Randomised controlled trial to test the effectiveness of an intensive home support Intervention for newly abstinent smokers leaving hospital

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Short title: Hospital to Home, Smoker Support Trial

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SYNOPSIS

Title	RCT to test the effectiveness of an intensive home support intervention for newly abstinent smokers leaving hospital
Acronym	HTH
Short title	Hospital to Home, Smokers Support Trial
Chief Investigator	Professor John Britton
Objectives	To test the effectiveness of an intensive home support intervention to maintain abstinence from smoking for newly abstinent smokers leaving hospital
Trial Configuration	Individually-randomised controlled trial comparing intervention and usual care after hospital discharge
Setting	Nottingham City Hospital
Sample size estimate	We will recruit from all acute medical wards for 12 months, and from experience of recruitment in the proposed setting expect to identify 800 eligible smokers, and for at least 300, and possibly 400, to agree to participate. A sample size of 300 will generate 80% power to detect a 16 percentage point increase (from 38% to 54%) in cessation at 4 weeks; if we succeed in recruiting 400 the power to detect a difference of this magnitude is increased to 90%. We also aim to engage approximately 50 patients (25 from intervention and 25 from usual care) in a qualitative evaluation of the intervention components.
Number of participants	400 in randomised trial and 50 in qualitative interviews.
Eligibility criteria	All self-reported current or recent (smoked within 7 days before admission) smokers aged 18 or over admitted to one of the acute medical wards at Nottingham City Hospital.
Description of interventions	Usual care: Smoking cessation support as recommended in NICE PH48 guidance, including advice to quit and cessation pharmacotherapy, offer of referral to local NHS Stop Smoking Services (SSS) after discharge, and contact at four weeks after discharge to ascertain and if appropriate validate (with exhaled CO) smoking cessation. Intervention: Usual care plus provision, if accepted, of a home visit (or telephone call if a home visit is refused) as soon as practicable after discharge and typically within 48 hours, to deliver a multi-component intervention which includes: • Advice on changing routines to avoid smoking cues when in the home. • Help with strategies to deal with cravings and high risk situations. • Help to remove physical smoking cues (e.g. cigarettes, ashtrays, other paraphernalia) from the home. • Ensuring continuity of supply and advice on optimal use of pharmacotherapy. • Engagement with and provision (if accepted) of nicotine replacement therapy to promote smoking cessation or at least

	temporary abstinence in the home by family or other household members or regular visitors who smoke • the offer of 24-hour indoor air quality monitoring as motivation to sustain a smoke-free home • Continued home visits and telephone contacts to provide behavioural support, and/or transfer to community NHS SSS support where appropriate and according to participant preference. • For those choosing to use electronic cigarettes, advice on product choice and use in conjunction with a transdermal NRT patch, with signposting to a reputable retailor • Exhaled CO readings as a motivational tool and to validate cessation at 4 weeks and three months. • Telephone access to SCPs for use if in danger of, or in the event of, relapse • Self-help materials and direction to online and mobile phone apps to support cessation. For the qualitative interviews, approximately 50 patients will be interviewed. We aim to sample 25 patients randomised to receive the intervention and 25 randomised to usual care who continued with support received in hospital post discharge (pharmacotherapy or NHS SSS support). Interviews will consider reasons for taking up support, which components of support were received, reasoning for choices of different support components, the perceived role of support components in supporting smoking cessation, and how the intervention could be improved.
Duration of study	Study Duration: 12 months. Participant Duration: Maximum 14 weeks.
Randomisation and blinding	Patients providing informed consent will be individually randomised using concealed allocation to receive either usual care or intervention. The randomisation sequence (1:1 in permuted blocks of random size up to size 6) will be generated using a computer random number generator and patients allocated sequentially, and overseen by the University of Nottingham clinical trials unit. The trial interventions cannot be blinded but all analysis will be carried out blind to treatment allocation.
Outcome measures	Primary outcome: • CO-validated (<6 ppm) continuous abstinence from smoking four weeks after discharge from hospital Secondary outcomes: • Un-validated self-reported continuous abstinence from smoking for four weeks after discharge • Proportion of smokers accepting the enhanced intervention and consenting to take part in follow-up • Components of the enhanced intervention (see above) utilised by smokers, in total and in relation to achievement of primary outcome • For those who continue to smoke, reduction in number of cigarettes smoked relative to pre-admission usual consumption • Proportion of smokers reporting smoke-free homes at four weeks post-discharge

	• Self-reported continuous cessation at three months post-discharge • CO validated cessation at three months post-discharge
Statistical methods	Primary analysis will be by intention-to-treat, including all those randomised to usual care or enhanced intervention, and assuming in primary analysis that those with missing data at 4 weeks or 3 months have relapsed to smoking. We will estimate the proportion consenting to take part in the study (with a 95% confidence interval). For those who take part, we will estimate the proportion who are retained in the study and provide data up to 4 weeks and up to 3 months, and compare the characteristics of those who provide outcome data and those who do not to examine the patterns of missingness. We will estimate the effect of the intervention by comparing our primary and secondary outcomes between intervention and usual care groups, expressing effect size as the percentage point difference and 95% confidence interval, and using multiple logistic regression to adjust for prognostically important variables. Sensitivity analysis will explore alternative missing data assumptions. Qualitative data will be analysed using the Framework approach and Nvivo software will be used to aid data management, interpretation and synthesis.

