Randomised controlled trial to test the effects of smoking cessation interventions for smokers attending for lung cancer screening in Yorkshire (YorQuit)

Version 2.4
15/12/2025

Short title: Supporting people in Yorkshire who smoke to Quit: The YorQuit study

Trial Registration: ISRCTN10364896

IRAS Project ID: 341699

Trial Sponsor: University of Nottingham

Sponsor reference: 24050

Funding Source: Yorkshire Cancer Research

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SYNOPSIS

Title	Randomised controlled trial to test the effects of smoking cessation interventions for smokers attending for lung cancer screening in Yorkshire
Acronym	*YorQuit*
Short title	Supporting people in Yorkshire who smoke to Quit: The YorQuit study
Chief Investigator	Professor Rachael Murray (University of Nottingham)
Medical Expert	Professor Matthew Callister (University of Leeds)
Objectives	To test the acceptability, accessibility, effectiveness, and cost effectiveness of smoking cessation interventions within Lung Cancer Screening programmes
Trial Configuration	A pragmatic, parallel-group, three-arm, randomised controlled trial with embedded economic and process evaluations
Setting	Mobile Lung Screening units sited in various locations in and around Bradford, Leeds, Hull and Manchester as part of Lung Cancer Screening (LCS)
Sample size estimate	Assuming a significance level of 1.7% to allow for the three pairwise comparisons, 516 low dose CT (LDCT) screen-eligible smokers per treatment group will give 90% power to detect significant differences in the primary outcome of 10%. In addition, 387 LDCT screen-ineligible participants will be recruited and randomised to the study. The figure of 387 LDCT screen-ineligible is not informed by a power calculation and is based on the expected proportion of invitees not eligible for LDCT screening of 20%.
Number of participants	1935 (1548 screen eligible and 387 screen ineligible) in total which equates to 645 (516 screen eligible and 129 screen ineligible) per group
Eligibility criteria	Study eligible participants will be selected from invitees/returners to the Lung Cancer Screening programme which operates from various mobile screening units locations in Leeds, Hull, Bradford District and Craven, North Kirklees, and Manchester Lung Cancer Screening teams. **Inclusion criteria** Smoked at least one cigarette in last 7 days at point of consent 55-75 years of age Able to provide informed consent **Exclusion criteria** Previously randomised to YorQuit
Description of interventions	**Treatment group 1: Digital app and referral to community stop smoking services** Study participants will be referred to their local stop smoking services as per current recommendations. In addition, participants who have access to a

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	smart phone will also be offered a subscription to the "Smoke Free" digital app. As part of the Smoke Free app subscription participants will be provided with an 'onboarding' session to support with downloading, installing, and using the app and either NRT (Nicotine Replacement Therapies) or pharmacotherapies and/or e-cigarettes. **Treatment group 2: Telephone intervention** Participants randomised to treatment group 2 will receive an initial telephone consultation with a Smoking Cessation Practitioner (SCP), trained to National Centre for Smoking Cessation and Training standards. The SCP will explain, advise, and deliver smoking cessation support in accordance with NHS Stop Smoking Service best practice (and NICE NG209 guidance). This will include one-to-one behavioural support and provision of pharmacotherapy. Participants will be offered free, commercially available nicotine replacement therapies and/or a commercially available e cigarette and/or GP/pharmacist/secondary care-prescribed pharmacotherapies as appropriate and according to participant preference. Bupropion, Varenicline or Cytisine (where available and if not contraindicated) will be offered if requested via GP/pharmacist/secondary care prescription. If the participant requests NRT and/or e-cigarette (a choice of liquid flavours will be available) a supply of products will be posted to the participant's home address. The support described will be delivered for as long as required by the participant up to a maximum of 12-weeks from the Commencement of Smoking Cessation Intervention (CSCI)*. **Treatment group 3: Telephone intervention plus financial incentive** Study processes in treatment group 3 will be the same as described for treatment group 2. In addition, participants will be provided with a financial incentive in the form of a Love2shop or Amazon voucher if they are CO-validated (<10ppm) as not smoking at the 4 week (£25), 3 month (£50) and 12 month (£100) follow up assessments. *Each treatment group will have a 2-week 'set-up' period before the CSCI.
Duration of study	Trial start: April 2024 Recruitment: June 2025 for 24 months Trial end: April 2028 12-months duration per participant
Randomisation and blinding	Enrolled participants will be randomised to each treatment group using block randomisation, stratified by site and LDCT eligibility, with an allocation ratio of 1:1:1. Blocks will be randomly permuted and of randomly varying size. The randomisation schedule will be generated by a trial statistician not otherwise involved in the recruitment or randomisation of individuals, and implemented via a central, web-based randomisation system designed and managed by the York Trials Unit (YTU).
Outcome measures	**Primary outcome measure:** 7-day point prevalent Carbon Monoxide (CO) validated smoking cessation at three months after the CSCI **Secondary outcome measures:** • Uptake of stop smoking support offered

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	• 7-day point prevalent CO validated and self-reported abstinence from smoking at 4-weeks after the CSCI • 7-day point prevalent self-reported abstinence from smoking 3-months after the CSCI • 7-day point prevalent CO validated and self-reported abstinence from smoking 12-months after the CSCI • Prolonged CO validated and self-reported abstinence from smoking at 3 and 12-months after the CSCI • Acceptability of the intervention delivered in each treatment group • Reasons for decline in those not accepting stop smoking support • EQ-5D-5L score • Use of smoking cessation support and other healthcare resources • Motivation to quit (4 weeks, 3 months and 12 months after CSCI) • Self-efficacy/confidence in stopping smoking/staying quit (4 weeks, 3 months and 12 months after CSCI)
Statistical methods/ Cost effectiveness and Qualitative evaluation	Baseline data will be summarised descriptively by treatment group. All outcome data at all timepoints will be summarised descriptively by treatment group. The primary analysis of the primary outcome will be carried out on an intention-to-treat basis using a mixed-effects logistic regression model, with the location of the LHC mobile unit at the point of recruitment being included as a random effect. Randomised treatment group, age, sex, smoking severity, and other clinically important participant-level baseline covariates will be included as fixed-effects. An additional sensitivity analysis will also impute missing data under the missing at random assumption via multiple imputation by chained equations. Secondary outcomes will be analysed using appropriate regression techniques. **Cost effectiveness analyses** An incremental cost-effectiveness analysis will be conducted from an NHS and personal social services perspective. Patient costs and quality-adjusted life years (QALYs) will be combined to estimate incremental cost-effectiveness ratios (ICERs) in terms of cost per QALY, with a primary endpoint of 12-months post-CSCI. Uncertainty in the ICER estimates will be assessed using the bootstrap re-sampling technique. An additional analysis will use quit rates as the outcome measure, indicating the cost-effectiveness of achieving one additional quitter at various time points. A Markov model will be used to project lifetime costs, QALYs, and cost-effectiveness for the three interventions. **Qualitative analyses** Anonymised interview transcripts will be analysed using a Framework approach. This approach will enable us to map thematic differences/ similarities within and between groups e.g. for treatment group 1 participants, comparisons could be made between those who utilised a digital app and those who were referred to a local stop smoking service. Data will be coded both deductively (informed by the COM-B Model) and inductively, deriving from the spontaneous accounts from participants. Initial readings will facilitate familiarisation and will lead to the generation of initial codes. Further reading and immersion will result in more substantive themes and sub-themes, resulting in the generation of an analytical framework.

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Please note in the protocol we refer to participant treatment with NRT and e-cigarettes in the treatment groups in weeks (up to12-weeks) and data collection using a combination of weeks and months (4 weeks, 3-months and 12 months)

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ABBREVIATIONS

AE	Adverse Event
ASH	Action on Smoking and Health
CACE	Complier Average Causal Effect
CI	Chief Investigator
CO	Carbon Monoxide
CONSORT	Consolidated Standard of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
COVID	Coronavirus
CRF	Case Report Form
DMC	Data Monitoring Committee
CSCI	Commencement of Smoking Cessation Intervention
E-cigarette	Electronic cigarette
ECRF	Electronic Case Report Form
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GP	General Practitioner
HRA	Health Research Authority
ICER	Incremental Cost Effectiveness Ratio
ICF	Informed Consent Form
LCS	Lung Cancer Screening
LDCT	Low Dose Computed Tomography
LHC	Lung Health Check
MHRA	Medicines and Healthcare Products Regulatory Authority
NCSCT	National Centre for Smoking Cessation Training
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NLST	National Lung Screening Trial
NRT	Nicotine Replacement Therapy
PI	Principal Investigator at a local centre
PIS	Participant Information Sheet
PPIE	Patient and Public Involvement and Engagement
PPM	Particles per million
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-Adjusted Life Year
R&D	Research and Development department
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
REDCAP	Research Electronic Data Capture
SCP	Smoking Cessation Practitioner
SSW	Study Support Worker
TANG	Tobacco and Nicotine Discussion Group
TMG	Trial Management Group
TSC	Trial Steering Committee
UCL	University College London
UK	United Kingdom
YESS	Yorkshire Enhanced Stop Smoking Study
YLST	Yorkshire Lung Screening Trial
YTU	York Trials Unit

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TRIAL / STUDY BACKGROUND INFORMATION AND RATIONALE

Lung cancer is the third most common cancer in the UK and the leading cause of cancer death; both incidence and mortality are highest in the most disadvantaged groups of society(1). Smoking is the cause of over 70% of lung cancer cases in the UK(1) and an even greater proportion of lung cancer deaths(2). Smoking cessation is the most effective way to reduce risk from lung cancer(3), and quitting at any age reduces the risk of dying from smoking-related diseases(4). For those aged 65, it is estimated that those who quit smoking between the ages of 55 and 59 will have half the risk of lung cancer death compared to current smokers(5). Sheikh et al. reported that for high-risk individuals aged 55-74, seven years of smoking cessation reduced lung-cancer specific mortality by 20%; in those diagnosed with non-small cell lung cancer, quitting smoking resulted in a 21.6 months longer median overall survival time compared to those who continued to smoke, and reduced risk for all-cause mortality and disease progression(6). Furthermore, continued smoking in cancer patients has been shown to increase the risk of developing a second primary cancer(3).

The effects of smoking cessation extend beyond lung cancer, both in terms of health benefit and cost-effectiveness. The 2020 Surgeon General report identified eleven additional cancers caused by smoking, the risk of all can be reduced with smoking cessation(7). Further, people who smoke are also at risk of premature death due to chronic obstructive pulmonary disease (COPD), heart disease and stroke. In 2011, the US National Lung Screening Trial (NLST) demonstrated a 20% reduction in lung cancer specific mortality, and a 6.7% reduction in all-cause mortality by annual low-dose CT (LDCT) screening. Modelling by Cao and colleagues have highlighted that adding tobacco treatment to lung cancer screening will decrease deaths by an additional 14% and increase the overall number of life years gained by 81%(8). Given long term conditions such as those listed above are more prevalent in more deprived groups (people in the poorest social class have a 60 per cent higher prevalence than those in the richest social class and 30 per cent more severity of disease(9)), any intervention addressing these conditions has potential to decrease health inequalities, and smoking cessation is one of the most effective interventions available.

