STATISTICAL ANALYSIS PLAN

VERSION 1

ISRCTN99531779

intEgrating Smoking Cessation treatment As part of usual Psychological care for dEpression and anxiety (ESCAPE): a randomised and controlled, multicentre, acceptability, feasibility and implementation trial

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ETHICAL APPROVAL

Ethics approval for this study was received from the NHS Research Ethics Committee on 19/03/2018.

CONFLICTS OF INTEREST

Marcus Munafò and Gemma Taylor previously received funding from Pfizer, who manufacture smoking cessation products, for research unrelated to this study.

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1. INTRODUCTION

Smoking is the world's leading cause of cancer and death worldwide.[1,2] People with common mental illness, such as depression and anxiety, are twice as likely to smoke than those without. In the UK, smoking prevalence in people with depression or anxiety is 32% compared to 14% in the general population.[3,4] People with mental illness have a 19% reduction in the odds of achieving abstinence when making a quit attempt[5] but are as motivated-to-quit as those without mental illness.[6] These differences increase mortality in people with mental illness when compared to the general population resulting from cancer (mortality rate ratio: 1.92 [95% confidence interval: 1.91-1.94])[7] and cardiovascular disease (mortality hazard ratio: 1.85 [95% CI: 1.53-2.24]).[8] Integrating cessation treatment into mental health settings could prevent to 78,000 deaths in the next 80 years.[9]

Recent evidence suggests that smoking can cause mental illness,[10,11] and that stopping smoking can improve mental health.[12–14] Qualitative studies suggest that although people with mental illness report perceived psychological benefits of smoking, they also accept evidence that smoking tobacco may harm mental health and that quitting might benefit mental health; furthermore that framing cessation as a treatment for mental illness could motivate them to quit smoking.[15]

A Cochrane review of smoking cessation treatments for people with current and historical depression found that adding psychosocial mood management to usual smoking cessation treatment (e.g., nicotine replacement therapy) increased cessation rates when compared to usual smoking treatment alone (risk ratio of 1.47; 95% CI 1.13 to 1.92).[16] In the UK, people with depression/anxiety have access to psychological therapy services, known as 'Improving Access to Psychological Therapies' (IAPT), in which service users receive evidence-based therapies to improve mood and wellbeing. IAPT receives over 1.5 million referrals a year[17] and could offer smoking cessation treatment, but it currently does not. Integrating smoking cessation support within IAPT treatment for mental illness could improve physical and psychological outcomes for its service-users.

Therefore, we have conducted a randomised and controlled, multicentre, acceptability, feasibility and implementation trial to test the integration of a smoking cessation intervention into usual IAPT care. We have pre-registered the trial and published the trial protocol and summary analysis plan including our primary and secondary outcomes.[18] In this protocol we describe our statistical analysis plan and will pre-register this protocol on the Open Science Framework's study homepage (10.17605/OSF.IO/GJ36B).[19]

2. OVERVIEW OF TRIAL METHODS

For full trial methodology please see the study protocol (ESCAPE, ISRCTN99531779, DOI:10.17605/OSF.IO/D79AX).[18,19] See Table 1 for schedule of enrolment, interventions, and assessments.

2.1. DESIGN

A randomised and controlled, multicentre, feasibility trial to test the acceptability, feasibility and implementation of smoking cessation treatment offered alongside usual psychological care.

2.2. ETHICAL REVIEW

This study received ethics approval from the National Health Service (NHS) Research Ethics Committee on 19/03/2018 (IRAS ID: 239339).

2.3. SETTING

This is a multicentre study involving six Improving Access to Psychological Therapies (IAPT) sites in the UK, across four NHS trusts.

2.4. PARTICIPANTS

Adults aged ≥18 years, with depression or anxiety, regular daily tobacco smokers of at least 1 year, eligible to start 1:1 treatment in IAPT.

2.5. INTERVENTION

Described in detail in our trial protocol.[18] A behavioural and medicinal smoking cessation intervention delivered as integrated into usual CBT sessions for depression and anxiety. The intervention was delivered by psychological wellbeing practitioners (PWPs) and was delivered over the telephone or face-to-face as per usual care. Participants received as many sessions as required for their depression/anxiety treatment, and the integrated session lasted up to 60 minutes, with approximately 5-15 minutes dedicated to smoking cessation treatment.