ABBREVIATIONS

AE Adverse Event

CI Chief Investigator overall

CO Carbon Monoxide

CRF Case Report Form

DMC Data Monitoring Committee

GCP Good Clinical Practice

GP General Practitioner

ICF Informed Consent Form

NCSCT National Centre for Smoking Cessation and Training

NHS National Health Service

NICE National Institute for Health and Care Excellence

PIS Participant Information Sheet

R&D Research and Development Department

REC Research Ethics Committee

SAE Serious Adverse Event

SCP Smoking Cessation Practitioner

SSS Stop Smoking Service

TABLE OF CONTENTS

TRIAL / STUDY BACKGROUND INFORMATION AND RATIONALE

Tobacco smoking is the largest avoidable cause of premature death and disability in the UK. Half of all lifelong smokers die as a consequence of their smoking, typically from lung cancer, chronic obstructive pulmonary disease or cardiovascular disease (1). Average life expectancy among smokers is 10 years less than in never-smokers, equivalent to nearly 3 months of life lost for every year smoked after the age of 35. Quitting smoking at almost any age significantly increases both expectancy and quality of life (1). Helping as many of the 10 million current smokers in the UK as possible to quit smoking is therefore one of the highest public health priorities, and also one of the most cost effective of medical interventions.

Our analysis of electronic primary care records has recently estimated that approximately 1.1 million smokers are admitted to English hospitals every year (2). Every one of these admissions represents a prime opportunity to intervene to promote smoking cessation, particularly since most smokers abstain from smoking while in hospital. Recent NICE guidance (PH48)(3) recommends that smoking cessation interventions should be provided in routine care pathways for all smokers admitted to hospital , and our earlier work(Evaluation of the impact of a systematic delivery of cessation interventions on delivery of smoking cessation in secondary care. REC Reference Number:10/H0403/34) in this Programme (RP-PG-0608-10020) has demonstrated that default delivery of cessation support to all smokers significantly increases uptake of support and doubles the proportion of smokers who quit long term (4). Clinical experience indicates that many smokers admitted to hospital, particularly those with an illness caused or exacerbated by smoking, are motivated not to smoke again after discharge but are also likely to be heavily dependent on smoking and in many cases are disabled by lung or heart disease, socially isolated, and socio-economically deprived. On leaving hospital, many return to a home environment where smoking has been an integral part of daily life for many years. It is therefore not surprising that whilst many smokers manage to stay smoke-free during their hospital stay, relapse after discharge is common. In our study, among smokers who received care similar to that now recommended by NICE, 62% of those abstinent at discharge had relapsed by 4 weeks, and 81% by 6 months (4). We hypothesise that many of these relapses could be prevented by interventions that help to sustain cessation and the maintenance of smoke-free home after discharge.

We therefore propose, as an extension to our hospital inpatient study (4) to test the effectiveness of an intensive home support intervention for newly-abstinent smokers leaving hospital and involving home visits to support cessation and establishment of a smoke-free home; ensure receipt and correct use of smoking cessation pharmacotherapy; deliver behavioural support or else, where local services are preferred, transfer to local community Stop Smoking Services (SSS) occurs and these services are delivered; and other components likely to support sustained abstinence from smoking.

TRIAL / STUDY OBJECTIVES AND PURPOSE

PURPOSE

The present study is proposed to build on our demonstration of the effectiveness of default delivery of smoking interventions in hospital inpatients by testing a multi-component intervention to prevent relapse to smoking after hospital discharge. The proposed intervention is designed to integrate easily with existing services, and hence be widely implemented if shown to be effective.

PRIMARY OBJECTIVE

To determine the effectiveness of a multi-component intervention to prevent relapse to smoking after hospital discharge with usual care on CO-validated smoking cessation one month after discharge

SECONDARY OBJECTIVES

To determine the effect of the intervention compared to usual care on smoking cessation at three months after discharge; uptake of the various intervention components and the odds of cessation associated with uptake of each component; cigarette consumption in smokers who relapse; time to relapse; and reported achievement of a smoke-free home.

