Quit Sense feasibility trial

Feasibility randomised controlled trial among online smokers of a smoking cessation smartphone app that delivers 'context aware' behavioural support in real time

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Sponsor	University of East Anglia
Trial registration	ISRCTN12326962.
NRES #	19/WA/0361

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1. Table of Contents

2. Administrative information

This document was constructed using the Norwich Clinical Trials Unit (NCTU) Protocol template Version 4. It describes the Quit Sense feasibility trial, sponsored by the University of East Anglia and co-ordinated by NCTU.

It provides information about procedures for entering participants into the trial, and provides sufficient detail to enable: an understanding of the background, rationale, objectives, trial population, intervention, methods, statistical analyses, ethical considerations, dissemination plans and administration of the trial; replication of key aspects of trial methods and conduct; and appraisal of the trial's scientific and ethical rigour from the time of ethics approval through to dissemination of the results. The protocol should not be used as an aide-memoire or guide for the treatment of other participants. Every care has been taken in drafting this protocol, but corrections or amendments may be necessary. These will be circulated to registered investigators in the trial. All staff referring to the protocol should confirm they have the correct version.

NCTU supports the commitment that its trials adhere to the SPIRIT guidelines. As such, the protocol template is based on the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2012 Statement for protocols of clinical trials [1]. The SPIRIT Statement Explanation and Elaboration document [2] can be referred to, or a member of NCTU Protocol Review Committee can be contacted for further detail about specific items.

2.1 Compliance

The trial will be conducted in compliance with the approved protocol, the Declaration of Helsinki (2008), the principles of Good Clinical Practice (GCP) as laid down by the Commission Directive 2005/28/EC with implementation in national legislation in the UK by Statutory Instrument 2004/1031 and subsequent amendments, the Human Tissue (Quality and Safety for Human Application) Regulations 2007, the UK Data Protection Act, and the UK Policy Framework for Health and Social Care Research, and other national and local applicable regulations.

2.2 Sponsor

The University of East Anglia is the trial sponsor and has delegated responsibility for the overall management of the Quit Sense feasibility trial to the Chief Investigator and NCTU. Queries relating to sponsorship of this trial should be addressed to the Chief Investigator or via the trial team.

2.3 Structured trial summary

Primary Registry and Trial Identifying Number	Name of primary registry, and the unique ID number assigned by the primary registry to this trial.
Date of Registration in Primary Registry	Date when trial was officially registered in the primary registry.
Secondary Identifying Numbers	Other identifiers besides the trial identifying number allocated by the primary registry, if any. These include: • IRAS number 270432 • Other trial registration numbers issued by other registries (both primary and partner registries in the WHO Registry Network, and other registries) • Identifiers issues by funding bodies, collaborative research groups, regulatory authorities, ethics committees, institutional review boards etc.
Source of Monetary or Material Support	National Institute for Health Research (NIHR) Public Health Research programme
Sponsor	University of East Anglia
Host Organisation	South Norfolk Clinical Commissioning Group (SNCCG)
Contact for Public Queries	Ctu.enquiries@uea.ac.uk
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Short Title or Acronym	Quit Sense feasibility trial
Scientific Title	Feasibility randomised controlled trial of a smoking cessation smartphone app that delivers 'context aware' behavioural support in real time
Countries of Recruitment	England
Health Condition(s) or Problem(s) Studied	Smoking
Intervention(s)	Usual care plus the Quit Sense smartphone app

	• An app that provides support to help smokers trying to quit to manage environmental cues to smoke as they arise in real time. • The user sets a quit date and trains the app to learn about their smoking behaviour via the app's smoking logging tool. This requires the user to log in the app each smoking episode and the situational context when they 'light up' in real time while the app records geolocation using location sensors. • After their quit date has passed, the app monitors the user's location and if they enter a location where they previously reported smoking, lapse prevention support is triggered, individually tailored using the context information collected while training the app. Support continues for up to 3 months. • Additional features include: tailored feedback after smoking behaviour is logged, an End of Day (EoD) survey with feedback, a 'my profile' section to display the smoking-related data collected by the app, a library of quitting advice, once daily support messages (up to 28 days post-quit attempt) and an option to reset their quit date in case of relapse. Usual care • A web-link, by text message and, if requested, by email after enrolment, to the NHS SmokeFree website (www.smokefree.nhs.uk). This website provides access and signposting to digital, telephone and in-person cessation support.
Key Inclusion and Exclusion Criteria	Inclusion criteria • Current smokers (at least 7 cigarettes per week). • Willing to make a quit attempt in the next 14 days. • Has primary use of an Android smartphone. • Age 16 years and above. • Resident in England. • Able and willing to provide informed consent using the web-based form. • Not previously participated in this trial.
Study Type	A parallel, two-armed, randomised controlled trial.

	Randomisation will be stratified by smoking rate (<16 vs. ≥ 16 cigarettes/day) and socioeconomic status (low vs. high). Participants will not be blind to allocation, but assessors will be blinded, excluding participants volunteering for a qualitative process evaluation interview at 6 weeks follow up. Participants will be followed up at 6 weeks and 6.5 months (referred to as 6-month follow up) after enrolment. The key research question is "Can a randomised controlled trial of a smoking cessation smartphone app (Quit Sense) be feasibly delivered online among smokers?" The qualitative process evaluation will be nested within the trial, with participants in both arms invited to take part in a telephone interview after the 6 weeks follow up.
Date of First Enrolment	March 2020
Target Sample Size	Trial: 200 smokers, split evenly between the Quit Sense and usual care arms. Qualitative process evaluation: Approximately 20 participants, 15 from the intervention arm and 5 from the usual care arm.
Primary and Secondary Outcome(s)	As this is a feasibility trial, there is no primary outcome. Key estimates the trial will provide are: • Rates of completion of the anticipated primary outcome (smoking cessation at 6-months) for a full trial. • Usual care arm cessation rate. • Cost of recruitment using online advertising. • Rates of app installation, use and support delivery fidelity. • Completion of smoking cessation-related resource use and quality of life data. • Participant views of the app. • Intervention effect on anticipated primary outcome. • Intervention effect on hypothesised mechanisms of action of app.

2.4 Roles and responsibilities

These membership lists are correct at the time of writing; please see terms of reference documentation in the TMF for current lists.

2.4.1 Protocol contributors

Name	Affiliation	Role
Felix Naughton	UEA	Led on protocol development
Juliet High	Norwich CTU	Contributed to regulatory and CTU related content
Aimie Hope	UEA	Contributed to protocol development
Caitlin Notley	UEA	Contributed to the qualitative process evaluation section
Lee Shepstone	Norwich CTU	Contributed to the statistical analysis section
Garry Barton	Norwich CTU	Contributed to the health economics section
Tim Coleman	University of Nottingham	Detailed comments on draft

2.4.2 Role of trial sponsor and funders

Name	Affiliation	Role
Helen Sutherland	South Norfolk CCG ('Host')	Representative of the host organisation
Graham Horne	UEA ('Sponsor')	Representative of the sponsor
Jo Lunn	NIHR	Representative of the funder

2.4.3 Trial Team

Name	Affiliation	Role and responsibilities
Felix Naughton	UEA	Chief investigator
Juliet High	Norwich CTU	Coordination of CTU contribution to project
Aimie Hope	UEA	Senior Research Associate; supporting trial delivery
Chloe Brown	University of Cambridge	Computer scientist leading app optimisation