CURRENT EVIDENCE ON SMOKING CESSATION IN LUNG CANCER SCREENING

Currently available evidence suggests that smoking cessation rates in LCS trials are promising, with more intensive, personalised, and multi-modality interventions delivered by a clinician appearing to be most successful. However further research is needed to understand optimal treatment types, timing and content to maximise the potential benefit(10), and the impact of integrating stop smoking provision within the Lung Cancer Screening (LCS) programme.

The first and one of only two published research studies to provide evidence regarding the integration of smoking cessation support within English LHC programmes comes from QuLIT(11). On randomly allocated days, QuLIT offered either immediate access to free pharmacotherapy to support quit attempts plus six sessions of face-to-face, one-to-one cessation support; or usual care, which comprised very brief advice. The trial was delivered as part of a LCS programme at the Royal Brompton Hospital in London and the authors reported 7-day point prevalent smoking abstinence of 21.5% in the intervention arm and 7.2% in the usual care arm. As a result of the Covid-19 pandemic, face-to-face support delivered as part of the QuLIT-1 trial was suspended and the trial modified to provide six sessions of remote smoking cessation support via telephone, with attempts to deliver the first call on the same day as the LCS (QuLIT-2)(12). All other study processes remained the same as in the QuLIT-1 trial. 152 individuals who smoked attended on intervention days and 163 on usual care days, with 112 and 115 smokers respectively providing 3-month follow up data and 32 and 14 smokers reporting 7-day point prevalent smoking abstinence (21.1% and

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8.6% respectively, assuming those not contactable were continuing to smoke). Of note, 80 smokers (52.6%) attending on intervention days explicitly declined contact from the smoking cessation practitioner (SCP) and a further 16 dropped out after the initial consultation.

The Yorkshire Enhanced Stop Smoking (YESS) study organised by the Chief Investigators (CI) tested the uptake and effectiveness of a co-located, opt out smoking cessation delivery model offered to all smokers attending for a lung health check (LHC)(13) as part of the Yorkshire Lung Screening Trial (YLST)(14) between December 2018 and December 2020. Smoking cessation support was offered in line with National Institute for Health and Care Excellence (NICE) PH48 guidance(15) comprising one face-to-face session of behavioural support at the time of the LHC and provision of pharmacotherapy. The study found that of 2150 eligible smokers attending for LCS, 89% agreed to a consultation with SCP at the time of the screening appointment. Of these, 84.5% agreed to ongoing cessation support and 20.1% of these were self-reported quit at 4-weeks (16.5% validated) (15% self-reported;12.4% validated of all eligible smokers)(16).

The YESS model continued into the second round of LCS as part of YLST and offered smoking cessation support to individuals who were unsuccessful in their quit attempt, who declined to accept smoking cessation support or did not attend for the baseline screening round. Provisional results indicate that 1905 (89%) eligible smokers agreed to meet the SCP on the mobile unit, of which,1609 (75%) agreed to ongoing smoking cessation support and 15% (n=323) self-reported a quit at 4-weeks.

SUMMARY OF CURRENT EVIDENCE, RESEARCH GAPS AND LIKELY POLICY DIRECTION

There is clear evidence from the YESS and QuLIT studies that provision of bespoke smoking cessation support alongside LCS is effective, with approximately 1 in 5 current smokers quitting within 4-weeks of attending for screening, increasing to 1 in 3 within three months. Various models are available for delivering bespoke smoking cessation services to screening attendees. The most resource-intensive approach is delivery of face-to-face smoking cessation interventions at the time of the first screening visit. However, research into possible smoking cessation interventions alongside screening needs to test options that are deliverable in the 'real-world' of a future national screening programme. The majority of LCS programmes in England are delivered in mobile units, and so provision of face-to-face services requires additional physical space on the mobile units to facilitate the initial consultation, a logistical concern for many candidate sites for participation in research studies. Whilst YESS and YLST were co-designed from the outset (and thus space for smoking cessation consultations was an integral part of the mobile unit provision), most current LCS mobile units do not have space in their current units, and provision of an additional adjacent mobile unit may cause problems due to the requirement for a larger 'footprint' in community locations such as supermarket car parks. Experience to date from other LCS programmes has indicated that some co-located services provided in additional mobile units have had to be dropped from certain screening locations where space is more limited.

As noted earlier, an alternative model, used by QuLIT-2 as a COVID-adaptation is to offer the initial consultation by telephone. Whilst there are clear logistical advantages to this arrangement, there is an obvious concern that services delivered entirely by phone may be less effective as the participant and SCP may be less able to develop a therapeutic relationship in the absence of a face-to-face meeting. However, comparing quit rates from QuLIT-2 and YESS (when considering all people currently smoking attending for screening) revealed similar smoking cessation rates indicating that the 'premium' of face-to-face contact over telephone support may not be as significant as initially suspected. However, telephone

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support compared to referral to local services has only been evaluated in one study (QuLIT-2) with a total recruitment of around 300 participants. There is therefore a need to confirm efficacy of this approach across multiple sites with a larger sample size to confirm that this is the optimal model of delivery.

Even with the impressive quit rates demonstrated by co-delivery of smoking cessation alongside screening (as shown in QuLIT-2 and YESS), still only 20 to 30% of participants successfully quit smoking during the follow-up period. There is therefore still an urgent need to explore interventions that might help most service users who do not currently quit. One of the most effective smoking cessation interventions from other contexts (e.g. pregnancy) has been financial incentives(17). Whilst financially rewarding successful quit attempts might appear somewhat unfair to the general population (in that these payments might be seen as essentially rewarding people who should perhaps never have taken up the habit), the amounts spent on financial incentives are likely to be outweighed by the potential long-term cost savings from treating fewer smoking-related illnesses if people successfully quit. However, again there is a need to test this intervention in the target population. Whilst efficacy in pregnancy is encouraging, we cannot assume that this approach will be efficacious in a screening population without specifically testing in this context.

Finally, in designing studies consideration needs to be given to what smoking cessation services might otherwise look like in due course. The current funding model of the LCS programme does not involve specific provision for smoking cessation services, and discussions with the National Cancer Programme at NHS England have indicated that this is unlikely to change in the foreseeable future. The default position therefore remains that individuals screened via LCS programmes who continue to smoke will be referred to local services. In addition, the Tobacco Dependency Programme at NHS England have indicated that digital provision of services is likely to form an increasingly prominent role in smoking cessation support. Whilst there are concerns from within the research community about this approach (specifically the potential for this to widen the 'digital divide' whereby less digitally literate people might be further disadvantaged(18)) this appears to be the clear national direction of travel and it is important that future studies are designed accordingly. A future study that demonstrated efficacy of a bespoke telephone-delivered service versus referral to local smoking cessation services without access to digital provision might no longer be considered relevant if future services increasingly rely on mobile-phone apps for delivery. Thus, despite some reservations about the appropriateness of digital resources for this population, including them in a usual-care arm might future-proof the results of this study.

TRIAL / STUDY OBJECTIVES AND PURPOSE

This study aims to compare two smoking cessation interventions (integrated telephone support and integrated telephone support plus a financial incentive) with usual care (referral to local stop smoking services and/or provision of a digital app*) for smokers who participate in four local LCS programmes.

*Provision of a digital app does not currently constitute usual care, but is a potential/future direction of travel, hence will be considered usual care for the purposes of this protocol

STUDY HYPOTHESIS

The study hypothesis is that providing gold standard stop smoking support delivered via telephone, by a SCP specifically trained to work with people who smoke and are at high risk for lung cancer, will be more acceptable and effective than referral to a community stop smoking service and/or use of a digital app. Further, the study hypothesis is also that provision of a financial incentive for successful quitting will further increase quit rates, over and above gold standard stop smoking support delivered via telephone alone.

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PURPOSE
The purpose of the study is to test the acceptability, accessibility, effectiveness and cost effectiveness of smoking cessation interventions within LCS programmes.

DETAILS OF PRODUCT(S)
This study is not a clinical trial of investigative medicinal products. All participants will be provided with advice and behavioral support plus up to12-weeks of free commercially available nicotine replacement therapies and/or a commercially available e-cigarette, or GP/pharmacist/secondary care-prescribed pharmacotherapies as appropriate and according to participant preference.

DESCRIPTION
In the absence of any specific contraindications, study participants will be offered NRT that are routinely provided by NHS stop smoking services for use in quit attempts, for example, any combination of patches, gum, lozenges, or mouth sprays will be made available. Participants in whom nicotine is contraindicated or who express a preference for an alternative to NRT will be referred to their GP, secondary care team, or an MK Medicals pharmacist and after a consultation, provided with a prescription for a course of Bupropion, Varenicline or Cytisine (where available*), with dosing as recommended in the British National Formulary (19-21). MK Medicals contract their dispensing of pharmacotherapies to their sister pharmacy company, Shri Pharmacy, who shall dispense medications to participants. They will be able to contact the participants directly prior to dispending medications. Dosing and products recommended and used for treatment groups will be decided according to information collected by the SCPs (employed to the study, local stop smoking service or the Smoke Free app) during weekly or fortnightly consultations with study participants. With permission, information related to product preference will be shared with the GP/pharmacist/secondary care team if they request a specific medication from those listed above. If pharmacotherapies are prescribed by the MK Medicals pharmacist (and dispensed by sister pharmacy company, Shri Pharmacy), notification of prescription will be sent to the GP by Shiri pharmacy for medical record documentation. NRT will be posted directly to participants homes via the supplier for NRT, MK Medicals and e-cigarette supplier, Totally Wicked.

E-cigarettes will be provided to participants who wish to use them, in line with the National Centre for Smoking Cessation and Training (NCSCT) guidelines(22). E-cigarettes and related supplies will be purchased from the reputable retailer ‘Totally Wicked’ and posted directly to the participants by the retailer within 24hrs of their consultation with the study SCP (72 hours if participant is seen on a Friday). The e-cigarette will be a third-generation tank model, as these have been demonstrated to achieve greater nicotine delivery than the earlier ‘cigalike’ models. Again, dosing and products recommended and used for all treatment groups will be decided according to information collected by the SCPs (employed to the study, local stop smoking service or the Smoke Free app) during weekly or fortnightly consultations with study participants.