DETAILS OF PRODUCT(S)

All participants who have not been discharged with a supply of a smoking cessation medication will be offered free nicotine replacement therapy (NRT) by the NCSCT trained (5) smoking cessation practitioner (SCP) employed by the University of Nottingham(clinically supervised and with honorary contracts from our local NHS stop smoking service, New Leaf) at the 2hr/48hr home visit. For those who accept, products will be dispensed by the smoking cessation practitioner in accordance with General Sales License (GSL) protocols established by the NHS SSS ('New Leaf') in Nottingham, and will typically comprise a transdermal patch to be used daily, and a short-acting product (typically the inhalator, or else nasal spray, gum, or mouth spray) for supplementary use to treat breakthrough withdrawal symptoms, according to participant preference. Participant's use of NRT will be reviewed at each contact, and further product dispensed for up to 12 weeks. Participants will be able to contact the smoking cessation practitioner for help and advice on NRT use at any time during this period, and will be able to switch between NRT products if required. Participants who prefer to change to therapy with either varenicline or bupropion will be helped to do so by the advisor, who will contact the patient's general practitioner (GP) to discuss the patients options, and if agreed by the GP ,ensure that the GP provides a suitable prescription and that the medication is, dispensed and used correctly.
NRT will not be prescribed to patients with contraindications or acute heart conditions/stroke. In Secondary Care Bupropion and Varenicline can only be prescribed by a clinician due to the risk of side effects, therefore patients desiring these will be referred to the clinician responsible for their care.

Electronic cigarettes will not be provided directly to participants who wish to use them; however, researchers will provide information on the broad types of electronic cigarettes available, recommend the use of a tank (as opposed to 'cigalike' device) and recommend participants to seek out a local or online retailer to choose and purchase a product. Participants who prefer an electronic cigarette will be advised to use it in conjunction with a nicotine transdermal patch.

Description

In absence of specific contraindication, study participants will be recommended to use a transdermal patch (either the NiQuitin CQ 21 mg 24-hour patch, or Nicorette 15 mg 16-hour patch; the latter for individuals experiencing adverse effects from the 24 hour formulation) in conjunction with the Nicorette 15 mg inhalator. Alternative short-acting products offered will include the Nicorette nasal spray (500µg nicotine per spray), mouth spray (1mg nicotine per spray) or NiQuitin 4 mg gum. Participants in whom nicotine is contraindicated or who express a preference for an alternative to NRT will be offered varenicline (dose increased over 7 days to 1mg twice daily) or bupropion (dose increased to 150 mg twice daily), as recommended in the British National Formulary.

Participants preferring to use an electronic cigarette will purchase their own product according to personal preference; researchers will recommend a tank model, as these have been demonstrated to achieve greater nicotine delivery than the earlier 'cigalike' models (6) but will not recommend specific brands.

Manufacture

NiQuitin products and bupropion are manufactured by Glaxo Smith Kline; Nicorette products by McNeil, and varenicline by Pfizer. All of the above products are licensed by the MHRA for use in promoting smoking cessation.

Packaging and labelling

Products will be used in the manufacturer's standard packaging and labelling, and for licensed medicines, dose instructions included in the packaging and manufacturers' information sheets will be reiterated verbally to participants.

Electronic cigarettes purchased by participants will be obtained as packaged and labelled by the manufacturer; further verbal advice on use will be provided to individual participants in line with recommendations by NCSCT (7) by study staff as necessary.

Storage, dispensing and return

Nicotine Replacement products will be stored in a securely locked, fireproof cupboard, In the Clinical Sciences Building, City Hospital Site, below 25°C, only accessible to the Trial Manager and the 5 NCSCT (5) trained smoking cessation practitioners who will have clinical supervision provided by our local SSS (New Leaf, Nottingham Citycare) . NRT products will be dispensed by the study smoking cessation practitioners, who will have honorary employment contracts with our local stop smoking service and will dispense according to current Local SSS dispensing policy and practice. Surplus or unused stock will be returned to our local SSS to be added to their stock or destroyed in line with organisational policy for unused NRT.

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 (8) British National Formulary; Medicines Complete, Accessed February 2016, https://www.medicinescomplete.com/mc/bnf/current/PHP3201-nicotine.htm#PHP46731-side-effects.