Claire West	Norwich CTU	Development of study database and web-platform

2.4.4 Trial Management Group

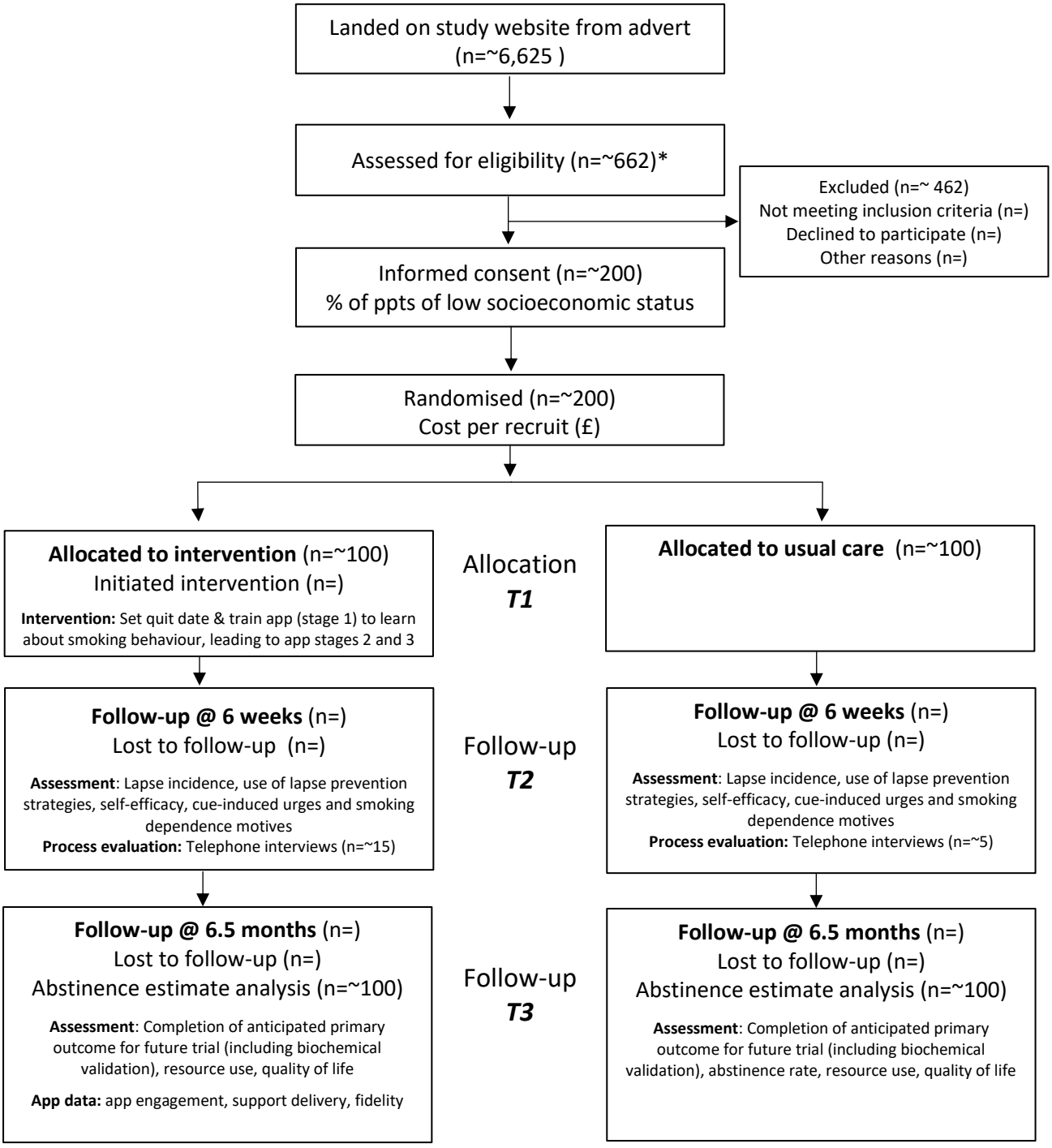
Name	Affiliation	Role and responsibilities
Felix Naughton	UEA	Chief investigator
Juliet High	Norwich CTU	Coordination of CTU contribution to project
Aimie Hope	UEA	Senior Research Associate; supporting trial delivery
Tim Coleman	UEA	Co-applicant; mentoring support for CI
Caitlin Notley	UEA	Co-applicant; qualitative process evaluation advisor
Garry Barton	Norwich CTU	Co-applicant; health economics oversight
Chloe Brown	University of Cambridge	Computer scientist leading app optimisation
Ann Marie Swart	Norwich CTU	CTU oversight
Claire West	Norwich CTU	Development of study database and web-platform
Graham Horne	UEA	Representative of trial sponsor

2.4.5 Trial Steering Committee

Name	Affiliation	Role and responsibilities
Michael Ussher	St Georges/University of Stirling	Independent chair (clinical/behavioural science)
Aleksandra Herbec	UCL	Independent member (behavioural science)
Simon Coulton	University of Kent	Independent member (statistics/HE)
Qasim Chowdary	Public Health England	Independent member (services/clinical/policy)
Jo Hardy	PPI	Independent member (PPI)
Felix Naughton	UEA	Non-independent member (voting)
Juliet High	Norwich CTU	Observer

Helen Sutherland	South Norfolk CCG	Observer (host organisation)
Graham Horne	UEA	Observer (sponsor)
Aimie Hope	UEA	Observer

3. Trial Diagram



*Based on Emery et al (2018; *Journal of Medical Internet Research)* – online uptake of text message smoking cessation intervention. Approximately 10% of those visiting landing page from paid-for Google and Facebook adverts completed eligibility question, and 30% of those signed up

4. Abbreviations

CI	Chief Investigator
CRF	Case Report Form
DMC	Data Management Committee
EU	European Union
GCP	Good Clinical Practice
GTS	Geofence-Triggered Support
HRA	Health Research Authority
ICH	International Conference on Harmonisation
ITT	Intention to Treat
MHRA	Medicines and Healthcare products Regulatory Agency
MRC	Medical Research Council
NCTU	Norwich Clinical Trials Unit
PHE	Public Health England
PI	Principal Investigator
PID	Participant Identification Number
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
QMMP	Quality Management and Monitoring Plan
R&D	Research and Development
REC	Research Ethics Committee
TMF	Trial Master File
TMG	Trial Management Group
TMT	Trial Management Team
ToR	Terms of Reference
TSC	Trial Steering Committee
UEA	University of East Anglia

5. Introduction

5.1 Background and Rationale

Tobacco smoking is the largest single contributor to the UK disease burden [3] and costs the NHS £5 billion annually [4]. Quitting smoking reduces the risk of cancers, heart disease, stroke, Chronic Obstructive Pulmonary Disease (COPD), and improves mental health [5,6]. Three million UK smokers attempt to quit smoking each year, but over 80% relapse [7]. A major cause of relapse is smoking cravings brought about by environmental cues. These 'cue-induced cravings' are implicated in almost half of all lapses (any smoking) [8] and are not alleviated by the most commonly used cessation medications [9]. Lapses to smoking in the early stages of a quit attempt are highly predictive of long-term relapse [10,11]. One large study found that 22% of smokers who lapsed early in their quit attempt (mean days to lapse = 10) were abstinent at 6 months compared to 71% who did not lapse early on [11]. The strong relationship between an early lapse and longer term relapse remains when restricting analyses to individuals who return to abstinence for more than two weeks after the initial lapse or lapses (secondary analysis of iQuit in Practice study data) [12], and is also found when a lapse is experimentally induced [13]. However, smokers are far less likely to lapse when they use a cognitive or behavioural lapse prevention strategy (e.g. using self-talk or avoiding other smokers) to avoid or manage cue-induced cravings [9,14,15] but few are skilled in applying these [16]. If smokers trying to quit used effective lapse prevention strategies at the time of need, this would very likely increase their chances of success. This project is focused on evaluating a way of helping smokers become more skilled at applying these strategies to prevent lapse and ultimately relapse.