MANUFACTURE
NiQuitin products and Bupropion are manufactured by Glaxo Smith Kline and Nicorette products by McNeil. Varenicline manufactured by Pfizer was withdrawn in October 2021 but a generic form of Varenicline is due to be reintroduced before the end of 2024. The licence for Cytisine is held by Bonteque Consulting Ltd in the UK on behalf of Aflofarm in Poland. Distribution of this medication is by Consilient Health, whose UK office is based in

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London(19). All the above products, when available, are licensed by the Medicines and Healthcare Products Regulatory Authority (MHRA) for use in promoting smoking cessation.

***Availability of pharmacotherapy products**

Participants will always be referred to their GP,secondary care team, or the MK Medicals pharmacist for pharmacotherapies. The availability of these products has changed over the years, but current availability is as follows: Varenicline - In October 2021, Department of Health and Social Care confirmed that there was no resupply date for Varenicline from Pfizer and an alternative supplier was not available. A nitrosamine-compliant, unlicensed (generic) Varenicline product has been available in the UK since 2023 and is due to be reintroduced to pharmacies before the end of 2024.
Bupropion - Production was withheld in December 2022 and a review of manufacturing processes undertaken. Bupropion was made available again in the UK in October 2023.
Cytisine - Available as a prescription only stop smoking medication from 22nd January 2024.

E- CIGARETTES

Third generation e-cigarettes, often called personal vaporisers or vapes have a battery linked to a heating element or coil (atomiser) and a 'tank.' The user fills the tank with their choice of e-liquid which may include flavours and contain nicotine in different concentrations (34). The user takes a puff to activate the heating coil, which vaporises the e-liquid, creating a vapour that can be inhaled.

The Tobacco Products Directive 2014/14/EU (TPD) (23) introduced new rules for nicotine-containing e-cigarettes and refill containers (Article 20) from May 2016, and amended in 2020 (24, 25). The MHRA is the competent authority for the notification scheme for e-cigarettes and refill containers in the UK and is responsible for implementing the majority of provisions under Article 20(24, 25). From 20 May 2016, the new requirements include:

- Restricting e-cigarette tanks to a capacity of no more than 2ml.
- Restricting the maximum volume of nicotine-containing e-liquid for sale in one refill container to 10ml.
- Restricting e-liquids to a nicotine strength of no more than 20mg/ml.

In addition, the MHRA require all e-cigarettes and e-liquids be notified to them before they can be sold. Consumers and healthcare professionals can report side effects and safety concerns with e-cigarettes or refill containers to MHRA through the Yellow Card reporting system(26).
The study will recommend third generation 'tank' e-cigarettes/vaporisers in line with MHRA guidance and from the list of products already 'notified' to the MHRA.

PACKAGING AND LABELLING

All products will be provided to participants as packaged and labelled by the manufacturer. Dose instructions included in the packaging and manufacturers' information sheets for licenced medicines will be reiterated verbally to participants. Further verbal advice on use of e-cigarettes will be provided by study staff or the e-cigarette supplier (Totally Wicked) necessary to individual participants and in line with NCSCT(22) recommendations.

NCSCT have produced a quick reference guide explaining NRT and e-cigarette dosing and instructions for use please follow this link for information(27).
https://www.ncsct.co.uk/library/view/pdf/NCSCT%20stop%20smoking%20aids%20quick%20reference.pdf

STORAGE, DISPENSING AND RETURN

NRT products and e-cigarettes will be stored and dispensed by the suppliers MK Medicals (NRT) and Totally Wicked (E-cigarettes) according to the manufacturer's instructions and the

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NCSCT dispensing policy and suggested practice(22). Pharmacotherapies will be dispensed by MK Medicals sister pharmacy company, Shri Pharmacy, or GP/secondary care provider. Products will be posted to participants homes directly by the suppliers. Faulty and incorrect items will be returned directly to the supplier according to their policies and protocols.

PLACEBO
No placebos or other comparators will be used.

KNOWN SIDE EFFECTS
Documented side effects from the use of NRT include: Bloating; blurred vision; constipation; coughing; diarrhoea; dry mouth; dyspepsia; dysphagia; epistaxis; flatulence; gastritis; gastro-intestinal disturbances (may be caused by swallowed nicotine); hiccup; increased salivation; irritation of the throat; mild local reactions at the beginning of treatment are common because of the irritant effect of nicotine; minor skin irritation; mouth ulcers; nasal irritation; nausea; oesophagitis; paraesthesia; sneezing; vomiting; watery eyes(28) British National Formulary; Medicines Complete, Accessed March 2024 https://www.medicinescomplete.com/mc/bnf/current/PHP3201-nicotine.htm#PHP46731-side-effects.

Exposure to e-cigarettes appears to pose few risks, similar to oral NRT products. Mouth and throat irritation are the most commonly reported symptoms, and these subside over time(23, 24, 28-31) .
Reference source:https://www.medicinescomplete.com/mc/bnf/current/PHP3201-nicotine.htm#PHP46731-side-effects.

Bupropion may lead to insomnia, dry mouth, headaches, nausea, and a rare risk of seizures. Varenicline can cause nausea, vivid dreams, insomnia, and headache, with rare reports of severe neuropsychiatric effects like anxiety or depression. SCP's will monitor side effects for medications as part of their weekly consultations with study participants and will, in consultation with the medical expert on the study and the participant, report any noticeable side effects to the participants GP.

TRIAL / STUDY DESIGN
A pragmatic, parallel-group, three-arm, randomised controlled trial with embedded economic and process evaluations. An overview of the trial design is shown in figure 1.

PRIMARY OUTCOME
7-day point prevalent CO validated smoking cessation at three months after the CSCI*.

*CSCI – commencement of smoking cessation intervention which will begin in all treatment arms after the 2-week set-up period post randomisation.

SECONDARY OUTCOMES
- Uptake of stop smoking support offered (use of Smoke Free app, behavioural support, NRT, e-cigarettes and pharmacotherapies)
- 7-day point prevalent CO validated and self-reported abstinence from smoking at 4-weeks after the CSCI
- 7-day point prevalent self-reported abstinence from smoking 3-months after the CSCI
- 7-day point prevalent CO validated and self-reported abstinence from smoking 12-months after the CSCI
- Prolonged CO validated and self-reported abstinence from smoking at 3 and 12-months after the CSCI

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- Acceptability of the intervention delivered in each treatment group
- Reasons for decline in those not accepting stop smoking support
- EQ-5D-5L score
- Use of smoking cessation support and other healthcare resources
- Motivation to quit (4 weeks, 3 months and 12 months after CSCI)
- Self-efficacy/confidence in stopping smoking/staying quit (4 weeks, 3 months and 12 months after CSCI)

SAFETY ENDPOINTS

The study assesses the effect of personalised behavioural support using smoking cessation therapies (including e-cigarettes) and not the effectiveness of specific drug therapies. Any adverse effects reported during the trial will be recorded. However, as the study will assess access to smoking cessation therapies and not the effectiveness of untested drug therapies it is not anticipated that the study will require termination on safety grounds. Safety concerns with NRT, e-cigarettes or refill containers will be reported to MHRA through the Yellow Card reporting system(26).

STOPPING RULES AND DISCONTINUATION

As this trial will use smoking cessation interventions already available to the public, we do not anticipate there to be a need to discontinue the trial due to adverse outcomes or for any other reasons. However, if recommendations or guidance around the use of any of the products dispensed (e-cigarettes and NRT) to study participants changes during the trial, we will amend our protocol accordingly, but do not anticipate stopping the trial completely.

RANDOMISATION AND BLINDING

Enrolled participants will be randomised to each treatment group using block randomisation, stratified by site and LDCT eligibility, with an allocation ratio of 1:1:1. Blocks will be randomly permuted and of randomly varying size. The randomisation schedule will be generated by a trial statistician not otherwise involved in the recruitment or randomisation of individuals, and implemented via a central, web-based randomisation system designed and managed by the York Trials Unit (YTU).

Enrolment and randomisation will be conducted by the YorQuit Study Support Worker (SSW). Central, online randomisation will ensure the randomisation sequence is concealed from researchers and participants up to the point of randomisation. Following randomisation, participants will be informed of their treatment allocation by the SSW.

TRIAL/STUDY MANAGEMENT

This study represents a joint application between the University of Nottingham and Leeds Teaching Hospitals NHS Trust in collaboration with YTU. Professor Rachael Murray (University of Nottingham) will be the CI leading the study and take overall responsibility for the running of the trial and delivery of the smoking cessation intervention. Professor Matthew Callister (Leeds Teaching Hospitals NHS Trust), as medical expert will provide essential clinical input and serve as a liaison between the proposed trial and LCS sites.

The data custodian will be the Chief Investigator.

TRIAL OVERSIGHT

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TRIAL MANAGEMENT

The Trial Manager at YTU will be responsible for all aspects of trial management and will be supported by other relevant staff members (e.g. trial co-ordinator(s) responsible for the day-to-day support of trial sites, project manager, trial statistician, data manager and trial health economist).

The YTU team will meet on a weekly basis and will work closely with the PI's, particularly at the start of the project, including regular videoconferences to ensure that all aspects of preparation of study material, study site setup and the start of recruitment progress smoothly. The trial coordinator, on behalf of the CI, will submit and, where necessary, obtain approval from all relevant parties for the study and all substantial amendments to the original approved documents. Regular progress reports will be submitted as required to the funding body.

TRIAL MANAGEMENT GROUP

A Trial Management Group (TMG) will monitor the day-to-day management (e.g. protocol and ethics approvals, set-up, recruitment, data collection, data management) of the study. Membership will include the CI, medical expert, co-investigators, and research staff on the project. Throughout the project there will be regular videoconference contact supplemented by face-to-face meetings where required. Frequency of meetings will vary depending on the stage of the trial but will be at least monthly during the early stages. We will keep in close contact via email and telephone throughout.

JOINT TRIAL STEERING AND DATA MONITORING COMMITTEE

A joint Trial Steering Committee (TSC) and Data Monitoring Committee (DMC) will monitor progress of the study and data arising from the study, provide independent advice and the independent chair will make recommendations to the funder. The project will also be monitored by the Sponsor and a representative will be invited to attend the TMG and joint TSC/DMC meetings. Other study collaborators may also attend the meetings at the discretion of the Chair.

CHIEF INVESTIGATOR AND CO-INVESTIGATORS

The team includes experts in lung cancer, LCS and smoking cessation; individuals with experience of LCS; and methodologists with expertise in the design, delivery and analysis of multi-centre RCTs in the field of smoking cessation.

PRINCIPLE INVESTIGATORS/LOCAL SITE CO-ORDINATORS

Each site will have a Principal Investigator (PI) who will be responsible locally for the study.