TRIAL / STUDY DESIGN

TRIAL / STUDY CONFIGURATION

An single centre, individually randomised open controlled trial

Primary endpoint

The primary outcome of this study will be self-reported continuous smoking cessation since discharge from hospital, validated by exhaled CO less than 6ppm at 4 weeks (defined as 25-42 days after discharge)

Secondary endpoint

The secondary outcomes are:

- Self-reported continuous smoking cessation at 3 months post discharge, validated by exhaled CO less than 6ppm.
- Self-reported continuous smoking cessation at four weeks post-discharge
- self-reported continuous smoking cessation at 3 months post-discharge.
- Reduction in number of cigarettes smoked per day at four weeks post-discharge compared to usual consumption before hospital admission
- Self-report of having a smoke-free home (defined as a home in which no-one smokes at any time) at four weeks post-discharge
- Acceptance and utilisation of the different components of the enhanced intervention
- Relation between complex intervention component acceptance and primary outcome

Safety endpoints

The study assesses the effect of enhanced behavioural support and access to smoking cessation therapies, not the effectiveness of specific drug therapies. Any adverse effects or discontinuations reported during the trial will be recorded, and incidence compared between intervention and usual care groups. However, as the study assess the effect of the enhanced behavioural support and access to smoking cessation therapies, not the effectiveness of untested drug therapies it is not anticipated that the study will require termination on safety grounds

Stopping rules and discontinuation

Data collection will end on 28th July 2017, in accordance with our funding limits. There are no other predefined rules for stopping or discontinuation.

RANDOMIZATION AND BLINDING

Patients will be randomised to one of the two treatment arms based on a computer generated pseudo-random code using random permuted blocks of randomly varying size, created by the Nottingham Clinical Trials Unit (CTU) in accordance with their SOP and held on a secure server. Access to the sequence will be confined to the CTU Data Manager. Allocation to treatment arms will be in the ratio 1:1 and investigators will access the treatment allocation for each subject by means of a remote, internet-based randomisation system developed and maintained by the Nottingham CTU. STATA will be used generate the treatment allocations list using the RALLOC function.

Members of the research team (Rebecca Thorley, or 2 further research assistants who have yet to be appointed) or one of the smoking cessation practitioners (Five full time equivalent posts which have yet to be filled) will be involved in the recruitment of the patients to the study, and obtaining written informed consent.

Once consent has been obtained, a unique identification number will be allocated to the participant and the researcher will then contact the randomisation database (online or via telephone) and will establish which treatment group the participant has been allocated to, based on their identification number.

Due to the nature of the intervention and how it will be delivered research staff, smoking cessation practitioners and participants will not be blinded to treatment group allocation. The trial statistician and the trial steering group will however remain blind to treatment allocation until the study analysis is complete.

No interim analyses of the data are planned and no stopping rules for the trial have been formulated.

Maintenance of randomisation codes and procedures for breaking code

The sequence of treatment allocations will be concealed until interventions have all been assigned and recruitment and data collection are complete. At the end of the study, when primary and secondary data from both treatment groups have been analysed by the trial statistician the groups will be un-blinded to the trial management group.

TRIAL/STUDY MANAGEMENT

The trial will be overseen by a Trial Management Group who will meet regularly to monitor trial progress. This group shall consist of the chief investigator, trial statistician and two other members of the research team.

The Chief Investigator has overall responsibility for the study and will oversee all aspect of study management.

The data custodian will be the Chief Investigator.

DURATION OF THE TRIAL / STUDY AND PARTICIPANT INVOLVEMENT

Study Duration: 12 months.

Participant Duration: Participants will be enrolled in the trial for a maximum of 14 weeks; this will also include completion of qualitative assessment by a subsample of participants from the intervention group.

End of the Trial

The end of the trial will be the 12 week appointment of the final participant enrolled into the trial, unless the final participant is selected for participation in a telephone or face-to-face evaluation interview, in which case the end of the interview, which will be carried out up to four weeks later, will represent the end of the trial.

SELECTION AND WITHDRAWAL OF PARTICIPANTS

Recruitment

All adults admitted to any of the acute medical wards (and their associated emergency outlying wards) at Nottingham City Hospital who are self-reported smokers at time of admission, or report smoking regularly until the onset of the episode causing admission (if not more than 7 days prior to admission) will be eligible to participate.
All new admissions to these wards, including their shared acute admissions areas, will be screened as early as possible in their admission pathway by a SCP employed by the University

of Nottingham (with an honorary NHS contract), who under recommendation 2 of NICE PH48 guidance; "Smoking: acute, maternity and mental health services" (2013) would form part of the patients usual care team, to ascertain smoking status from medical notes for the current admission or, in the presence of doubt, by direct questioning of patients (3).

Those who meet the study entry criteria will be given an information sheet by the SCP explaining that we are conducting a study comparing different methods of supporting abstinence from smoking after discharge, and that shortly before discharge they will be contacted again by a researcher in the study team and invited to consent to participate. Information about the trial will also be on display in the relevant clinical areas and if required, hospital interpreter and translator services will be available to assist with communication at this and all later stages of informing and recruiting participants. It will be made clear that entry into the trial is entirely voluntary and that inpatient treatment and care will not be affected by their decision.