Supported by an MRC Public Health Intervention Development (PHIND) grant, we have developed, refined and acceptability tested a 'context aware' smartphone app (Quit Sense) that provides behavioural support to help smokers manage environmental cues to smoke as they arise. Quit Sense is designed to train smokers to use lapse prevention strategies when they experience environmental smoking cues e.g. other smokers. Quit Sense shares part of its 'library' of supportive messages with two theory-guided cessation text message systems previously developed that show evidence of effectiveness [12,17,18]. Two 'proof of principle' studies have shown that Quit Sense can provide 'in the moment' support to smokers, including lapse prevention strategies, and that this is engaged with and is found acceptable by users [19,20]. Participants in our Quit Sense development studies were positive about real time support and only 10% would not use the app again. Engagement rates were high; the mean number of discrete sessions of use of the app, defined as more than one minute between usage sessions, was 70 (SD 75) over a period of approximately 38 days when the app was active (median engagement 25 days [IQR 7-41]). Quit Sense is the only app we are aware of that delivers behavioural support triggered by the real time activity of the smoker as sensed by their smartphone. As there have been very few evaluations of smoking cessation apps, this work addresses an important knowledge gap.

Since our MRC funded project ended, we have adapted Quit Sense so that decisions about support delivery happen locally (on the smartphone), rather than relying on internet connectivity (i.e. a connection to the server). This local decision making also increases privacy as only limited data is needed to be sent to the server. We have also made several further optimisations of Quit Sense. We updated the user interface to ensure it has a contemporary style with maximal appeal and ease of use. We also enhanced the app's energy efficiency to reduce its battery use, given operating system

advances since original development. Furthermore, we have implemented machine learning to help identify high risk moments to determine support delivery when the user is within a location they have previously reported smoking in to the app. In addition, we have integrated an audio recording feature within the app in order to provide a means for users to audio record their views of the app.

In this project we will undertake a randomised controlled trial to test whether or not smokers can be randomised to use either Quit Sense or standard online cessation support. This feasibility trial would produce essential data to inform a definitive trial of this app which, if effective, could be offered to smokers outside the NHS to help address a key support gap. This intervention is highly scalable, could be combined with almost any other type of cessation support and could be highly cost-effective or cost-saving. E-cigarettes may emerge as an effective lapse prevention tool which Quit Sense could also potentially support. The work we propose fits closely with Public Health England's digital strategy within their strategic plan (2016 to 2020) and digital public health agenda, which has a large focus on protecting and improving health via new technologies. The proposal also closely aligns with the NHS Five Year Forward View, where the digital environment features as a key enabler for improving health in England, and the UK Government's Industrial Strategy for the Life Sciences sector, which is supporting the use of new technology in health, particularly the use of machine learning.

5.1.1 Explanation for choice of comparators

The comparator will be a web-link to the NHS SmokeFree website (www.smokefree.nhs.uk). As online smokers are unlikely to receive formal cessation care routinely, we consider the SmokeFree website equivalent to 'usual care' for an online population. This website provides access and signposting to digital, telephone and in-person cessation support. In-person cessation support offered through the SmokeFree website is effective [21], telephone counselling is broadly effective [22], though the SmokeFree National helpline has yet to be evaluated against a non-helpline comparator, and there have been no assessments yet of the effectiveness of the digital support offered on the SmokeFree website, though the SMS support is based on the txt2stop system which is effective [23].

5.2 Objectives

Key research question: Can a randomised controlled trial of a smoking cessation smartphone app (Quit Sense) be feasibly delivered online among smokers?

The main objective is to conduct a feasibility randomised controlled trial of Quit Sense to inform a definitive effectiveness trial, by estimating:

a. Completion rates for the anticipated primary outcome for a full trial (6-month self-reported abstinence with biochemical validation, based on the Russell standard).
b. Usual care arm cessation rate.
c. Cost of recruitment using online advertising.
d. Rates of app installation, use and support delivery fidelity.
e. Completion of smoking cessation-related resource use and quality of life data.
f. Participant views of the app, as part of a qualitative process evaluation.
g. Intervention effect on anticipated primary outcome.

h. Intervention effect on hypothesised mechanisms of action of app at 6 weeks post-enrolment.

5.3 Trial Design

A two arm parallel-group randomised controlled feasibility trial allocating smokers recruited online to a 'usual care' arm (link to NHS SmokeFree website) or an intervention arm who will receive 'usual care' plus access to the Quit Sense app (link with a code to app via Google Play app store, method used in prior Quit Sense studies).

5.4 Site Selection

The trial sponsor has overall responsibility for site and investigator selection and has delegated this role to the CI and NCTU.

5.4.1 Study Setting

The setting is online with the intervention delivered on the participants' smartphone. This matches the 'real world' setting after implementation to maximise validity. Recruitment will take place online via paid-for advertising through Google and social media platforms (e.g. Facebook, Instagram), limited to England-based IP addresses.

5.4.2 Site/Investigator Eligibility Criteria

As the setting is online, there are no external sites, only a central site (UEA) where the research will be carried out. A Trial Master File (TMF) will be kept in this central site.

5.5 Site approval and activation

The central site (UEA) will conduct the trial in compliance with the protocol as agreed by the Sponsor and by the NHS Research Ethics Committee (REC).

5.6 Participants

We will recruit online a population of smokers who meet the eligibility criteria stated below.

5.6.1 Eligibility Criteria

Inclusion criteria:

- Current smokers (at least 7 cigarettes per week).
- Willing to make a quit attempt in the next 14 days.
- Has primary use of an Android smartphone (version 5.0 and above).
- Age 16 years and above.
- Resident in England.
- Able and willing to provide informed consent using the web based form.
- Not previously participated in this trial.

5.6.1.1 *Participant selection*

There will be **NO EXCEPTIONS** (waivers) to eligibility requirements at the time of randomisation. Questions about eligibility criteria should be addressed PRIOR to attempting to randomise the participant.

The eligibility criteria for this trial have been carefully considered and are the standards used to ensure that only appropriate participants are entered. Participants not meeting the criteria should not be entered into the trial for their safety and to ensure that the trial results can be appropriately used to make future treatment decisions for other smokers. It is therefore vital that exceptions are not made to these eligibility criteria.

Participants will be considered eligible for enrolment in this trial if they fulfil all the inclusion criteria and none of the exclusion criteria as defined below.

5.6.1.2 *Screening Procedures and Pre-randomisation Investigations*

People interested in taking part in the trial will complete screening questions relating to the eligibility criteria using the study website. If eligible, and after having been provided with an explanation of the aims, methods, benefits and potential hazards of the trial on the website, individuals will be invited to provide informed consent to enter and be randomised into the trial on the study website and **BEFORE** any trial-specific procedures. After providing online consent, participants will complete a baseline questionnaire before then being randomised to one of the trial arms.

5.7 Interventions

5.7.1 Usual Care Arm

Usual care will be a web-link, sent to participants by text message and, if requested, also by email after enrolment, to the NHS SmokeFree website (www.smokefree.nhs.uk). This website provides access and signposting to digital, telephone and in-person cessation support in England. At the time of writing the support offered on the SmokeFree website includes information and links to six main types of cessation support; in-person (via a Stop Smoking Service), the SmokeFree National telephone helpline, an online chat facility with an advisor, an email cessation programme, an SMS text message programme and the NHS SmokeFree smartphone app. The main difference between the NHS app and Quit Sense is that the NHS app does not proactively deliver real time support to help smokers manage urges, and in addition it is not tailored to the user, does not involve users logging their smoking behaviour and most of the tips and support it provides are user rather than phone-triggered.