SITE MONITORING

Participating sites may be asked to assist in trial related monitoring when required, for example audits, ethics committee review and regulatory inspections. The YTU will undertake central monitoring of sites. This may include review of consent forms; review of screening forms to confirm eligibility; cross checking delegation logs; and annual audits completed by sites and returned to the YTU.

DURATION OF THE TRIAL / STUDY AND PARTICIPANT INVOLVEMENT

STUDY DURATION

Trial start: April 2024
Recruitment: June 2025 for 24 months
Trial end: April 2028

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PARTICIPANT DURATION

Stop smoking support will be provided for as long as the participant requires, up to a maximum of 12-weeks. Follow up contact will be requested at 4-weeks, 3-months and 12-months post CSCI. Where participants are invited for interviews as part of the process evaluation, these will take place within a two-week window, where possible, at 4-weeks, 3-months, and 12-months post CSCI.

END OF THE TRIAL

The end of the study will be when the 12-month questionnaire is completed and, if required, CO reading collected for the last participant.

SELECTION AND WITHDRAWAL OF PARTICIPANTS

RECRUITMENT

YorQuit aims to recruit people who currently smoke who are contacted by the LCS Programme. The LCS programme contacts people who have an ever-smoking diagnostic code in their Primary Care electronic record. People then undergo a telephone lung cancer risk assessment, and if found to be at higher risk of lung cancer are invited for an initial LDCT screen (called T0). Provided participants remain in the target age range and don't develop another contra-indication to LDCT screening, they are invited back every 2 years for further LDCT screening scans (termed T1 scan at 2 years, T2 scan at 4 years and so on). At the point of first interaction/triage, information about the trial may be conveyed in person when patients visit the LDCT vans for their screening scan. Patients can provide the site team with their phone number and email address so that a member of the research team can get in contact with the patient to go over the study in more detail.

YorQuit will approach people regarding recruitment at two points in the screening programme: first, people being risk-assessed at entry into the programme (subsequently called the baseline risk assessment group); and second, people who have already undergone LDCT screening who are returning for subsequent regular screening rounds (subsequently called the T1/T2/T3 screening group). People in the baseline risk assessment group who currently smoke but are found to be ineligible for LDCT screening, are still eligible for recruitment to YorQuit.

The processes for identification, screening and eligibility assessment will differ between these two groups as described below.

IDENTIFICATION AND SCREENING

Baseline Risk Assessment Group:

Everyone undergoing lung cancer risk assessment for entry into the LCS programme will be asked about their current smoking status by the LHC staff, as this is a required parameter for lung cancer risk assessment. At the end of the risk assessment phone call (and irrespective of whether the participant is eligible for LDCT screening), the LHC staff member will introduce the study to people who currently smoke and ask for permission to pass their contact details to the study team who will be in touch within 1-2 working days. If the individual is not interested in participating in YorQuit, smoking cessation advice +/- referral will be delivered as per standard practice for the local LCS programme. Limited non-identifiable data will be entered into a screening log for those approached about the study.

T1/T2/T3 Screening Group:

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The YorQuit SSW (employed by the healthcare trust organising the LHC) will telephone all people who are listed for a repeat routine screening round who were recorded as currently smoking at the time of their last screening visit. The primary purpose of this phone call will be to schedule the screening appointment – i.e. this is a task that would normally be undertaken by the LHC team, but the SSW will make this contact for convenience. A voice message or text can be sent if the participant does not pick up to inform them of the reason for the call. Once the appointment has been arranged, the SSW will check the current smoking status of the individual, and if still smoking introduce the study. If the individual declines entry into the study, smoking cessation advice +/- referral will be delivered as per standard practice for the local LCS programme. Limited non-identifiable data will be entered into a screening log for those approached about the study.

GP Practices in NHS Trusts participating in YorQuit will also display posters to inform patients that their local area is taking part in the YorQuit study and that they may be invited to take part in the study if they are contacted by the LCS programme. Hospitals and mobile CT vans involved in the study may also choose to display the flyer.

ELIGIBILITY ASSESSMENT

For the baseline risk assessment group, the SSW will contact the individual within 1-2 working days following the risk assessment to discuss the study further and undertake eligibility assessment. Prior to this telephone call, the SSW will send a text-message to the individual from the mobile number from which the call will be made. This is to remind them of the call and to familiarise them with the mobile phone number of the SSW. If the individual is unavailable at the first attempt, two further attempts will be made at different times of the day.

For the T1/T2/T3 screening group, the eligibility assessment will be undertaken as a continuation of the phone discussion described above.

For both groups, on successful contact the SSW will check eligibility against study criteria (specifically that the individual had smoked within the last 7 days) and ascertain their preference for receiving the Participant Information Sheet (PIS) (text/email/post). The SSW will agree a time within the next week to recontact the individual to discuss the study again and take consent if appropriate. Finally, the SSW will deliver Very Brief Advice about smoking cessation in line with current NCSCT guidance during this phone call if not already delivered.

CONSENT, RANDOMISATION AND BASELINE DATA COLLECTION

All participants will provide informed consent before they undergo any interventions related to the study, including the process evaluation. The Investigator will explain the details of the trial and provide a Participant Information Sheet, ensuring that the participant has sufficient time to consider participating or not. The Investigator will answer any questions that the participant has concerning study participation.

Consent will be collected during a second phone call from the SSW, the timing of which will have been previously arranged. A text-message will be sent to the participant prior to this second phone call to remind them of the appointment and to familiarise them with the phone number from which it will be made. Depending on the individual's preference, consent will either be collected verbally over the telephone, or alternatively via an emailed link to an online consent form within the electronic database, REDCap, detailing the same information. If the online consent form is used, the telephone conversation may need to be temporarily ended whilst the participant completes the consent online, then the SSW will recontact the participant thereafter for further tasks. Verbal consent will be obtained following a pre-drafted script. The SSW will read out the same statements (identical to the online consent form) and potential participants will be asked to provide explicit verbal agreements. The SSW will mark

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each item on the form as agreed by the participant. The SSW will have undergone Good Clinical Practice (GCP) and Informed Consent training and be named on the delegation log for this task.

Where participants do not agree to consent to the study, SSW's will ask if participants can be contacted by members of the research team from Cardiff University as part of the process evaluation. Those people who provide verbal consent to being contacted by Cardiff University will have their contact details recorded in a password protected spreadsheet stored on the University of Nottingham shared drive and accessed only by the researcher from Cardiff University. It will be made clear to people agreeing to share their contact details for the process evaluation that they might not be contacted (as this is dependent on several factors related to prior recruitment and desired sample), and that being contacted does not mean they are under any obligation to participate in the process evaluation. Participants will be reminded of their rights to not participate and to withdraw.

One copy of the consent form will be emailed or posted to the participant, another copy will be filed in the medical records and another copy will be kept in the Investigator site file. Should there be any subsequent amendment to the final protocol, which might affect a participant's participation in the trial, continuing consent will be obtained using an amended consent form using the same methods as above.

Once consent has been obtained, baseline data will be collected by the SSW, and once this has been completed, randomisation will take place (real-time online during the phone call). The participant will then be informed which group they have been allocated to. For participants randomised to treatment group 1, they will be informed that their details will be passed to the local stop smoking service who will be in touch in due course. Participants will also be asked whether they wish to receive and use a free stop-smoking mobile phone app, Smoke Free. If so, they will be provided with a QR code/clickable link to download the app and can organise a phone call with the app team to talk them through app set-up if required. For participants randomised to treatment groups 2 or 3, they will be informed to expect a telephone call from a YorQuit SCP within 1-2 working days. Further details are given for all three groups in the "Trial/Study Treatment and Regimen" section below. Participants who agree to be contacted as part of the process evaluation will be advised that a colleague from Cardiff University will contact them in due course. Process evaluation participants will be provided with a participant information sheet relating to the process evaluation and supported to complete a consent form using the same verbal procedure as described above, prior to taking part in the interviews. Researchers will reiterate consent and the right to withdraw at the beginning of all audio recordings.

All consenting participants will be informed that they will be contacted in approximately 4-weeks, 3-months and 12-months post CSCI to ascertain their smoking status.

It will be explained to the potential participant that entry into the trial is entirely voluntary and that their treatment and care will not be affected by their decision. It will also be explained that they can withdraw at any time. In the event of their withdrawal, it will be explained that their data collected so far will be used in the final analyses.

ELIGIBILITY CRITERIA

Study eligible participants will be selected from invitees/returners to the LCS programme which operates from various mobile screening units locations in Leeds, Hull, Bradford District and Craven, North Kirklees, and Manchester lung health check teams.

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INCLUSION CRITERIA

Smoked at least one cigarette in last 7 days at point of consent
55-75* years of age
Able to provide informed consent

* LCS programme offers screening to people up to 74 years and 364 days. Upper age of 75 used here to allow people to be included in YorQuit if they become 75 in between first contact and consent to YorQuit study