Eligibility criteria

Inclusion criteria

- All patients aged 18 and over (with no upper age limit).
- Have been admitted for 24 hours or more to any participating inpatient ward at Nottingham City Hospital.
- Who report that they are current smokers, or had smoked within 7 days before the current admission.
- Are capable of understanding and consenting to the trial.

Exclusion criteria

Patients will be excluded;

- If they are pregnant; Pregnant smokers (of whom very few are admitted to medical wards) will be offered cessation advice in line with NICE PH48 guidance.
- If they do not consent to participate,
- If they are too ill or otherwise lack capacity to understand the information and consent forms.
- If they live more than 50 miles from the City Hospital (these patients will be referred to their local community cessation services, in line with NICE recommendations).

Eligible participants who have already been recruited to the study during a previous admission will remain in the same treatment group as before and continue to receive usual care or intervention support accordingly.

Expected duration of participant participation

Participants will be enrolled for a maximum period of 14 weeks of follow-up in the intervention or usual care groups. In the subsample selected for qualitative interviews a further four weeks will be allowed in which to carry out the interview, though where possible the interview will be completed at the three-month follow-up home visit. Interviews are not expected to exceed 1 hour.

Removal of participants from therapy or assessments/participant withdrawal

Participants will be free to withdraw from the trial at their own request at any time and without prejudice to any aspect of their care. Participants will be made aware (via the information sheet and consent form) that should they withdraw, the data collected to date cannot be erased and may still be used in the final analysis.

Informed consent

All participants will provide written informed consent. The Informed Consent Form will be signed and dated by the participant before they enter the trial. 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.

Informed consent will be collected from each participant before they undergo any interventions (including physical examination and history taking) related to the study. One copy of this will be kept by the participant, one will be kept by the Investigator, and a third will be retained in the patient's hospital records.

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 which will be signed by the participant.

TRIAL / STUDY TREATMENT AND REGIMEN

Patients who consent to participate will be asked to provide contact details (personal or in the case of a patient being bedbound or having mobility difficulties for someone who can answer the phone on their behalf)) so that they can be contacted to ascertain smoking status 4 weeks and 3 months after discharge, arrange CO validation in those who report abstinence. They will be informed that if randomised to the intervention group they will be contacted (typically within 24 hours, and hence either immediately before or soon after discharge) to arrange a home visit to deliver further smoking cessation support, and ascertain the number of other regular smokers in the home. Participants will then receive the following:

Usual care group: Participants in the usual care group will be offered and, if accepted, provided with smoking cessation support that meets the recommendations of NICE PH48 guidance including pharmacotherapy and behavioural support before leaving hospital, referral to NHS SSS for continued care after discharge, and ascertainment of smoking status at 4 weeks; participants will also be asked to consent to smoking status ascertainment at three months. Those who report cessation at 4 weeks and/or three months will be requested to agree to a home visit for CO validation. All will be asked at four weeks and 3 months to list the cessation support, in terms of pharmacotherapy and behavioural support from local or other services, delivered since the last contact.

Intervention group: A home visit will be carried out as soon as practicable after discharge and typically within 48 hours, to deliver a multi-component intervention. Intervention components all have an existing evidence base proving or suggesting potential efficacy for smoking cessation and/or relapse prevention(9-17), though their feasibility and importance when delivered as a combined package have not been tested, whilst indoor air quality monitoring has been shown in our analysis of data from work-stream 3 of the present programme (paper in preparation) to be effective in promoting the maintenance of a smoke-free home, and hence supporting smoking cessation. These include:

- Advice on changing routines to avoid smoking cues when in the home.
- Help with strategies to deal with cravings and high risk situations.
- Help to remove physical smoking cues (e.g. cigarettes, ashtrays, other paraphernalia) from the home.

- Ensuring continuity of supply and advice on optimal use of pharmacotherapy.
- Engagement with and provision (if accepted) of nicotine replacement therapy to promote smoking cessation or at least temporary abstinence in the home by family or other household members or regular visitors who smoke
- the offer of 24-hour indoor air quality monitoring, using a using a battery-operated Sidepak Aerosol Monitor AM510 (TSI Instruments Ltd, High Wycombe UK) positioned in the main living area, in the first week after discharge from hospital and again at 12 weeks, as motivation to sustain a smoke-free home
- Continued home visits and telephone contacts to provide behavioural support, and/or transfer to community NHS SSS support where appropriate and according to participant preference.
- For those choosing to use electronic cigarettes, advice on product choice and use in conjunction with a transdermal NRT patch, with signposting to a reputable retailor
- Exhaled CO readings as a motivational tool and to validate cessation at 4 weeks and three months.
- Telephone access to SCPs for use if in danger of, or in the event of, relapse
- Self-help materials and direction to online and mobile phone apps to support cessation.