5.7.2 Quit Sense Arm

Quit Sense is a context-aware smartphone app designed for smokers willing to make a quit attempt. It is informed by learning theory (LT) [24,25] and two theory-guided SMS text message systems,[12,18] which is in turn informed by Social Cognitive Theory (SCT) [26]. Quit Sense targets three key determinants that map onto LT and six mapping onto SCT: learned associations between smoking and an individual's physical environment (LT); learned associations between smoking and mood triggered by the environment (LT); the presence of other smokers (LT, SCT); awareness of smoking triggers (antecedents) (SCT); outcome expectancies of a lapse (SCT); goal/intention for complete abstinence (SCT); self-efficacy in resisting urges to smoke (SCT); knowledge of and self-efficacy for lapse prevention strategy use (SCT). Twenty-one corresponding Behaviour Change Techniques (BCTs) [27] are used to target these determinants. See logic model for further details and evidence citations.

The main feature is 'Geofence-Triggered Support' (GTS), which is orientated around three stages within the app:

Stage 1 (training phase): The user sets a quit date (default suggestion is 7 days' time) and trains the app to learn about their smoking behaviour via the app's smoking reporting tool. This requires the user to report in the app each smoking episode and the situational context when they 'light up' in real time (stress, mood, urge strength, setting description, presence of other smokers), while the app records geolocation using location sensors. If a user reports smoking more than once in the same location (as defined by the app) the app creates a geofence (a circular virtual perimeter) around the location. Each geofence zone represents a high-risk area for smoking for that user.

Stage 2 (28 day abstinence challenge): After their quit date has passed, the app monitors the user's location. If they enter (and remain in for at least 5 minutes) a geofence, as part of a machine learning system, the app will then determine whether to trigger a GTS message. This decision is primarily informed by the users smoking reporting history, including time of day, for that location. Messages are individually tailored using the context information collected in stage 1 and provide lapse prevention support (strategies, motivation enhancement, encouragement etc.) to help users avoid or cope with triggers they are likely to experience in that location that cue urges to smoke. Further decisions about whether to trigger messages are made after each 3-hour interval of remaining in that location (default between 8am-9.30pm, or defined by the user).

Stage 3 (maintaining abstinence): The app continues to deliver GTS for 2 further months but reduces the frequency by one-half every month. After 3 months post-quit date, the GTS support will stop, unless the user opts to restart their quit attempt, which they can do at any time (see feature description below).

Quit Sense has six additional features (relevant to all stages, unless specified otherwise):

1. After each smoking report is submitted, tailored feedback is provided on screen. This feedback in stage 1 includes messages focused on preparing to quit, boosting motivation and self-efficacy. These messages are tailored to nine characteristics collected during app initiation (hardest situation to avoid smoking, number of cigarettes smoked, living with a smoker, longest quit attempt to date, primary reason for quitting, perceived primary downside to quitting, self-efficacy, gender and pregnancy status). In stage 2, the feedback after a smoking report is submitted is orientated around lapse and relapse prevention.
2. An 'End of Day' (EoD) survey that users are invited to complete each day, recording the number of cigarettes smoked that day, craving [28] and self-efficacy [18,26] (stages 1 and 2 only). After the EoD survey is completed, the app provides a feedback message. If the number of cigarettes reported in real time during the day is different from the number reported in the EoD survey, the feedback message provided promotes adherence to logging smoking behaviour.
3. A 'my profile' section including number of days quit, money saved (based on smoking rate), a calendar showing a heat map (use of red, yellow and green to denote values) for smoking, cravings and self-efficacy for each day. In addition, smoking pattern feedback is provided using graphical and written summaries for smoking triggers based on the user's historical reporting of smoking behaviour.

4. A 'Library' of quitting advice split into six categories: 'getting ready', 'boost your motivation', effects of smoking and quitting', 'early days of quitting', 'staying quit', 'smoking after your quit date'. Includes an option for users to write and submit their own support messages.
5. Scheduled non-tailored daily support messages delivered each morning orientated around the quit date (stages 1 and 2 only) – targeting outcome expectancies, motivation, preparation, self-efficacy (three sets of different messages to prevent message duplication in successive attempts).
6. The option for the user to reset their quit date in stage 1, if they are not feeling ready, or stage 2 if they relapse. Relapse is defined as multiple smoking episodes that are reported over two days during a quit attempt (either through smoking episode logs or the EoD survey). If this occurs, users are invited to either re-commit to their quit attempt and continue or reset their quit date, and they go back to stage 1.

Quit Sense users are also able to use an audio record feature imbedded into the app where they can provide feedback on their views and experiences of using Quit Sense, as part of the process evaluation.

5.7.3 Accountability

To reduce the chances of participants entering the study more than once (e.g. after allocation), we will take steps to use IP addresses used by visitors to the study website in an attempt to prevent re-enrolment.

To ensure only those in the intervention arm have access to Quit Sense, we will send intervention participants, by text message, a unique one-time code to enable them and only them to install and initiate the Quit Sense app from the Google Play app store.

5.7.4 Concomitant Care

All participants will have access to treatment as usual for smoking cessation regardless of randomisation into this trial.

5.7.5 Protocol Treatment Discontinuation

In consenting to the trial, participants are consenting to trial treatments, trial follow-up and data collection. However, an individual participant may stop treatment early, either through their own disengagement with the app and follow up requests or through contacting the trial team to formally request withdrawal.

As participation in the trial is entirely voluntary, the participant may choose to discontinue trial treatment at any time without penalty or loss of benefits to which they would otherwise be entitled. Although not obliged to give a reason for discontinuing their trial treatment, a reasonable effort should be made to establish this reason, whilst remaining fully respectful of the participant's rights.

Participants who discontinue using the app for any of the above reasons, should remain in the trial for the purpose of follow up and data analysis.

5.8 Outcomes

5.8.1 Feasibility Outcomes

As this is a feasibility trial there is no primary outcome. Outcomes will be collected to enable an estimation of key parameters to inform a future trial, in line with MRC guidance [29], and to provide preliminary information about the impact of the intervention:

i. Completeness of the anticipated primary outcome for a future definitive trial (6-month self-reported abstinence with biochemical validation; see smoking outcomes section below for definition).
ii. Abstinence rate of usual care arm, using the anticipated primary outcome for a future definitive trial.
iii. Cost per recruit, based on recruitment advertising costs.
iv. Rates of app installation, use and support delivery fidelity.
v. Completion of smoking cessation-related resource use and quality of life (EQ-5D-5L) [30] data.
vi. Hypothesised mechanisms of action of Quit Sense (see below).

Download rates, use rates and delivery fidelity of Quit Sense (iv) will help assess whether initiation and engagement with the intervention and its delivered dose is sufficient to bring about changes in behaviour [31,32].

5.8.2 Smoking and Smoking-related Outcomes

The main abstinence outcome for which we will monitor completeness of ascertainment in this study will be the anticipated primary outcome for a future definitive trial. This measure is based on the Russell standard [33], considered a gold standard approach for defining abstinence. Abstinence will be defined as: self-reported abstinence in the previous 6 months allowing for no more than five cigarettes and not smoking in the previous week, biochemically validated by a saliva cotinine concentration of less than 10 ng/ml [33,34] or anabasine concentration of less than 2 ng/ml for those using nicotine substitution (e.g. Nicotine Replacement Therapy, e-cigarette) [34,35]. These thresholds will be reviewed prior to analysis in case of any changes in guidance or relevant evidence. Given recent evidence that some e-liquid, believed to be that made outside of the UK, can contain anabasine [34], we will monitor the proportion of e-cigarette users who report abstinence from smoking but have an anabasine level above the chosen threshold. We will follow up participants at 6.5 months (referred to as 6-month follow up) to allow up to two weeks to initiate a quit attempt and so be able to record abstinence for 6 months.