EXCLUSION CRITERIA

Previously randomised to YorQuit

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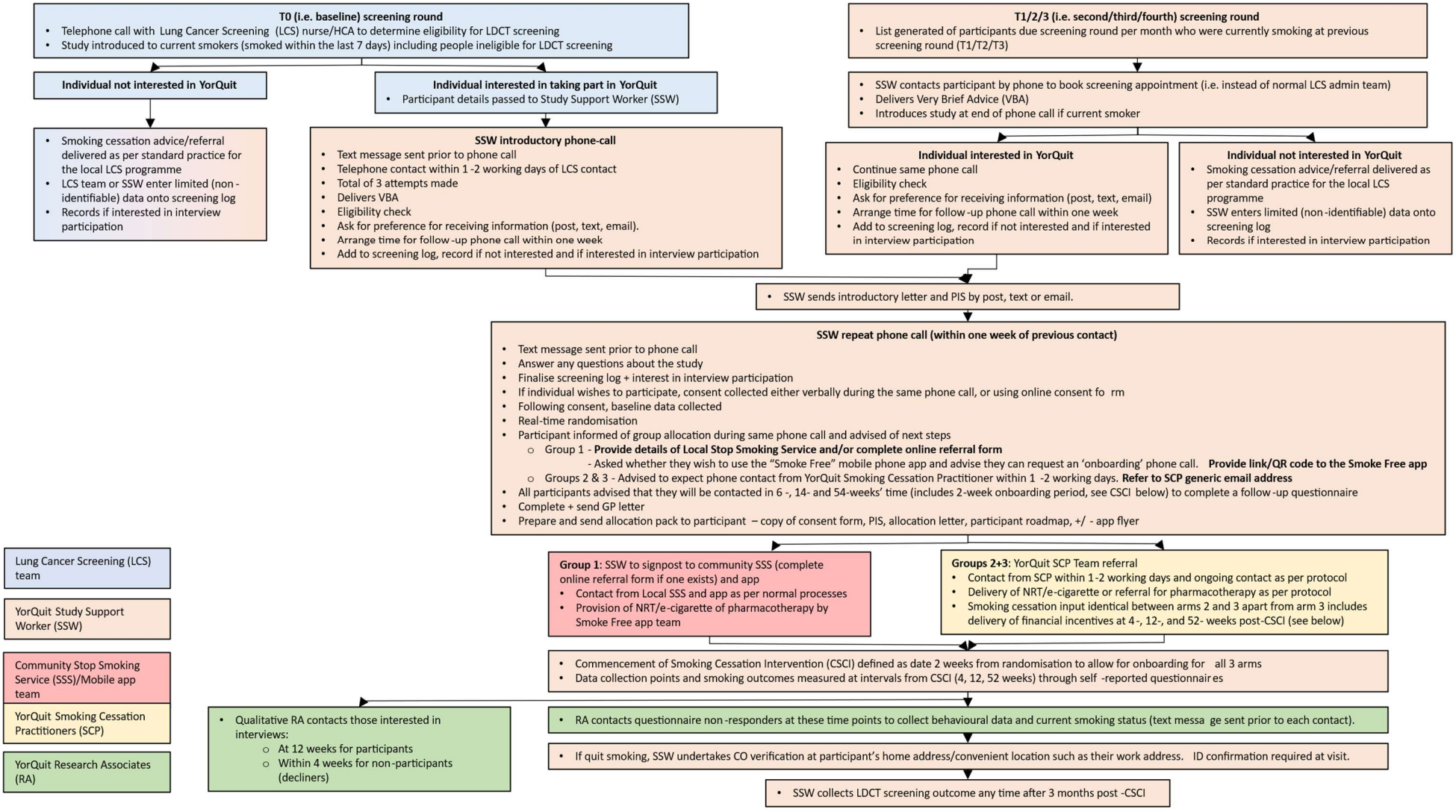
YorQuit process map – Version 1.8 – 14/07/2025



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REMOVAL OF PARTICIPANTS FROM THERAPY OR ASSESSMENTS/PARTICIPANT WITHDRAWAL

Participants may be withdrawn from the trial either at their own request or at the discretion of the investigator. The participants will be made aware that this will not affect their future care. Participants will also be made aware (via the information sheet and consent form) that if they choose to withdraw from the study, we will keep their data collected to date and will use this in the final analysis.

TRIAL / STUDY TREATMENT AND REGIMEN

After consent and prior to randomisation, participants will complete a baseline questionnaire during the phone call with the SSW. The questionnaire will be completed interview-style, with the SSW reading aloud the questions and inputting the participants answers directly into the eCRF held within REDCap. The baseline questionnaire collects demographic information and information on smoking history. Further follow-up questionnaires at 4-weeks, 3-months and 12-months post-CSCI will be self-reported and completed either via a link to an online questionnaire in REDCap or postally. Non-responders to follow-up questionnaires will be contacted by a researcher to complete the questionnaire over the phone.

TREATMENT GROUP 1: DIGITAL APP AND REFERRAL TO COMMUNITY STOP SMOKING SERVICES

Study participants will be referred to their local stop smoking services as per current recommendations(32, 33). In addition, participants who have access to a smart phone will also be offered a subscription to the “Smoke Free” digital app. As part of the Smoke Free app subscription participants will be provided with pharmacotherapies (Bupropion, Varenicline or Cytisine (where available)) or NRT and/or e-cigarettes plus an ‘onboarding’ session to support with downloading, installing, and using the app, if required.

TREATMENT GROUP 2: TELEPHONE INTERVENTION

Participants randomised to treatment group 2 will receive an initial telephone consultation with a YorQuit SCP, trained to NCSCT standards(34). The SCP will explain, advise, and deliver smoking cessation support in accordance with NHS Stop Smoking Service best practice (and NICE NG209 guidance)(33). This will include the use of one-to-one behavioural support and provision of pharmacotherapy. Pharmacotherapy will take the form of either single or dual NRT and/or e-cigarettes. Bupropion, Varenicline or Cytisine (where available) will also be recommended to patients (who are not contraindicated) by the SCP and if agreeable prescribed by the GP, pharmacist or secondary care team subject to the satisfactory completion of a contraindications form If pharmacotherapies are prescribed by MK Medicals pharmacist (and dispensed by sister pharmacy company, Shri Pharmacy), notification of prescription will be sent to the GP by Shri pharmacy for medical record documentation. As part of ongoing consultations with participants, SCPs will regularly enquire about their pharmacotherapy usage and report and any concerns back to the relevant prescriber and/or GP and/or clinical lead for the YorQuit study. If the participant requests NRT and/or e-cigarettes (a choice of liquid flavours will be available) a supply of products will be posted to the participant’s home address. The support described will be delivered for as long as required by the participant for up to a maximum of 12-weeks from CSCI.

TREATMENT GROUP 3: TELEPHONE INTERVENTION PLUS FINANCIAL INCENTIVE

Study processes in treatment group 3 will be the same as described for treatment group 2. In addition, participants will be informed that they will be provided with a financial incentive in the form of a Love2shop or Amazon voucher if they are carbon monoxide (CO) validated

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(<10 parts per million (ppm)) as not smoking at the 4 week (£25), 3 month (£50) and 12 month (£100) follow up assessments.

DESCRIPTION OF STUDY INTERVENTIONS USING TIDIER FRAMEWORK

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Brief Name	Treatment Arm 1 – Usual Care + digital app	Treatment Arm 2 – Telephone Intervention	Treatment Arm 3 - Telephone Intervention plus financial incentive
Why	Current practice at most LCS programmes – Use of Smoke Free app anticipated to become 'usual care' going forward	Dedicated smoking cessation service linked to the LCS programme with specialist advisors trained to support this patient group may deliver better outcomes than referral to local stop smoking services	Testing to see if adding financial incentives has the same benefit as seen in pregnancy services
What	Referral to local stop-smoking services as per current recommendations. In addition, participants who have access to a smart phone will also be offered a subscription to the "Smoke Free" digital app which includes an 'onboarding' session to support with downloading, installing, and using the app	Referral to YorQuit Stop smoking service	Referral to YorQuit Stop smoking service plus financial incentives
Who Provided	Living Well Smokefree Service Craven; Living Well Stop Smoking Service Bradford; Smokefree Hull (Change, Grow Live); Leeds Stop Smoking Service; Manchester Stop Smoking Services; Smoke Free digital app	NCSCT trained SCPs employed to the YorQuit Study	NCSCT trained SCPs employed to the YorQuit Study plus financial incentives organised by YorQuit researcher
How	After randomisation into treatment groups the SSW will refer participants into the LSSS by completing the referral form. If appropriate the SSW will also refer to the Smoke Free app team by providing a QR code/clickable link. NRT and e-cigarettes will be dispensed by LSSS according to local dispensing policies and procedures. Participants may be referred to their GPfor pharmacotherapies (Cytisine, Bupropion or Varenicline) by the LSSS. The Smoke Free app team will post NRT and e-cigarettes to study participant's home address. The Smoke Free app team will	After randomisation into treatment groups the SSW will refer to the YorQuit cessation service by completing the referral form. NRT will be requested by the YorQuit SCP and posted to participant's home address by the supplier MK Medicals. E-cigarettes will be posted to participant's home address by the supplier Totally Wicked, within 24 hrs of the request. Participants will be referred to their GP, MK Medicals pharmacist or secondary care team for pharmacotherapies (Cytisine, Bupropion or Varenicline).	After randomisation into treatment groups the SSW will refer to the YorQuit cessation service by completing the referral form. NRT will be requested by the YorQuit SCP and posted to participant's home address by the supplier MK Medicals, within 24hrs of making the request. E-cigarettes will be posted to participant's home address by the supplier Totally Wicked, within 24 hrs of the request. Participants will be referred to their GP, MK Medicals pharmacist or secondary care team for pharmacotherapies (Cytisine, Bupropion or Varenicline). Incentives (electronic Love2shop or Amazon vouchers) will be organised and

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Brief Name	Treatment Arm 1 – Usual Care + digital app	Treatment Arm 2 – Telephone Intervention	Treatment Arm 3 - Telephone Intervention plus financial incentive
	also refer study participants to their GP for pharmacotherapies if requested.		emailed to study participants by the researcher employed to the study as follows: £25 if CO validated quit at 4-weeks, £50 if CO Validated quit at 3-months and £100 if CO validated quit at 12-months
Where	Services are located in Bradford District and Craven and North Kirklees, Leeds, Hull and Manchester. Study participants will be referred to their local service organised by postcode. Consultations will take place either face-to-face, over the telephone or video call depending on the practice and procedures of the service. The Smoke Free app is a national service and is accessed by using a smartphone. Study participants using the Smoke Free app will have access to subscription only app features and will also have access to telephone consultations provided by trained cessation advisors employed to the app	YorQuit Cessation service will be based at the University of Nottingham. Cessation support will be delivered over the telephone or via Microsoft Teams if preferred by the study participant	YorQuit Cessation service will be based at the University of Nottingham. Cessation support will be delivered over the telephone or via Microsoft Teams if preferred by the study participant
When and how much	Study participants will be contacted by their local service and/or download the Smoke Free app and provided with support according to local policy and procedure. Study participants who opt to use the Smoke Free app will be provided with an 'on-boarding' telephone call explaining how to download and use the app. It is anticipated that study participants will be contacted between 6 to 12 times over the 12-week intervention period and provided with smoking cessation	Study participants will be contacted within 24hrs of referral to the YorQuit Stop Smoking Service (48hrs if referred on a Friday) and provided with stop smoking support as described in the NCSCT Standard Treatment Programme https://www.ncsct.co.uk/publications/ncsct-standard-treatment-programme Study participants will be offered telephone consultations with a trained NCSCT smoking cessation advisor lasting 15-30 minutes, once per week for 12-weeks.	Study participants will be contacted within 24hrs of referral to the YorQuit Stop Smoking Service (48hrs if referred on a Friday) and provided with stop smoking support as described in the NCSCT Standard Treatment Programme https://www.ncsct.co.uk/publications/ncsct-standard-treatment-programme Study participants will be offered telephone consultations with a trained NCSCT smoking cessation advisor lasting 15-30 minutes, once per week for12-weeks.