For participants who decline a home visit, the above support options will be offered as far as possible through telephone contact and delivered to the extent accepted by the participant.

Qualitative evaluation:
Interviews will be arranged at 12 weeks with the sub-sample of patients who provided consent to take part at the point of recruitment. Approximately 50 patients will be interviewed (25 usual care and 25 intervention). We will purposively sample patients to ensure varying levels of engagement with the intervention and support offered via usual care are represented (e.g. stopped smoking, relapsed, used all components of intervention versus less utilisation, referral set up in usual care taken up (or not)).
Semi-structured interviews will be conducted either face-to- or via telephone.
To minimise study burden, we will strive to coincide interviews with the 12 week CO validation appointment.

For patients randomised to receive the intervention, the semi-structured interview guide will explore reasons for taking up the intervention, the components of the intervention that were utilised, the reasons for these choices and views on each aspect received and how it related to outcomes (e.g. smoking status). The guide will also consider areas for improvement, particularly how the service could be improved to enhance uptake. For patients randomised to receive usual care, those eligible for interview will be those who report continued use of either pharmacotherapy and/or support from a NHS SSS post-discharge; which will be ascertained at 4 weeks. Again, interviews will be completed at 12 weeks and will explore the products used (pharmacotherapy, e-cigarette), nature of support received (from NHS SSS or other sources), reasons for these choices and the role they play in outcomes (e.g. smoking status).

Similar to our previous work (18), we will interview approximately 50 smokers (25 from the intervention group and 25 from the usual care group). We will continue to recruit until we reach saturation of new opinions and themes being generated from each group of individuals. Interview participants will be provided with a shopping voucher worth £20 as recompense for the inconvenience of participation.

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 however and data from all consenting participants will be included in the analysis with the assumption that those in whom validated abstinence is not confirmed by and exhaled CO < 6ppm have relapsed to smoking.

Criteria for terminating trial

Recruitment to the trial is time limited since all data have to be collected by the end ofJuly 2017. There are no other termination criteria.

STATISTICS

Methods

The analysis will be conducted in Stata 14 (or later version) using University of Nottingham computers and backed up on University servers. Primary analysis will be by intention-to-treat, including all those randomised to usual care or enhanced intervention. For smoking cessation outcomes, participants who do not provide data at 4 weeks or 3 months, and those who do not provide an exhaled CO reading for validated outcomes, will be presumed to have relapsed to smoking.

We will estimate the proportion consenting to take part in the study (with a 95% confidence interval), and for those who take part, the proportion who are retained in the study and provide data up to 4 weeks and up to 3 months. We will then compare the characteristics of those who provide outcome data and those who do not to examine the patterns of missingness. We will compare baseline characteristics descriptively between those randomised to intervention and usual care. We will estimate the effect of the intervention on our primary outcome by comparing CO-validated 4-wek cessation between intervention and usual care groups, expressing effect size as the percentage difference between groups (as in the power calculation) with a 95% confidence interval, and as the unadjusted and adjusted odds ratios from multiple logistic regression, with adjustment for prognostically important variables which will be defined in our analysis plan. Binary secondary outcomes will be explored using similar analyses. We will explore alternative assumptions about the missing data as described below. Change in numbers of cigarettes is expected not to be normally distributed and will be compared between groups using Mann Whitney U test. All analysis will be carried out by Dr Opazo-Breton under supervision by Professor Lewis. No interim analyses are planned.

Sample size and justification

We will recruit from acute medical wards for 8 months, aiming to achieve a sample size of at least 300. From past experience of recruiting smokers in the same study environment (4) we expect to identify 800 eligible smokers, and for between 300 and 400 to agree to participate. As a wort-cas scenario, recruitment of a sample of 300 will generate 80% power to detect a 16 percentage point increase (from the 38% achieved in our previous study (4) to 54%) in CO-validated cessation at 4 weeks at a two-tailed significance level of 5% (estimated using SPSS Sample Power). If we achieve our intended sample size of 400, the study would have 90% power to detect a 16 percentage point increase (from 38% to 54%) in cessation at 4 weeks.

Assessment of efficacy

Primary outcome:

Self-reported continuous smoking cessation since discharge from hospital, validated by exhaled CO less than 6ppm, at 4 weeks after discharge, expressed as the difference in proportion between treatment groups, with 95% confidence interval, and the unadjusted and adjusted odds ratios from multiple logistic regression.

Secondary outcomes:

- Un-validated self-reported continuous smoking cessation at four weeks
- Self-reported continuous cessation at three months post-discharge
- CO validated (< 6ppm) cessation at three months post-discharge

All of the above will be expressed as the difference in proportion between treatment groups, with 95% confidence interval, and the unadjusted and adjusted odds ratios from multiple logistic regression.