Smoking cessation experts highlight the value of additional smoking outcomes based on different time periods of abstinence and time-points [36], and these can help to identify behaviour change at earlier time-points and shorter periods of abstinence. We will therefore also measure:

- 7-day point prevalence abstinence at 6 months (self-report and biochemically verified)
- 7-day point prevalence abstinence at 6 weeks follow-up (self-report)

We will collect the following hypothesised mechanisms of action at 6-week follow-up:

- Lapse incidence (any smoking, even a puff) [37], which is highly predictive of relapse [10,38,39].
- Lapse prevention strategy use [16], which is associated with lapse prevention [9].

- Self-efficacy [18,26], which prospectively predicts lapse and relapse to smoking [40].
- The Strength of Urges to Smoke (SUTS) measure [28], which prospectively predicts abstinence and is superior to other urge measures in doing so [41], and Frequency of Urges to Smoke (FUTS) [41].
- Automaticity and associative processes subscales from the Wisconsin Inventory of Smoking Dependence Motives (WISDM-37) [42], which is a validated measure with good psychometric properties.

5.8.3 Qualitative Study/Process Evaluation

The aims of the qualitative process evaluation are:

1. To understand participant experiences of participating in the study.
2. To gather user views on app usage in order to inform further optimisation of the final app.

We will invite a purposively selected subsample of participants to take part in a qualitative interview. This activity will be guided by the MRC guidance on process evaluation of complex interventions [43]. Part of this is to use interview data to better understand participant experiences of the intervention and how these experiences might help explain the causal pathway towards smoking behaviour change, as recommended. Qualitative interview topic guides will probe for in depth descriptions of experiences, e.g. of cravings experienced and how app delivered support may have helped 'in the moment', or not. Detailed information gathered qualitatively will allow a richer understanding of situations and experiences than would be possible to gather through the app or quantitatively. In addition to using interview data, to meet the second aim of the process evaluation study, we have embedded an audio record feature into Quit Sense where users are invited to audio-record feedback on their views and experiences of using the app. This would in part be assessing the feasibility of a user-initiated process evaluation approach where data would be collected in a high ecologically valid context. Any relevant data submitted, will be analysed alongside the interview data, to potentially provide a broader range of views from a more user-controlled perspective.

At the 6-week follow-up, participants, including those in the intervention (~n=15) and usual care arms (~n=5), will be invited to participate in a telephone qualitative interview as part of the process evaluation. We will use purposive sampling for intervention participants where possible by aiming to recruit individuals with high and low SES (as per study stratification), varied rates of app engagement and including abstainers and continuing smokers. For control participants, a mixture of high and low SES individuals will be purposively sampled. During the interview, intervention participants will be asked about their experience and views of self-monitoring smoking using the app, including any environmental context factors/triggers missing from the smoking report survey, probing for detail and specific examples in order that we can begin to tease out causal pathways to behaviour change. We will also ask about ease of use of the app, types of messages liked most and least, views on timing of messages when entering or dwelling in a smoking zone (geofence), views on the 'my profile' and 'library' sections of the app, views on features they would like that are not currently provided, how personalisation of the app be improved etc. Control participants will be asked about their experience of participating in the study, informing an assessment of the feasibility of randomised study design for a definitive trial. Both groups of participants will be asked about their use or interest in use of other smoking cessation aids and different types of cessation support

available, including e cigarettes, use of other smoking cessation apps, other health and wellbeing apps and NHS-orientated smoking cessation support options.

5.9 Participant Timeline

Table 1 Schedule of enrolment, interventions, and assessments

	STUDY PERIOD			
	Enrolment (online)	Allocation (online)	Post-allocation (online or telephone)	Close-out (online or telephone)
TIMEPOINT	*0*	*0*	**6 weeks FU (from enrolment)*	***6 months FU (from enrolment)*
ENROLMENT:				
Eligibility screen	X			
Informed consent	X			
Allocation		X		
INTERVENTIONS:				
Usual care (link to www.smokefree.nhs.uk)		X		
Quit Sense app + usual care		X		
ASSESSMENTS:				
Demographics	X			
Use of smartphone and apps	X			X
Smoking behaviour and dependence	X			X
Smoking beliefs	X			X
Cessation self-efficacy	X		X	X
Strength and frequency of urges to smoke	X		X	X
Automaticity and associative processes subscales (WISDM-37)	X		X	
EQ-5D-5L	X			X
Smoking lapse incidence			X	

Smoking abstinence outcomes			X	X
Use of lapse prevention strategies			X	
Smoking cessation resource use				X
Views on the app (Quit Sense arm only)				X
Assessment of Tobacco Exposure (postal saliva sample)				X

*Follow up at 6 weeks (one month, plus 2 weeks to cover the likely quitting period/phase 1 of the app).

** Follow up at 6 months. Follow up will be scheduled approximately 6 months post enrolment in the study, allowing for an additional 2 weeks to cover the likely quitting period (phase 1 of the app). Although in practice this will be 6 months plus 2 weeks, we will refer to it simply as the '6 month follow up' for convenience.

5.9.1 Human Tissue Samples

Participants reporting abstinence at 6 months will be invited to return a saliva sample by post for biochemical verification (cotinine, or anabasine if using a nicotine delivery device e.g. e-cigarette), to be posted (prepaid) to ABS laboratories [17,44]. Each salivette will be labelled by the research team with a unique identifying code. Samples will be assessed by ABS laboratories for the presence of the biochemical listed above, and then destroyed. No identifiable information will be sent to third parties such as ABS laboratories. Results will be reported back to the trial team for entry into the study database.

ABS laboratories will centrifuge the samples on receipt to check that there is enough saliva for analysis, then the samples will be stored at -20 degrees Celsius until analysis. Samples are likely to be stored for up to 2 months until numbers are sufficient for a batch to be analysed.

5.9.2 Early Stopping of Follow-up

If a participant chooses to discontinue their trial treatment, they should continue to be followed up as closely as possible to the follow-up schedule defined in the protocol, providing they are willing. They should be encouraged and facilitated not to leave the whole trial, even though they no longer take the trial treatment. If, however, the participant exercises the view that they no longer wish to be followed up, this view must be respected and the participant withdrawn entirely from the trial. Data already collected will be kept and included in analyses according to the intention-to-treat principle for all participants who stop follow up early. Participants who stop trial follow-up early will not be replaced.

5.9.3 Loss to Follow-up

Participants not completing follow-up measures on the study website after prompts to complete these are sent by text message, email and telephone, will be contacted by telephone (up to six attempt occasions (e.g. getting an engaged/answerphone response and then getting through shortly

afterwards would count as one attempt occasion) to collect the data. We will not attempt following up participants through other means.

5.9.4 Trial Closure

The end of the trial is defined as 6 months following the last follow-up visit of the last participant randomised, to allow for data entry and data cleaning activities to be completed.

5.10 Sample Size

As this is a feasibility study it is not powered to detect a difference in smoking outcome between the two arms. Therefore, no power calculation has been performed.

The proposed sample size for this feasibility trial is 200 smokers (100 per arm). Participants will be randomised to the usual care or Quit Sense arms on a 1:1 ratio. This sample size will enable key parameters to inform a future definitive trial to be estimable within the following precision (defined as the 95% confidence interval [CI] half-width):

- Primary outcome completion – we estimate a follow-up rate for self-reported smoking status at 6 months of 80%, with precision of +/- 6%. This is based on smoking cessation evaluation trials with online recruitment that are most similar to the proposed trial, namely trials of a cessation smartphone app [45] (2-month follow-up = 84%) and a cessation website [44] (7-month follow-up = 72%). A Cochrane review of web-based cessation trials shows that few report retention rates higher than 80% [46]. For biochemical validation, we estimate that 75% of participants reporting abstinence will return a saliva sample by post, with precision of +/- 22%. This is based on estimates from a cessation website trial with 6 months follow-up [44] (75%) and an SMS text message cessation intervention trial with a 3-month follow-up [18] (80%).
- Cessation rate in usual care arm – based on the control arm abstinence rate in a Cochrane review of mobile phone-based cessation interventions [47], we estimate an abstinence rate of 5% at 6 months follow-up, providing precision of +/- 4%
- App installation and initiation – we estimate that 85% of intervention participants will install the app, with precision of +/- 7%. This is based on installation rates (92%) provided by a study examining engagement with a cessation app among an online population of smokers [48] - we assume slightly lower installation rates as, unlike this other study, we will not use any financial incentives to promote initial engagement.
- App engagement - in our acceptability study, 71% used the app for more than one week (a timeframe deemed meaningful by our PPI panel). With a similar rate in the trial, precision would be +/- 9%. This is in line with engagement rates reported in other studies [48].