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Brief Name	Treatment Arm 1 – Usual Care + digital app	Treatment Arm 2 – Telephone Intervention	Treatment Arm 3 - Telephone Intervention plus financial incentive
	advice/behavioural support and access to a range of nicotine replacement therapies, e-cigarettes or pharmacotherapy to support their quit attempt. Consultations will either be face-to-face or delivered via the telephone or video call and should last approximately 15 minutes. Study participants will use the app 'features' at their discretion.	Telephone consultations will comprise of behavioural support discussing motivations, barriers and facilitators to the quit attempt, provision of NRT (usually a transdermal patch (21/14/7/mg)) plus another fast-acting product (Lozenge, Gum or Mouth spray for example). E-cigarettes will also be offered to study participants to use either on their own or as a 'fast acting product' alongside transdermal patches. E-liquids will be dispensed in either 16/10/6 mgs of nicotine and according to participant 'heaviness of smoking'. Study participants can change or select new NRT products at any point during the 12-week intervention period. If appropriate and requested by the study participant, the SCP may refer the participant to their GP, pharmacist or secondary care team for a prescription for pharmacotherapies. The SCP will continue to provide behavioural support to the participant while using pharmacotherapies. A quick reference to stop smoking aids is provided here https://www.ncsct.co.uk/publications/stop-smoking-medications-quick-reference https://www.ncsct.co.uk/library/view/pdf/Cytisine-summary-and-dosing-guide.pdf	Telephone consultations will comprise of behavioural support discussing motivations, barriers and facilitators to the quit attempt, provision of nicotine replacement therapies (usually a transdermal patch (21/14/7/mg)) plus another fast-acting product (Lozenge, Gum or Mouth spray for example). E-cigarettes will also be offered to study participants to use either on their own or as a 'fast acting product' alongside transdermal patches. E-liquids will be dispensed in either 16/10/6 mgs of nicotine and according to participant 'heaviness of smoking'. Study participants can change or select new NRT products at any point during the 12-week intervention period. If appropriate and requested by the study participant, the SCP may refer the participant to their GP, pharmacist or secondary care team for a prescription for pharmacotherapies. The SCP will continue to provide behavioural support to the participant while using pharmacotherapies. A quick reference to stop smoking aids is provided here https://www.ncsct.co.uk/publications/stop-smoking-medications-quick-reference https://www.ncsct.co.uk/library/view/pdf/Cytisine-summary-and-dosing-guide.pdf Incentives (electronic Love2shop or Amazon vouchers) will be organised and emailed to study participants by the researcher employed to the study as follows: £25 if CO validated quit

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Brief Name	Treatment Arm 1 – Usual Care + digital app	Treatment Arm 2 – Telephone Intervention	Treatment Arm 3 - Telephone Intervention plus financial incentive
			at 4-weeks, £50 if CO Validated quit at 3-months and £100 if CO validated quit at 12-months
Tailoring	It is anticipated that LSSS will tailor use of NRT and liquids for e-cigarettes in line with study participants heaviness of smoking and nicotine withdrawal guidelines	SCPs will tailor use of NRT and liquids for e-cigarettes in line with study participants heaviness of smoking and nicotine withdrawal guidelines	SCPs will tailor use of NRT and liquids for e-cigarettes in line with study participants heaviness of smoking and nicotine withdrawal guidelines

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COMPLIANCE
Compliance will be measured in relation to acceptance of usual care cessation support reported by participants in the usual care group at follow-up visits, and intervention components delivered to those in the intervention group. Non-smoking status will be validated objectively using exhaled CO. There will be no defined level of acceptable compliance. Data from all consenting participants will be included in the analysis with the assumption of relapse to smoking where validated abstinence is not confirmed by an exhaled CO of less than 10ppm.

CRITERIA FOR TERMINATING TRIAL
There are no other termination criteria.

DATA COLLECTION

TABLE 1: DATA COLLECTION MEASURES FROM STUDY PARTICIPANTS

	Baseline	4-weeks post CSCI	3-months post CSCI	12-months post CSCI
Smoking behaviour (*including CO validation if abstinence is reported)	X	X*	X*	X*
Motivation to quit smoking	X	X	X	X
Quit confidence	X	X	X	X
Self-efficacy of quitting smoking	X	X	X	X
Use of smoking cessation support	X		X	X
Quality of life (EQ-5D-5L)	X	X	X	X
Lung screening outcome			X	
Wider healthcare resource utilisation	X		X	X
Qualitative evaluation		X	X	X

Screening logs:
Screening logs will be kept by participating centres throughout the trial. We will collect data on the number of eligible people: approached for consent; not approached for consent and reasons why; who provide consent; do not provide consent and reasons why; randomised. We will also collect data on the number of participants randomised who do not receive the randomly allocated treatment and reasons why. With appropriate permissions and where feasible we will collect information on participants who have accepted and undertaken a lung

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screening appointment so that we can monitor any variation across these metrics by treatment group.

Baseline:
The SSW will collect information relating to current and past smoking history, Fagerström scores, previous quit attempts, self-efficacy of quitting, motivation to quit, EQ-5D-5L, smoking cessation support, and other wider healthcare resource utilisation.

Follow up data collection (4-weeks, 3-months, and 12-months post-CSCI):
The study protocol allows a two-week window post randomisation for the CSCI - this includes downloading the app, attending the local stop smoking service and collecting quit aids and is applicable to all treatment arms. Data will be collected at 4-weeks, 3-months and 12-months after the CSCI date (which will be 2 weeks after the date of randomisation).

The researcher will collect information relating to smoking status, use of stop smoking support, self-efficacy of quitting, motivation to quit smoking, EQ-5D-5L and wider health and social care usage. The researcher will email the participant a link to the questionnaire in the first instance. If the questionnaire is not completed, then the researcher will make two further attempts to contact participants over the telephone at different times of the day. If the participant does not respond to the email or telephone calls, then a copy of the follow-up questionnaire will be sent by post along with a freepost envelope for return.

All individuals who report abstinence from smoking at any time point will be asked to provide an exhaled CO measure to validate smoking status. This may take place at the individuals' home or alternative community location (according to individual preference and logistic capacity). A CO reading below 10ppm will be considered a CO validated quitter in line with the Russell Standard(35). CO readings will be collected by the SSW at a time convenient to the participant. These readings should be collected within 14 days of being notified of the quit.

PROCESS EVALUATION

A mixed methods process evaluation will be carried out to understand intervention usage, acceptability, implementation and anticipated impact of each intervention arm.

DESIGN

Quantitative data collected for the purpose of the main trial will be used to support the qualitative element of the process evaluation and substantiate the findings. We will report findings related to intervention implementation including number of times participants accessed the digital app and number of NRT products requested through the app.

Semi-structured interviews with a purposive sample of participants from each intervention arm will be conducted. Interview data collection and analysis will be guided by the COM-B Model as a framework for understanding Capability, Opportunity and Motivational barriers and facilitators to supporting smokers attending LCS(36, 37). Participant interviews (n=60) will take place at four weeks, three months, and twelve months over the study period for each of the three intervention arms, and, where possible, with individuals who declined to take part in the study (n=15).

RECRUITMENT

Interviews with intervention participants: Participants will be purposively sampled by age (≤65 years, >65 years), gender (male/female) and smoking status (quit, not quit, or quit and relapsed). Interviews will explore participant's smoking history, their most recent or current

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quit attempt (depending on participant smoking status) and reflections on the nature and quality of the smoking cessation intervention that they have received. Interviews with non-participants (those who are eligible to take part in the study and decline to do so) will be conducted. These interviews will explore reasons for declining, previous quit attempts, any future planned smoking cessation attempts and what could encourage participation in the study.

Anyone agreeing to be contacted about the process evaluation will be contacted via the telephone by colleagues in the research group from Cardiff University, using details collected by the SSW during the initial conversation relating to the main study and as described earlier (p26). Contact details will have been added to a spreadsheet already stored in the University of Nottingham secure shared folder. The researcher will describe the purpose and process of the interviews over the telephone and request permission from the potential participant to send out a copy of the participant information sheet either via email or through the post depending on their preference. The researcher will advise potential participants that they will be contacted at least 24 hours later (depending on their availability) to complete the consent form over the telephone and take part in an interview. The researcher will contact the potential participant at the agreed time and answer any queries before acquiring verbal consent using the procedures described on page 26. Verbal consent will be reiterated and confirmed at the beginning of each audio recording. Participants will be provided with a copy of their completed consent form for their records either via email or post according to preference. Completed consent forms will be saved in the University of Nottingham's secure shared folder.

QUANTITATIVE DATA COLLECTION AND PROCEDURE
See data collection section above.

QUALITATIVE DATA COLLECTION AND PROCEDURE
The COM-B Model will be used to ensure coverage of relevant topics. Due to previous research citing critical contextual factors (e.g. social networks and community mechanisms) related to smoking cessation in the target population, topic guide development will also be guided by the socio-ecological model(38). We will engage with our lay applicant and Patient and Public Involvement and Engagement (PPIE) representatives from the Nottingham based Tobacco and Nicotine Discussion Group (TANG), to co-design the interview topic guides. We will also pilot the interview guides with a representative from TANG.

Interviews: Interviews with **treatment group 1** (digital app and/or referral to community stop smoking services) (n=20) participants will seek to collect information relating to the acceptability of a digital app and the usability for the target population. We will explore barriers and facilitators to app use and whether the app has influenced change in the participant's smoking status/behaviour. We will also interview those who declined to use the app and those referred to a local smoking cessation service. These interviews will provide a richer understanding of issues in accessing and engaging with a digital smoking cessation app for a LCS population.

Interviews with participants enrolled in **treatment group 2** (telephone intervention) (n=20) will seek to understand participant's views of telephone support for smoking cessation and explore the acceptability and feasibility of this mode of delivery.

For participants from **treatment group 3** (telephone intervention plus financial incentive) (n=20) we will explore the above-mentioned topics from treatment group 2 as well as what impact a financial incentive has on a participant's smoking status and motivation to stop

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smoking. Interviews will also explore whether the interventions have any anticipated impact on subsequent screening participation.

Interviews with those who **decline (n=15)** to take part in the trial will be used to explore their reasons for doing so. Additionally, the interview will cover topics such as importance of smoking, readiness to quit and confidence in quitting.

Interviews will be carried out by telephone or Zoom/Microsoft Teams, according to preference. Interviews with participants are expected to last from 30 to 60 minutes, while interviews with decliners are expected to last up to 30 minutes. Participants will be offered a shopping voucher to compensate them for their time. Best efforts will be made to conduct interviews within a two-week timeframe from the study time-points (i.e. 4-week interviews will take place 4–6 weeks following the target quit date). Encrypted digital recorders will be used and files will be uploaded to the secure University network as soon as possible.