- Reduction in number of cigarettes smoked per day at four weeks post-discharge compared to before hospital admission

This is anticipated to be non-normally distributed and will be expressed as the median difference between groups in the change in cigarette consumption from baseline

- Self-report of having a smoke-free home (no-one smokes in the home at any time) at four weeks post-discharge expressed as the difference in proportion between treatment groups, with 95% confidence interval, and the unadjusted and adjusted odds ratios from multiple logistic regression.
- Acceptance and utilisation of the different components of the enhanced intervention.

  Expressed as proportions taking up and using each component, and indicators of the level of use, including proportions receiving a home visit, median numbers of support phone calls, amount of NRT provided, Number open to using air quality data as a motivational tool, number of other smokers in the household advised.

Qualitative Data Analysis

Interviews will be digitally audio-recorded and transcribed verbatim by a university approved external transcription service. Data will be stored and managed using NVivo® software. Following receipt of the transcripts, the researchers will ensure all personal identifiers are removed and that transcripts are accurate. Participants will be assigned a code that will only identify the group they represent (usual care or intervention). Data generated from the interviews will then be analysed (by the research assistants and Dr. Manpreet Bains) using the framework approach (19), which is a hierarchical, matrix based method developed for applied or policy-relevant research which allows focused interrogation of data. The framework approach will allow the research team to map whether there are differences/similarities according to the individuals sampled (usual care versus intervention groups). Data will be coded using inductive approaches, where the familiarisation stage will enable the identification of themes and sub-themes. Data will then be indexed according to the identified themes and sub-themes. Themes and sub-themes will then be discussed between the research team, which will allow clarification of the final framework. Using NVivo® software, data will then be charted according to each theme to synthesise the data and aid interpretation. Extracts from interviews will be included in the charts.

Assessment of safety

Since the main trial intervention is non-pharmacological and non-invasive, no significant safety issues are anticipated. Adverse events arising from use of NRT or other licensed cessation pharmacotherapy will be managed in accordance with standard clinical practice. Electronic cigarette use by participants at their initiative (with broad advice on product choice from the study team, but no specific direction to individual products) will be recorded and participants will be able to report their experience at the 4 week and 3 month endpoint assessments, and in the qualitative interviews carried out in a subsample of participants.

Procedures for missing, unused and spurious data

We will compare baseline characteristics of those with complete data and those with data missing at 4 weeks or 3 months, to describe the pattern of missingness. Our primary analysis will assume that missing = smoker, as is standard in smoking cessation trials. This is a missing not at random assumption, and we will test this assumption in a number of planned sensitivity analyses, using the Hedeker method to explore alternative associations between smoking and missingness (20). We will also consider a missing at random assumption, adjusting for baseline characteristics associated with missingness.

Definition of populations analysed

All analyses will be carried out on an intention to treat basis, including all patients who are randomised. Missing data at 4 weeks and/or 3 months will be handled as described above.

ADVERSE EVENTS

Potential adverse events from NRT, varenicline and bupropion have previously been well documented and will be discussed with participants in accordance with usual clinical practice at the time of prescription. All prescribing will be carried out in line with guidance in the British National Formulary. Participants who chose to use electronic cigarettes will be advised to do so in conjunction with a transdermal NRT patch, thus using the electronic cigarette as a substitute for a short-acting licensed NRT product, in line with NCSCT guidance(7). If any adverse event that could be related to cessation therapy occurs, management and decisions on continued treatment will be delivered by the smoking cessation practitioners or supervising clinicians in accordance with standard clinical practice. However the safety profile of NRT in particular, and of cessation therapies in general when used in accordance with BNF guidance, is extremely good. Major adverse events caused by uptake of usual care or the intervention package are therefore highly unlikely.

However the nature of the study population makes repeat hospital admissions and other adverse events of all severities possible during the study period, and data on these episodes will be collected for the purpose of comparison between study groups. All adverse events relating to intervention medicines will be reported according to local NHS procedures. Adverse experiences with electronic cigarettes (which will be used only at participants' initiative) will be recorded (see safety, above).

Definitions

Participant removal from the study due to adverse events

Any participant who experiences an adverse event may be withdrawn from the study at the discretion of the Investigator.

ETHICAL AND REGULATORY ASPECTS

ETHICS COMMITTEE AND REGULATORY APPROVALS

The trial will not be initiated before the protocol, informed consent forms and participant information sheets have received approval / favourable opinion from the Research Ethics Committee (REC), and Nottingham University Hospital National Health Service (NHS) Research & Development (R&D) approval. 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 information sheets (if appropriate) have been reviewed and been approved. 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 Department of Health Research Governance Framework for Health and Social care, 2005.