5.11 Recruitment and Retention

5.11.1 Recruitment

We will recruit through paid-for online adverts with Google Search and social media (e.g. Facebook, Instagram), limited to England-based IP addresses. The period of recruitment will depend on our advertising budget limit per day, which will be capped to ensure recruitment occurs over a long enough time period to enable follow ups to be undertaken feasibly (e.g. 6 weeks). We plan to use an organisation called Nativve who specialise in digital marketing for research study recruitment

https://www.healthresearch.study/ though we may also directly use paid-for online adverts ourselves.

Prior studies have found the cost per recruit to smoking studies varies from £7 to £40 [49,50]. We have recruited this way in previous studies [51], including to the Quit Sense acceptability study (£66 per recruit). Samples of smokers generated from paid-for online adverts are very similar to samples generated from offline approaches including by GP invitation, newspaper adverts and flyers [50,52,53]. Our PPI panel recommended we test out different wording for adverts to assess which leads to the highest recruitment rate, which we will undertake in conjunction with our proposed digital marketer Nativve alongside imbedded Google analytics in the study website. We will monitor the distribution of socioeconomic status (SES) by collating monthly summaries of baseline data from participants collected on the study website. Low SES will be defined as individuals who have a semi-routine or routine and manual occupation, class 5 in the National Statistics Socio-Economic Classification (NS-SEC) [44], or who have never worked or are long-term unemployed. In order to ensure our sampling strategy does not promote major socioeconomic inequalities of access, if, after 3 months of recruitment or when 35% of the target sample is reached, less than 45% of our sample are categorised as low SES [44] we will take action to increase low SES representation through targeting in our recruitment strategy (e.g. Facebook advertising can target users according to their education, job titles, workplace etc.).

As described in our study flow, based on a study assessing the online uptake of a text message smoking cessation intervention [54], we estimate approximately 3% of those visiting the study landing page from paid-for Google and social media adverts will be both eligible and enrol in the trial. This means we will require approximately 6,625 unique visitors to achieve a sample size of 200.

5.11.2 Retention

To improve retention at both the 6-week and 6-month follow-ups, participants will be sent a study text message, plus email for participants with a preference for this, four weeks after enrolment thanking them for their continued involvement in the study. They will also receive a reminder shortly before the six-week follow up that they will shortly be asked to complete a questionnaire. As suggested by our PPI panel, we will also communicate by text message to inform all participants that they have an important role in the study and their feedback is very valuable. After 12 weeks, participants will be sent a postcard (in an envelope for privacy) with study information (PPI recommendations were to provide information on participant characteristics such as age groups, recruitment rates and follow up rates) to promote continued engagement. Additional approaches to increase response rates are to provide participants with a £5 voucher following completion of the 6-week follow up survey and a £10 voucher following completion of the 6-month follow up survey. Among participants who self-report as abstinent at the 6-month follow up, a £5 gift voucher will be given to those who return a saliva sample. Interview participants (n ~20) will be given a £20 gift voucher.

5.12 Assignment of Intervention

1.1.1 Allocation and Sequence generation

Randomisation will be stratified by smoking rate (<16 vs. ≥ 16 cigarettes/day; based on mean smoking rates from trials recruiting smokers online) [44,55] and socioeconomic status, based on the National

Statistics Socio Economic Classification (NS-SEC) self-coded method [56]. Allocation sequences will be generated by a computer-based random number generator using random permuted blocks (varying block sizes). Randomisation will be integrated into the enrolment process on the study website and measures taken to prevent deliberate re-enrolment (e.g. IP address re-enrolment blocking).

5.12.1 Allocation concealment mechanism

As allocation will be integrated into the study website, the allocation sequence will be concealed from participants until assignment and concealed from members of the trial team, other than the statistician who generated the sequence and those team members who developed the study database.

5.12.2 Allocation Implementation

A statistician within the trial team will generate the allocation sequence. Enrolment and allocation/assignment will be an automated process within the study website. The allocation sequence will be stored on the server hosting the website.

5.12.3 Blinding

As the treatment being assessed is a behavioural intervention, it is not appropriate to blind participants from allocation. Other than the trial statistician who generated the allocation sequence, the developer of the study database and the researcher checking if Quit Sense participants have downloaded the app or not shortly after allocation, the remaining members of the team will be blinded to allocation. Those team members undertaking assessments by telephone at 6 weeks for participants not completing these online, if different to the researcher mentioned above, will remain blinded up until they collect the 6 week outcome data but may become unblinded if participants indicate which arm they were allocated to or they contact participants regarding participation in a process evaluation interview. Assessors will need to become unblinded if following participants up by telephone at 6 months as the final questionnaire includes some arm-specific questions, although all smoking outcome questions will be completed before these are asked.

5.13 Data Collection, Management and Analysis

5.13.1 Data Collection Methods

Relevant trial team members will receive trial protocol training. All data will be handled in accordance with the Data Protection Act 2018 and the General Data Protection Regulation (GDPR).

Each participant will be given a unique trial Participant Identification Number (PID). Data will be collected at the time-points indicated in the Trial Schedule.

Survey Data. The study website will collect all baseline data. The website will also be the primary method for collecting follow up data (outcomes i., ii., v., vi.) after prompts to complete follow up are sent by text message and email, or, if not completed after prompts, data will be collected by telephone. This approach follows an effective protocol for collecting data from smokers who have been recruited from online sources [44]. Data completed online will go directly into the central trial database stored on servers based at the NCTU and any data collected by telephone may be entered onto paper Case Record Forms (CRFs) prior to entry onto the database (but this is not an essential step). Staff will receive training on data collection and use of the online system.

Data collection, data entry and queries raised by a member of the Quit Sense trial team will be conducted in line with the NCTU and trial specific Data Management Standard Operating Procedure.

Participant identifiable contact data (telephone numbers, home addresses, email addresses, first/preferred name) will be collected in an online survey when participants enroll in the trial. This data will be stored on a Participants Database at UEA to enable participants to be contacted by the trial team for the purpose of sending questionnaires, retention text messages, saliva sample kits, and a study postcard during the trial. There will be a clear logical separation of participant identifiable data from the trial data.

Date of birth will also be collected in an online survey when participants enrol in the trial and will be securely stored on the Participants Database at UEA.

Saliva samples. Participants reporting abstinence will be sent a saliva sample kit, with a salivette tube labelled with their participant ID, to be posted (prepaid) to ABS laboratories [17,44]. ABS laboratories analyse the samples and securely send the resulting data to the research team who will then add it to the study database.

Recruitment data. Anonymised data required to calculate the advertising cost per recruit (outcome iii.) will be collected from the online research marketing company Nativve or obtained directly from Google, and social media advertising teams, as we have done in prior studies [20,51]. Data from Nativve and Google analytics will be used to assess the impact of different advert wording on recruitment rates, as suggested by our PPI panel.