STATISTICS

METHODS

Participant flow will be presented using a Consolidated Standards of Reporting Trials (CONSORT) diagram, with the number of participants withdrawing being summarised with reasons where available. Baseline data will be summarised descriptively by treatment group. All outcome data at all timepoints will be summarised descriptively by treatment group. The primary analysis of the primary outcome, which will include participants eligible for LDCT screening only, will be analysed on an intention-to-treat basis using a mixed-effects logistic regression model, with the location of the participant GP practice at the point of recruitment being included as a random effect. Randomised treatment group, age, sex, smoking severity, and other clinically important participant-level baseline covariates will be included as fixed-effects. Participants with missing primary outcome data will be assumed to be smokers as per the Russell Standard. The treatment effect in the form of an odds ratio will be extracted alongside the corresponding 95% confidence interval and p-value. The robustness of the primary analysis to deviations from the Russell Standard(35) will be assessed via sensitivity analyses using multiple imputation by chained equations under the missing at random assumption and a pattern-mixture model under the missing not at random assumption(39). Secondary outcomes will be analysed using appropriate regression techniques. Complier average causal effect (CACE) analysis will be used to assess the impact of compliance with the intervention. A secondary analysis will repeat the primary analysis with the inclusion of both LDCT screen-eligible and screen-ineligible participants, with the addition of whether the participant is LDCT screen-eligible as a fixed effect. This analysis will be repeated with the addition of an interaction term between LDCT screen eligibility and study allocation. Full analyses will be detailed in a statistical analysis plan, which will be reviewed and approved by the joint TSC/DMC committee and finalised before the end of participant recruitment. Analyses will be carried out by the statistician unblinded using Stata version 18 or later. No interim analyses are planned

QUALITATIVE EVALUATION

The process evaluation will be reported in line with EQUATOR guidelines. Relevant main trial quantitative data will be integrated into the process evaluation after the completion of the outcome data and will be analysed descriptively using SPSS. All qualitative process evaluation data will be analysed on Cardiff University password protected computers and backed up to the Cardiff University servers. Audio recordings will be transcribed verbatim by an external specialist transcription service, approved by the University of Nottingham.

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All interviews will be audio-recorded using an encrypted recorder with permission, transcribed verbatim, and the data anonymised. Anonymised interview transcripts will be analysed using a Framework approach(40). This approach will enable us to map thematic differences/ similarities within and between groups e.g. for treatment group 1 participants, comparisons could be made between those who utilised a digital app and those who were referred to a local stop smoking service.

Data will be coded both deductively (informed by the COM-B Model) and inductively, deriving from the spontaneous accounts from participants. Initial readings will facilitate familiarisation and will lead to the generation of initial codes. Themes will be derived initially from the process evaluation aims and topic guides. Further reading and immersion will result in more substantive themes and sub-themes, resulting in the generation of an analytical framework. Data will then be indexed according to the identified thematic framework. A sub-sample of data will also be double coded to ensure validity of interpretations(41). Finally, themes will be discussed and agreed between the research team, allowing clarification of the final framework that will then be applied across all the transcripts. Data will then be charted according to each theme to facilitate interpretation, synthesis, and reporting.

SAMPLE SIZE AND JUSTIFICATION

Recent estimates carried out jointly by ASH (Action on Smoking and Health) and UCL (University College London) reported an overall quit rate of 7% in the population of smokers aged over 50 years(42). A systematic review of studies of smartphone applications to aid smoking cessation found no evidence of an improvement in smoking abstinence compared to control(43). However, the systematic review mostly included studies of older apps, and a study published in 2018(44) provided some evidence that the full version of the Smoke-Free app increased the smoking abstinence rate from 13.8% to 19.3% compared to a reduced version of the app, a relative increase of 1.4. In treatment group 1 we therefore estimate a 3-month quit rate of 10%. Using the results from the QuLIT 2 trial, which used a telephone plus pharmacotherapy intervention, we estimate a quit rate of 21% in treatment group 2(12). No current research has investigated the use of financial incentives in the LCS population but a 2019 Cochrane review of incentives for smoking cessation reported a risk ratio of 1.49(45). We have, therefore, estimated a quit rate of 31% in treatment group 3. Assuming a significance level of 1.7% to allow for the three pairwise comparisons, 516 LDCT screen-eligible smokers per treatment group will give 90% power to detect a significant difference in the primary outcome.

In addition, 387 LDCT screen-ineligible participants will be recruited and randomised to the study. This is to provide additional information on the effectiveness of the study interventions in LDCT screen-ineligible participants. The figure of 387 LDCT screen-ineligible is not informed by a power calculation and is based on the expected proportion of invitees not eligible for LDCT screening being 20%.

ASSESSMENT OF EFFECTIVENESS

The smoking outcome measure to assess effectiveness will be 7-day point prevalent CO validated smoking cessation at three months after the CSCI.

PROCEDURES FOR MISSING UNUSED, AND SPURIOUS DATA

Our primary analyses will use an intention-to-treat approach analysing all participants' outcome data within the intervention group to which they were randomised, assuming, as is consistent with the Russell Standard that participants with missing smoking status data are smoking. We recognise that it is important to test the assumption that those who do not provide smoking data are smokers and also other assumptions about potential relationships between missing data and smoking status. We intend to employ similar methods to those

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used in previous trials(17, 46) to undertake a sensitivity analysis using multiple imputation techniques which will assess results' robustness to variation in missing data assumptions.

DEFINITION OF POPULATIONS ANALYSED
Safety set: All randomised participants.
Full Analysis set: All randomised participants.

All randomised participants will be included in effectiveness and cost-effectiveness analyses; participants will be analysed within the trial groups to which they were randomised and those lost to follow up will be assumed to be still smoking. The secondary CACE analysis investigates the relationship between intervention adherence and outcome.

ECONOMIC EVALUATION
We will conduct an economic evaluation alongside the trial to assess the cost-effectiveness of the digital app and/or referral to community stop smoking services, telephone intervention, and telephone intervention plus financial incentive. The analysis will adopt an NHS and personal social services (PSS) perspective, following the latest NICE guidance(47).

We will prospectively record and calculate the costs of training and providing all three interventions throughout the trial in terms of staff time, overheads, pharmacotherapy, e-cigarettes, and other consumables. Participants' use of smoking cessation support received outside the trial will be collected via self-complete Case Report Forms (CRFs) administered at baseline, 3 and 12-months post-CSCI. In addition, participants' other healthcare resource use in primary and secondary care, excluding uses for smoking cessation, will also be recorded in the CRFs. Costs of healthcare resources will be calculated using national average unit costs from the most up-to-date public sources, such as the National Cost Collection and the Personal Social Services Research Unit (PSSRU) unit costs of health and social care(48-50). A cost profile for each participant in each trial arm will then be constructed by adding the intervention costs to other NHS/PSS costs. We will also administer the EQ-5D-5L(51, 52) questionnaire at baseline and each follow-up, with the results used to derive quality-adjusted life years (QALYs) using the area under the curve method(53).

Patient costs and QALYs will be combined to estimate the incremental cost-effectiveness ratios (ICERs) in terms of cost per QALY using regression methods(54).The primary endpoint for economic evaluation is 12-months from CSCI. The calculated ICERs will then be compared to the NICE recommended maximum acceptable ICERs of £20,000 to £30,000 per QALY to determine the cost-effectiveness of the three interventions(55). Uncertainty around the point estimate will be assessed using the bootstrap re-sampling technique(56). Cost-effectiveness acceptability curves will be constructed using the bootstrap iterations to demonstrate the probability of each intervention being the cost-effective intervention over different willingness-to-pay threshold values(57). An additional cost-effectiveness analysis will be conducted using quit rates as the outcome measure. The results will indicate the cost-effectiveness of achieving one additional quitter at 12-months from CSCI and various other time points specified in the statistical analysis plan.

Missing data at follow-ups will be handled using the multiple imputation method, following Rubin's rule and assuming data are missing at random(58). In addition, by adapting models developed by one of the team members(59, 60), we will project lifetime costs, QALYs and cost-effectiveness for the three interventions. A series of sensitivity analyses will be performed to test the robustness of both the within-trial and model-based findings.

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ADVERSE EVENTS

The trial investigates a personalised behavioural intervention aimed at supporting current smokers attending for lung screening to quit or reduce their smoking and is therefore not a CTIMP.

Consequently, we do not anticipate any unexpected adverse events to be caused by the intervention and cannot foresee circumstances in which a participant would need to be withdrawn from the study due to an adverse event.

Adverse effects due to the use of NRT or e-cigarettes will be reported to the MHRA Yellow Card system(26) as outlined in the Safety Reporting section above.

ETHICAL AND REGULATORY ASPECTS

ETHICS COMMITTEE AND REGULATORY APPROVALS

The trial will not be initiated before the protocol, informed consent forms and participant and GP information sheets have received approval / favourable opinion from the Research Ethics Committee (REC), the respective National Health Service (NHS) or other healthcare providers' Research & Development (R&D) department, and the Health Research Authority (HRA) if required. Should a protocol amendment be made that requires REC approval, the changes in the protocol will not be instituted until the amendment and revised informed consent forms and participant and GP information sheets (if appropriate) have been reviewed and received approval / favourable opinion from the REC and R&D departments. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately providing that the REC are notified as soon as possible, and an approval is requested. Minor protocol amendments only for logistical or administrative changes may be implemented immediately; and the REC will be informed.

The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 1996; the principles of Good Clinical Practice, and the UK Department of Health Policy Framework for Health and Social Care, 2017.

INFORMED CONSENT AND PARTICIPANT INFORMATION

The process for obtaining participant informed consent will be in accordance with the REC guidance, GCP and any other regulatory requirements that might be introduced. The investigator and/or the participant (depending on mode of completion) shall sign and date the Informed Consent Form before the person can participate in the study.

Consent forms will be completed and signed by the SSW (or researcher for the process evaluation interview consent) during the telephone conversation with the study participant. The participant will receive either an electronic or paper copy of the signed and dated forms (depending on their preference), another copy will be filed in the medical records and the original will be retained in the Trial Master File.
The decision regarding participation in the study is entirely voluntary. The investigator or their nominee shall emphasise to them that consent regarding study participation may be withdrawn at any time without penalty or affecting the quality or quantity of their future medical care, or loss of benefits to which the participant is otherwise entitled. No trial-specific interventions will be done before informed consent has been obtained.

The investigator will inform the participant of any relevant information that becomes available during the study, and will discuss with them, whether they wish to continue with the study. If applicable they will be asked to sign revised consent forms.

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If the Informed Consent Form is amended during the study, the investigator shall follow all applicable regulatory requirements pertaining to approval of the amended Informed Consent Form by the REC and use of the amended form (including for ongoing participants).

RECORDS

CASE REPORT FORMS

Researchers and clinical care teams must ensure that participants' anonymity will be maintained and that their identities are protected from unauthorised parties. Participants will therefore be assigned a Unique Trial Number, allocated at randomisation, and this, together with the participant's initials (of first and last name) will be used on CRFs. CRFs will be treated as confidential documents and held securely in accordance with regulations and participants will not be identified by their name to maintain confidentiality. Each site will hold data according to the General Data Protection Regulations (GDPR) and the Data Protection Act 2018.