INFORMED CONSENT AND PARTICIPANT INFORMATION

The process for obtaining participant informed consent will be in accordance with the REC guidance, and Good Clinical Practice (GCP) and any other regulatory requirements that might be introduced. The investigator or their nominee and the participant shall both sign and date the Informed Consent Form before the person can participate in the study.

The participant will receive a copy of the signed and dated forms and the original will be retained in the Trial Master File. A second copy will be filed in the participant's medical notes and a signed and dated note made in the notes that informed consent was obtained for the trial.

The decision regarding participation in the study is entirely voluntary. The investigator or their nominee shall emphasize 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 course of 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.

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 (CRFs)

Each participant will be assigned a trial identity code number, allocated at randomisation if appropriate, for use on CRFs other trial documents and the electronic database. The documents and database will also use their initials and date of birth (dd/mm/yy).

CRFs will be treated as confidential documents and held securely in accordance with regulations. The investigator will make a separate confidential record of the participant's name, date of birth, local hospital number or NHS number, and Participant Trial Number (the Trial Recruitment Log), to permit identification of all participants enrolled in the trial, in accordance with regulatory requirements and for follow-up as required. Access to CRFs shall be restricted to those personnel approved by the Chief or local Principal Investigator and recorded on the 'Trial Delegation Log.'

All paper forms shall be filled in using black ballpoint pen. Errors shall be lined out but not obliterated by using correction fluid and the correction inserted, initialled and dated.
The Chief or local Principal Investigator shall sign a declaration ensuring accuracy of data recorded in the CRF.

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 the regulatory requirements listed below.

Direct access to source data / documents

The CRF and all source documents, including progress notes and copies of laboratory and medical test results shall made be available at all times for review by the Chief Investigator, Sponsor's designee and inspection by relevant regulatory authorities (e.g. DH, Human Tissue Authority).

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, 1998. The CRF will only collect the minimum required information for the purposes of the trial. 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.

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.

The University of Nottingham as research Sponsor indemnifies its staff, research participants and research protocols with both public liability insurance and clinical trials insurance. These

policies include provision for indemnity in the event of a successful litigious claim for proven non-negligent harm.

TRIAL CONDUCT

Trial conduct may be subject to systems audit of the Trial Master File for inclusion of essential documents; permissions to conduct the trial; Trial Delegation Log; CVs of trial staff and training received; local document control procedures; consent procedures and recruitment logs; adherence to procedures defined in the protocol (e.g. inclusion / exclusion criteria, correct randomisation, timeliness of visits); adverse event recording and reporting; accountability of trial materials and equipment calibration logs.

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. The Trial Coordinator and a nominated designee of the Sponsor, 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.

Interview data will be held on audio interview files and documents showing the transcribed recordings. A hard copy of data from the interviews will be kept securely in a locked filing cabinet within Clinical Sciences Building (University of Nottingham) for a period determined by the sponsor. Audio recordings will be anonymised (identifiable data removed and replaced with a code) prior to archiving in a secure facility at King's Meadow campus, University of Nottingham. Electronic files will be held securely on password protected computers within the Clinical Sciences Building, accessible only to the research team.

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 Chief Investigator on behalf of the Sponsor shall be finally 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 Trial Steering Committee and Data Monitoring Committee 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. Participant confidentiality will be further ensured by utilising identification code numbers to correspond to treatment data in the computer files.

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

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 the regulatory authorities.

PUBLICATION AND DISSEMINATION POLICY

The results of the study will be presented at appropriate conferences and submitted for publication in a peer-reviewed journal.

USER AND PUBLIC INVOLVEMENT

We will invite members of the Nottingham Smokers Panel (available to the investigators through their membership of the UK Centre for Tobacco and Alcohol Studies, see http://www.ukctas.net/public-engagement.html for detail) to comment on study information sheets and other documentation. The original concept of this study arises from repeated experience of clinical contact with smokers admitted to hospital, their expressed desire and intention to remain smoke- free after discharge, the obstacles that they face and their experiences reported at out-patient follow-up.

STUDY FINANCES

Funding source

This study is funded by the National Institute for Health Research as part of an extension to programme grant RP-PG-0608-10020.

Participant stipends and payments

Participants will not be paid to participate in the trial and no expenses will be incurred as a consequence of participation. Interview participants will be provided with a shopping voucher worth £20 as recompense for the inconvenience of participation.

SIGNATURE PAGES

Signatories to Protocol:

Chief Investigator: Professor John Britton

Signature: 

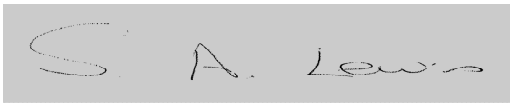
Date:

Co- investigator: Dr. Rachael Murray

Signature:_____

Date: _____

Trial Statistician: Professor Sarah Lewis



Signature:_____

Date:

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