App data. App download/installation, use (including smoking reports, location data, support message ratings and end of day surveys), and support delivery (outcome iv.) will be collected during participation in the study among intervention participants using the app and calculated using data from the server hosting Quit Sense (the Computer Laboratory, Cambridge), following approaches developed in the first Quit Sense development study [19]. The app will also collect participants' location data to facilitate the sending of geofence messages, and will also collect audio recorded feedback from participants if they choose to use this feature which will contribute to the qualitative evaluation.

Qualitative data. This will be collected through semi-structured telephone interviews (usual care ~5 and intervention arm ~15). Quit Sense app users will also be invited to audio record any feedback they have on the app and involvement in the study using the audio record feature on the app.

5.13.2 Data Management

Data provided by trial participants will be entered under the participants PID number onto the central database stored on the servers based at NCTU. Access to the database will be via unique, individually assigned (i.e. not generic) usernames and passwords, and only accessible to members of the Quit Sense trial team and external regulators if requested. The servers are protected by firewalls and are patched and maintained according to best practice. The physical location of the servers is protected physically and environmentally in accordance with University of East Anglia's General Information Security Policy 3 (GISP3: Physical and environmental security).

The database and associated code have been developed by NCTU Data Management, in conjunction with the Quit Sense trial team. The database software provides a number of features to help maintain data quality, including; maintaining an audit trail, allowing custom validations on all data, allowing users to raise data query requests, and search facilities to identify validation failure/ missing data.

After completion of the trial the database will be retained on the servers of NCTU for on-going analysis of secondary outcomes.

Any transcriptions from the telephone interviews or app collected qualitative data will be anonymised. Voice recordings from telephone interviews and app recordings will be deleted after transcription, or if not transcribed then after audio coding for analysis.

5.13.2.1 *Data collected by the Quit Sense app*

Storage of each participants' data is to be periodically sent to a server for safe-keeping. Data will be tied to an anonymised participant ID and the University of Cambridge will not store any information regarding the participant's details themselves apart from that ID. Data is stored in a restricted space with limited access. Integrity of the server itself is ensured by keeping standard industry practices including: encrypting communications via SSL/TLS, keeping operating system and related packages updated, restricting directory accesses to allowed personnel.

Voice recordings

All audio-recordings that are submitted through the app will be stored securely within the Medical School, University of Cambridge before being transferred to the University of East Anglia for storage prior to processing and analysis

Location data

The Quit Sense app uses the mobile phone's in-built location sensors (e.g. GPS) to record participant location. This data is therefore personally identifying and will be stored securely. Any datasets where location data is combined with anonymised study data will also be kept securely. Location data will be kept for 20 years before being destroyed. This data will not be made available as an open data set outside of Quit Sense collaborations.

5.13.3 Non-Adherence and Non-Retention

All participants, regardless of adherence/engagement with the interventions they receive or their smoking status, will have all outcomes and measures recorded unless they have withdrawn from the study beforehand or are lost to follow up.

5.13.4 Statistical Methods

5.13.4.1 *Outcomes*

Completeness of the anticipated primary outcome for a future trial (feasibility outcome i.) and the abstinence rate using this anticipate primary outcome for the usual care arm (outcome ii.) will be described as proportions with 95% CIs, and translated into interpretable probabilities using the Bayesian approach relevant in preliminary trials with the objective of powering the definitive trial.

Cost per recruit (outcome iii.), rates of app installation (outcome iv.) and completion of smoking cessation-related resource use and quality of life (EQ-5D-5L) (outcome v.) will also be described using summary statistics with 95% CIs.

We will estimate the preliminary intervention effect on abstinence, lapse incidence and use of lapse prevention strategies, using multiple logistic regression, providing odds ratios with 95% CIs, while adjusting for any potential baseline confounders defined by the analysis Plan. For the estimated intervention effect on abstinence we will assume missing=smoking, as recommended [33]. To estimate intervention effects on self-efficacy, urges and smoking dependence motives, we will use ANCOVA models involving adjustment for the baseline score and for pre-defined potential confounders, primarily using complete cases only. Missing outcome assumptions will be assessed through sensitivity analyses which will be defined in the SAP.

5.13.4.2 *Analysis Plan*

An Analysis Plan will be written prior to the completion of data collection and published on the Open Science Framework.

5.13.4.3 *Analysis Population*

All participants randomised to the study will represent the study population as part of an intention to treat approach, excluding any participants who withdraw and do not provide or agree for us to use of relevant data.

5.13.4.4 *Missing Data*

For analyses estimating the preliminary intervention effect on abstinence, we will primarily assume missing=smoking, as recommended [33], although missing outcome assumptions will be assessed through sensitivity analyses which will be defined in the SAP. For estimating mechanisms of action of the intervention effect we will primarily use complete cases only.

5.13.5 Economic evaluations

Estimation of cost-effectiveness, within a health-technology assessment, is an iterative process [57]. We aim to collect data that will enable us to inform the decision as to how cost (based on resource use data) and benefit (in terms of quality of life (QoL) data are estimated in any future, a more definitive study. In line with NIHR guidance [58] in this feasibility study we will monitor levels of resource-use and QoL (via baseline and 6 month questionnaires) with a view to optimise the way that such data is collected in a future trial.

In terms of costs we will estimate those associated with the intervention (e.g. maintaining the app), and smoking related costs to both the individual (e.g. nicotine replacement therapy) and the NHS (e.g. NHS stop smoking services / GP visits). In line with NICE guidance [59], QoL will be measured via the EQ-5D-5L [30], as this enables the calculation of QALY (Quality Adjusted Life Year) scores.

5.13.5.1 *Health Economic Analysis Plan*

The main purpose of the analysis is to inform the decision as to how the data on resource use and QoL would be collected within a more definitive study. Completion rates will thereby be estimated. Appropriate unit costs (e.g. Curtis & Burns [30]) will also be attached to all items of resource-use in order to identify major cost drivers.

5.13.5.2 *Within trial analysis*

Based on the intention to treat approach, a preliminary cost-effectiveness analysis will also be performed, though the results will need to be treated with caution. In the base-case analysis, costs will be estimated from the viewpoint of the NHS and personal social services.[59] Outcomes will be estimated in terms of QALYs, based on EQ-5D-5L data. We will estimate the mean incremental cost and mean QALY gain associated with the Quit Sense intervention compared to usual care. Assuming dominance does not occur (where one intervention is both more costly and less effective), then the incremental cost effectiveness ratio (incremental cost/QALY gain) will be estimated and assessed in relation to a range of cost-effectiveness thresholds (e.g. £20,000 to £30,000 per QALY)[59], in order to provide a preliminary assessment of whether the Quit Sense intervention constitutes value for money. The associated level of uncertainty will also be estimated.

5.13.6 Analysis of Qualitative Data

Analysis of process evaluation data will primarily focus on identifying key themes associated with the use of the app and views and experiences of using other relevant apps, supplemented with a descriptive analysis of relevant experiences to begin to hypothesise intervention causal pathways towards behaviour change. Interviews will be audio-recorded and transcribed verbatim. We may also transcribe audio-recordings submitted via Quit Sense's audio recording feature, depending on audio quality, quantity of recordings and resources. If transcription of recordings is not feasible, we will thematically analyse audio data.

We will undertake an inductive thematic analysis of the first 3-4 interview transcripts [60]. Following this initial coding, we will develop a coding framework, to be agreed by the research team. Once the coding framework is finalised, all data will be coded. We will check coding consistency by independently dual coding a proportion of the data. Based on our prior qualitative studies this is usually ~10% of the data with a further 10% if coding consistency is not satisfactory. After coding we will identify and iteratively refine emerging themes. We will seek input from our PPI panel to enable member checking, thereby increasing the trustworthiness of the final analysis. We will continue refining until the final themes are agreed upon. A second stage of analysis will work with descriptions of experiences that are particularly insightful to instances of lapse or lapse avoidance in the context of the app. These will be reported as vignettes to illuminate and describe participant experiences and begin to identify mechanisms of action and casual pathways towards behaviour change that can be used to refine the intervention logic model. We will use NVivo to support the qualitative analysis.