Data will be collated electronically on a REDCap (Research Electronic Data Capture) database on a secure server at YTU. Access shall be restricted to those personnel approved by the Chief or local Principal Investigator and recorded on the 'Trial Delegation Log'.

Trial data will be gathered from both participants and medical records and input to REDCap electronic case report forms (eCRFs) designed by the YTU trial team in conjunction with the CI. Data collected by site staff/investigators will be entered directly into the eCRFs. Data collected from participants by questionnaire will be entered directly into the eCRFs by participants themselves or by researchers where postal questionnaires are preferred. "Soft" data validation will be implemented during data entry to help improve the completeness and consistency of the entered data.

All participants (intervention and control arm) will be followed up for the purposes of the study via self-completed questionnaires at 4 weeks, 3- and 12-months post CSCI. We will ask participants for full contact details at baseline (including mobile phone number, email, and address), and any contact preferences. Due to the importance of email as a reliable and fast method of collecting follow-up data for our online database, participants will be required to provide an email address but will have the option to opt-out if they wish with no questions asked.

For questionnaire direct entry by participants, a researcher will email a questionnaire link to the participant in the first instance. If the participant does not respond to the email, then the researcher will make two further attempts to contact the participant preceding each attempt with a text. Direct entry on REDCap will be supported by a full audit trail. Research staff entering data shall sign a declaration confirming accuracy of data recorded in the CRF. All reporting of data collection will be undertaken in line with the CONSORT statement(32).

All YTU data recorded electronically will be held in a secure environment with permissions for access as detailed in the delegation log. The University of York has a backup procedure as part of the University's Disaster Recovery process for central IT systems, allowing data to be restored in the event of a catastrophic failure. Backups are made on central file stores, and the backup service takes periodic copies of data on the file stores, meaning they can be restored to that point in time if needed. All study files will be stored in accordance with Good Clinical Practice guidelines. Study documents (paper and electronic) held at YTU will be retained in a secure (kept locked when not in use) location for the duration of the trial. Once sites have completed a close out report and this is approved by the Sponsor, they will be

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instructed to archive their site file and trial data according to their local SOPs.

All work will be conducted following the University of York's data protection policy which is publicly available (Data Protection - Records Management and Information Governance, University of York).

All data management procedures (e.g., source data verification, data validation, archiving etc.) will be conducted in accordance with the trial data management plan which will be generated during the trial set-up phase. YTU will develop this plan and be responsible for all aspects of data management throughout the trial.

SOURCE DOCUMENTS

Source documents shall be filed at the investigator's site and may include but are not limited to, consent forms, current medical records, laboratory results and records. A CRF may also completely serve as its own source data. Only trial staff as listed on the Delegation Log shall have access to trial documentation other than for the regulatory requirements listed below.

DIRECT ACCESS TO SOURCE DATA / DOCUMENTS

CRFs and all source documents, including progress notes shall be made available at all times for review by the CI, Sponsor's designee, and inspection by relevant regulatory authorities.

DATA PROTECTION

All trial staff and investigators will endeavour to protect the rights of the trial's participants to privacy and informed consent, and will adhere to the Data Protection Act, 2018. CRFs will only collect the minimum required information for the purposes of the trial. Paper CRFs will be held securely, in a locked room, or locked cupboard or cabinet. Access to the information will be limited to the trial staff and investigators and relevant regulatory authorities (see above). Computer held data including the trial database will be held securely and password protected. All data will be stored on a secure dedicated web server. Access will be restricted by user identifiers and passwords (encrypted using a one-way encryption method). Information about the trial in the participant's medical records / hospital notes will be treated confidentially in the same way as all other confidential medical information.

Data with external parties shall be governed by formal data sharing agreements and subject to appropriate security controls. Data sharing agreements will be in place prior to any data collection or sharing occurring. Anonymised data will be shared by password protected zip file via a trusted source.

All participant data collected by Smoke Free will be stored on UK servers. Smoke Free's data deletion policy is to delete user data automatically after two years of non-use.

Electronic data will be backed up every 24 hours to both local and remote media in encrypted format.

QUALITY ASSURANCE & AUDIT

INSURANCE AND INDEMNITY

Insurance and indemnity for trial participants and trial staff is covered within the NHS Indemnity Arrangements for clinical negligence claims in the NHS, issued under cover of HSG (96)48. There are no special compensation arrangements, but trial participants may have recourse through the NHS complaints procedures.

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The University of Nottingham as research Sponsor indemnifies its staff with both public liability insurance and clinical trials insurance in claims made by research subjects.

TRIAL CONDUCT

YTU will develop a Trial Monitoring Plan which will be agreed by the Sponsor, TMG, TSC and CIs based on the trial risk assessment. No routine on-site monitoring will take place, however regular central monitoring will be performed according to GCP and the YorQuit Monitoring Plan. Data will be evaluated for compliance with the protocol and GCP and the applicable regulatory requirements.

TRIAL DATA

Monitoring of trial data shall include confirmation of informed consent; source data verification; data storage and data transfer procedures; local quality control checks and procedures, back-up and disaster recovery of any local databases and validation of data manipulation. YTU shall carry out monitoring of trial data as an ongoing activity.

Entries on CRFs will be verified by inspection against the source data. A sample of CRFs (10% or as per the study risk assessment) will be checked on a regular basis for verification of all entries made. In addition, the subsequent capture of the data on the trial database will be checked. Where corrections are required, these will carry a full audit trail and justification.

Trial data and evidence of monitoring and systems audits will be made available for inspection by REC as required.

RECORD RETENTION AND ARCHIVING

In compliance with the ICH/GCP guidelines, regulations and in accordance with the University of Nottingham Research Code of Conduct and Research Ethics, the Chief or local Principal Investigator will maintain all records and documents regarding the conduct of the study. These will be retained for at least 7 years or for longer if required. If the responsible investigator is no longer able to maintain the study records, a second person will be nominated to take over this responsibility.

The Trial Master File and trial documents held by the CI on behalf of the Sponsor shall be archived at secure archive facilities at the University of Nottingham. This archive shall include all trial databases and associated meta-data encryption codes.

DISCONTINUATION OF THE TRIAL BY THE SPONSOR

The Sponsor reserves the right to discontinue this trial at any time for failure to meet expected enrolment goals, for safety or any other administrative reasons. The Sponsor shall take advice from the joint TSC/DMC as appropriate in making this decision.

STATEMENT OF CONFIDENTIALITY

Individual participant medical information obtained as a result of this study are considered confidential and disclosure to third parties is prohibited with the exceptions noted above.

Such medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare.

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If information is disclosed during the study that could pose a risk of harm to the participant or others, the researcher will discuss this with the CI and where appropriate report accordingly.

Data generated as a result of this trial will be available for inspection on request by the participating physicians, the University of Nottingham representatives, the REC, local R&D Departments, and other regulatory authorities.

PUBLICATION AND DISSEMINATION POLICY

If the intervention is found to be effective and cost-effective this research has the potential to greatly improve how smokers attending for lung health screening are supported in their attempts to stop smoking.

Dissemination will focus on supporting the wider adoption and implementation of the intervention (if effective); the dissemination plan, which will be developed at the outset of the project, will be amended as results of the implementation become available. The study protocol will be published in a peer reviewed journal after the study commences. A Yorkshire Cancer Research report of the findings will be produced as well as publications in other peer reviewed journals, regardless of the findings.

A range of methods will be used to target groups for whom the results (and implementation plan) will be relevant. In addition to academic journals, we will use lay summaries targeted at specific stakeholders, presentations at relevant professional society events and press releases through the collaborating NHS organisations, stop smoking services and universities. Clinical co-applicants' regular attendance at professional events and conferences will allow cost-effective dissemination of the findings. Lung health experts, SCP's and lung cancer charities will be targeted through a range of organisations/bodies such as: Yorkshire Cancer Research.

Study results will be available to study participants via the study website, and participants will be regularly reminded of the website URL in letters and newsletters. The results will also be disseminated more widely to participants, via key websites that participants undergoing lung cancer treatments use, for example 'Breath easy'.

USER AND PUBLIC INVOLVEMENT

A Yorkshire lay representative previously diagnosed with lung cancer has been involved from the inception of this programme, contributing to the design of the study and the drafting of the funding application. The co-applicant has been involved in reviewing and commenting on the acceptability of patient-facing documents such as the participant information sheet, consent form, questionnaires, and letters to participants, questionnaire topic guides, and will be involved in any future revisions to these or new patient-facing documents. Our PPI members are part of the Trial Management Group and the joint Trial Steering Committee/Data Monitoring and Ethics Committee. Their opinions and voices are requested and listened to for operational decisions and the running of the trial. They will receive and review the reports associated with the TMG and TSC/DMEC, and the option to comment where they wish. Our PPI members will be involved in reviewing interview topic guides and pilot interviews. PPI members will be involved in reviewing study results prior to publication and reviewing lay summaries.

We will engage with the Nottingham TANG, a well-established (PPIE) group, which aims to obtain views on tobacco control polices, research ideas and current research projects. TANG was set up 2013 and is currently funded by the Shaping Public Health Policies to Reduce

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Inequalities and Harm (SPECTRUM) consortium. Although based in Nottingham TANG consists of current tobacco smokers, recent ex-smokers and vapers with members joining online from across the UK. Further we have established links with several members of the public interested in LCS as part of other research projects and will invite these individuals to participate in the drafting of study materials, interpretation of results, dissemination of study findings etc. As part of this project, we aim to establish an ongoing Yorkshire based PPIE group that will be available for future research projects in this area. We will do this by advertising to recruit interested individuals in the contexts of LCS and stop smoking interventions and seeking consent for future contact for related research that may be of interest, and regular engagement. Representatives will be reimbursed for their time spent on study activities and training will be provided for those who have not previously participated in research.

STUDY FINANCES

FUNDING SOURCE

This study is funded by Yorkshire Cancer Research.

PARTICIPANT STIPENDS AND PAYMENTS

Participants randomised to treatment arm three will receive shopping vouchers to the value of £25, £50, and £100 for validated abstinence from smoking at 4-weeks, 3- and 12-months respectively. Participants who agree to take part in a recorded interview as part of the process evaluation will receive a £20 shopping voucher.

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SIGNATURE PAGES

Signatories to Protocol:

Chief Investigator: (name)_____

Signature:_____

Date: _____

Co-Investigator: (name) _____

Signature:_____

Date: _____

Trial Statistician: (name)_____

Signature:_____

Date: _____

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