophilia in a smoker, relieved after smoking cessation with the use of electronic cigarette: a case report. *Clin Med Insights Case Rep* 2013;**6**:15–21. doi:10.4137/CCRep.S11175

35 Schneiderhan ME. A Case Report of Patient-Initiated E-Cigarette Use and Resulting 5-Months Smoking Cessation. *J Pharm Pract* 2012;**25**:297.

36 Polosa R, Caponnetto P, Morjaria JB, *et al.* Effect of an electronic nicotine delivery device (e-Cigarette) on smoking reduction and cessation: a prospective 6-month pilot study. *BMC Public Health* 2011;**11**:786. doi:10.1186/1471-2458-11-786

37 Polosa R, Morjaria JB, Caponnetto P, *et al.* Effectiveness and tolerability of electronic cigarette in real-life: a 24-month prospective observational study. *Intern Emerg Med* 2013;:[Epub ahead of print]. doi:10.1007/s11739-013-0977-z

38 Caponnetto P, Auditore R, Russo C, *et al.* Impact of an electronic cigarette on smoking reduction and cessation in schizophrenic smokers: a prospective 12-month pilot study. *Int J Environ Res Public Health* 2013;**10**:446–61. doi:10.3390/ijerph10020446

39 Caponnetto P, Campagna D, Cibella F, *et al.* EffiCiency and Safety of an eLectronic cigAreTte (ECLAT) as Tobacco Cigarettes Substitute: A Prospective 12-Month Randomized Control Design Study. *PLoS One* 2013;**8**:e66317. doi:10.1371/journal.pone.0066317

40 Etter J-F, Bullen C. Electronic cigarette: users profile, utilization, satisfaction and perceived efficacy. *Addiction* 2011;**106**:2017–28.

41 Farsalinos KE, Romagna G, Tsiapras D, *et al.* Evaluation of electronic cigarette use (vaping) topography and estimation of liquid consumption: implications for research protocol standards definition and for public health authorities' regulation. *Int J Environ Res Public Health Electron Resour* 2013;**10**:2500–14.

42 Cameron JM, Howell DN, White JR, *et al.* Variable and potentially fatal amounts of nicotine in e-cigarette nicotine solutions. *Tob Control* 2014;**23**:77–8.

43 Kloosterman K. Electronic Cigarette Kills Toddler in Israel. Green Prophet 29 May. 2013.Archived at http://www.webcitation.org/6QnAb1lS9 on 3 July 2014

44 National Institute for Health and Care Excellence. Tobacco harm reduction (PH45). London: : National Institute for Health and Care Excellence 2013. www.nice.org.uk/PH45 (accessed 9 Sep2014).

45 Hajek P, Etter J-F, Benowitz N, *et al.* Electronic cigarettes: review of use, content, safety, effects on smokers and potential for harm and benefit. *Addict Abingdon Engl* 2014;**109**:1801–10. doi:10.1111/add.12659

46 Hajek P. Withdrawal-oriented therapy for smokers. *Br J Addict* 1989;**84**:591–8.

47 Fagerström K. Determinants of tobacco use and renaming the FTND to the Fagerstrom Test for Cigarette Dependence. *Nicotine Tob Res Off J Soc Res Nicotine Tob* 2012;**14**:75–8. doi:10.1093/ntr/ntr137

48 West R, Hajek P. Evaluation of the mood and physical symptoms scale (MPSS) to assess cigarette withdrawal. *Psychopharmacology (Berl)* 2004;**177**:195–9. doi:10.1007/s00213-004-1923-6

49 Richardson G, Manca A. Calculation of quality adjusted life years in the published literature: a review of methodology and transparency. *Health Econ* 2004;**13**:1203–10. doi:10.1002/hec.901

50 West R, Hajek P, Stead L, *et al.* Outcome criteria in smoking cessation trials: proposal for a common standard. *Addict Abingdon Engl* 2005;**100**:299–303. doi:10.1111/j.1360-0443.2004.00995.x

51 Ferguson J, Bauld L, Chesterman J, *et al.* The English smoking treatment services: one-year outcomes. *Addict Abingdon Engl* 2005;**100 Suppl 2**:59–69. doi:10.1111/j.1360-0443.2005.01028.x

52 Hajek P, Goniewicz ML, Phillips A, *et al.* Nicotine intake from electronic cigarettes on initial use and after four weeks of regular use. *Nicotine Tob Res Off J Soc Res Nicotine Tob* Published Online First: 13 August 2014. doi:10.1093/ntr/ntu153

53 Blondal T, Gudmundsson LJ, Olafsdottir I, *et al.* Nicotine nasal spray with nicotine patch for smoking cessation: randomised trial with six year follow up. *BMJ* 1999;**318**:285–8.

54 Polosa R, Caponnetto P, Maglia M, *et al.* Success rates with nicotine personal vaporizers: a prospective 6-month pilot study of smokers not intending to quit. *BMC Public Health* 2014;**14**:1159. doi:10.1186/1471-2458-14-1159

55 Stapleton J. Cigarette smoking prevalence, cessation and relapse. *Stat Methods Med Res* 1998;**7**:187–203.

56 Fenwick E, Claxton K, Sculpher M. Representing uncertainty: the role of cost-effectiveness acceptability curves. *Health Econ* 2001;**10**:779–87.