5.13.7 Analysis of Tissue Samples

While no tissue samples will be analysed, ABS laboratories will assay saliva samples for the presence of the biochemical cotinine or anabasine (dependent on whether the participant reports using alternative sources of nicotine (e.g. nicotine replacement therapy or e-cigarettes) to validate smoking status at 6 month follow up among those reporting abstinence. Samples will be destroyed once assayed.

5.14 Data Monitoring

5.14.1 Data Monitoring Committee

As we do not anticipate there being any harms associated with the intervention or participating in the trial, we do not require a Data Monitoring Committee (DMC). The Trial Steering Committee will take on the role of DMC if required.

5.14.2 Quality Assurance and Control

5.14.2.1 *Risk Assessment*

The Quality Assurance (QA) and Quality Control (QC) considerations for the Quit Sense trial are based on the standard NCTU Quality Management Policy that includes a formal Risk Assessment, and that acknowledges the risks associated with the conduct of the trial and proposals of how to mitigate them through appropriate QA and QC processes. Risks are defined in terms of their impact on: the rights and safety of participants; project concept including trial design, reliability of results and institutional risk; project management; and other considerations.

QA is defined as all the planned and systematic actions established to ensure the trial is performed and data generated, documented and/or recorded and reported in compliance with the principles of GCP and applicable regulatory requirements. QC is defined as the operational techniques and activities performed within the QA system to verify that the requirements for quality of the trial related activities are fulfilled.

5.14.2.2 *Central Monitoring at NCTU*

NCTU staff will review Case Report Form (CRF) data for errors and missing key data points. The trial database will also be programmed to generate reports on errors and error rates. Essential trial issues, events and outputs, including defined key data points, will be detailed in the Quit Sense trial Data Management Plan.

5.14.2.3 *Trial Oversight*

Trial oversight is intended to preserve the integrity of the trial by independently verifying a variety of processes and prompting corrective action where necessary. The processes reviewed relate to participant enrolment, consent, eligibility, and allocation to trial groups; adherence to trial interventions and policies to protect participants; completeness, accuracy and timeliness of data collection; and will verify adherence to applicable policies detailed in the Compliance section of the protocol. Independent trial oversight complies with the NCTU trial oversight policy.

5.14.2.3.1 Trial Management Team

The Trial Management Team (TMT) has been set up to assist with developing the design, co-ordination and day to day operational issues in the management of the trial, including budget management.

5.14.2.3.2 Trial Management Group

A Trial Management Group (TMG) will be set up to assist with developing the design, co-ordination and strategic management of the trial. The membership, frequency of meetings, activity (including trial conduct and data review) and authority will be covered in the TMG terms of reference.

5.14.2.3.3 Independent Trial Steering Committee

The Independent Trial Steering Committee (TSC) is the independent group responsible for oversight of the trial in order to safeguard the interests of trial participants. The TSC provides advice to the CI, NCTU, the funder and sponsor on all aspects of the trial through its independent Chair. The membership, frequency of meetings, activity (including trial conduct and data review) and authority will be covered in the TSC terms of reference.

5.14.2.3.4 Trial Sponsor

The role of the sponsor is to take on responsibility for securing the arrangements to initiate, manage and finance the trial. The Sponsor satisfies itself that the study meets the relevant standards, and makes sure that arrangements are put and kept in place for management, monitoring and reporting.

6. Ethics and Dissemination

6.1 Research Ethics and Health Research Authority Approval

Before initiation of the trial, the protocol, all informed consent forms and any material to be given to the prospective participant were approved by the Wales REC7 NHS Research Ethics Committee (reference 19/WA/0361). Any subsequent amendments to these documents will be submitted for further approval.

The rights of the participant to refuse to participate in the trial without giving a reason must be respected. After randomisation the participant must remain within the trial for the purpose of follow up and data analysis according to the treatment option to which they have been allocated. However, the participant remains free to change their mind at any time about the protocol treatment and follow-up without giving a reason and without prejudicing their further treatment.

No NHS sites will be used in this study and HRA approval is not required.

6.2 Competent Authority Approvals

This is not a Clinical Trial of an Investigational Medicinal Product (IMP) as defined by the EU Directive 2001/20/EC. Therefore, a CTA is not required in the UK.

6.3 Amendments

Amendments to the Protocol and other documents (e.g. changes to eligibility criteria, outcomes, sample size calculations, analyses) will be agreed by the TMG. Such amendments will be forwarded to the Sponsor for confirmation as to whether it is either substantial or non-substantial and will then be submitted to the Ethics Committee for categorisation and approval prior to implementation.

6.4 Consent or Assent

Participants will be provided with an online Participant Information Sheet (PIS) and given time to read it fully. This information will be provided on the study website and also available to download from the same. If participants have questions, they will be able to submit these to the research team via email or telephone and providing any questions they have are satisfactorily answered and they are willing to participate, then informed consent will be obtained (online with an e-signature). During the consent process it will be made completely and unambiguously clear that the participant is free to refuse to participate in all or any aspect of the trial, at any time and for any reason, without incurring

any penalty. Consent will be re-sought if new information becomes available that affects the participant's consent in any way. This will be documented in a revision to the PIS and website content and the participant will be asked to complete an updated consent form. These will be approved by the ethics committee prior to their use. A copy of the approved consent wording will be made available from the NCTU team and on the trial website from which it will be possible for participants to download a copy.

6.5 Confidentiality

Any paper copies of personal trial data will be kept at the central site in a secure location with restricted access. Following consent, identifiable data will be kept on the trial database to allow authorised members of the trial team to contact participants in order to undertake follow up assessments. Only authorised trial team members will have password access to this part of the database. Personal contact information stored securely and destroyed 12 months after the end of the trial. Research data will be stored securely and destroyed 20 years after the end of the trial.

Participants will be asked to provide their first name in order that communications (e.g., SMS messages) can be personalised. This information will be collected in a separate area of the CRF with restricted access for contact purposes only and will not be sent for analysis. At trial enrolment the participant will be issued with a participant identification number and this will be the primary identifier for the participant.

6.6 Declaration of Interests

The investigators named on the protocol have no financial or other competing interests that impact on their responsibilities towards the scientific value or potential publishing activities associated with the trial.

6.7 Indemnity

UEA insurance shall apply.

6.8 Finance

Quit Sense is fully funded by the National Institute for Health Research (NIHR) grant number 17/92/31. It is not expected that any further external funding will be sought.

6.9 Archiving

The investigators agree to archive and/or arrange for secure storage of Quit Sense trial materials and records for 20 years after the close of the trial unless otherwise advised by the NCTU.

6.10 Access to Data

Requests for access to trial data will be considered, and approved in writing where appropriate, after formal application to the TMG or TSC. Considerations for approving access are documented in the TMG and TSC Terms of Reference.

6.11 Publication Policy

6.11.1 Trial Results

The results of the trial will be disseminated regardless of the findings.

6.11.2 Authorship

The publication policy will be in line with rules of the International Committee of Medical Journal Editors. The TMG will decide on the dissemination strategy including presentations, publications and authorship with any difficulties being resolved by the TSC. For main publications, the TMG will nominate a writing group, which will consist of members of the TMG supplemented by the site PIs and others who have made major contributions, who will be responsible for drafting the main manuscripts for publication. These individuals will be named on the final publication

6.11.3 Reproducible Research

The protocol will be published and made open access and the Analysis Plan will be published on the Open Science Framework. Any requests for non-identifiable data will be considered by the TMG.

7. Ancillary Studies

8. Protocol Amendments

9. References

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10.Appendices