2.6. CONTROL

Usual IAPT care with delayed signposting to NHS smoking cessation support.

3. OUTCOMES

See Table 1 for schedule of assessments and measures.

3.1. MAIN ACCEPTABILITY AND FEASIBILITY OUTCOME

Study completion

It could be that by offering patients smoking cessation support they disengage with IAPT services; therefore, this outcome is designed to determine if participants are engaging with the usual care or smoking cessation treatment as clinically expected. Participants will be considered a "study completer" if they continue with treatment up until the point of:

a) biologically validated 7-day point prevalence smoking cessation at 3- or 6-months follow-up (full definition in section **Error! Reference source not found.**),
b) or a quit attempt,
c) or completion IAPT care.

3.1. SECONDARY ACCEPTABILITY AND FEASIBILITY OUTCOMES

3.1.1. Recruitment into the trial

Recruitment rate was recorded by each recruiting site, monthly.

3.1.2. Participant and PWP acceptability and satisfaction smoking cessation treatment

We assessed participant acceptability and satisfaction of smoking cessation treatment at 3- and 6-month follow-up using a modified version of the "Stop Smoking Service Client Satisfaction Survey".[20] This measure asks participants to rate various items on a 3- or 5-point categorical scale (i.e., Question: "Would you recommend this service to other smokers who want to stop smoking?" Answer: "No/Unsure/Yes".

For PWPs we assessed acceptability and feasibility of the integrated smoking cessation treatment using: "Clinician Self-Report Intervention Acceptability Questionnaire", the "Acceptability of Intervention Measure (AIM)", "Intervention Appropriateness Measure (IAM)", "Feasibility of Intervention Measure (FIM)", and "Sustainability of Intervention Measure (SIM)".[21] Some measures ask clinicians to rate various items on a 5-point categorical scale (i.e., Statement: "I like the smoking cessation intervention." Answer: "Completely disagree/Disagree/Neither agree nor disagree/ Agree/Completely Agree") or have used a 1- to 10-point scale (i.e., Statement: "Please rate how well you think the smoking cessation intervention could be sustained in the service in the future.", Answer: 1= "not well at all", 10= "extremely well").

3.1.3. Service-related feasibility outcomes

We collected data to examine the impact of offering smoking cessation treatment on service-related outcomes at appointments and at 3- and 6-month follow-ups:

- The number of planned, completed and missed IAPT appointments,
- IAPT treatment status (active/discontinued/completed/discharged).

3.1.4. Smoking cessation treatment-related feasibility outcomes

We collected data to examine the feasibility of smoking cessation treatment at appointments and at 3- and 6-month follow-ups:

- Completion of smoking cessation treatment session (completed/not completed),
- Patient retention in smoking cessation treatment (continued/discontinued),
- Average PWP reported duration of smoking cessation treatment sessions in minutes,
- Patient use of smoking cessation medication (type of medicine and dose, and e-cig use).

3.1.1. Blinded outcome data collection

We aimed to conduct blinded data collection at 3- and 6-months follow-up. It was likely that researchers would become unblinded by the end of the follow-up call because of the nature of questions asked (i.e., the Stop Smoking Service Client Satisfaction Survey) or by extracting appointment data from clinical patient notes. Because of the possibility of unblinding we designed the sequence of outcome data collection so that a) researchers were less likely to become unblinded at the start of the call and b) collected the measures that were deemed more likely to be influenced by knowledge of treatment allocation before measures that were reported to lead to unblinding (i.e., the PHQ-9 and GAD were collected before the Stop Smoking Service Client Satisfaction Survey, followed by patient note data extraction). Biologically validated smoking cessation status is by proxy a "blinded outcome" as the readings obtained are acquired biologically and the devices used to measure carbon monoxide expiration or saliva cotinine levels are unlikely to be tampered with. Carbon monoxide monitors were regularly calibrated, and saliva samples were analysed by an external and blinded lab.

We asked researchers "At the very start of the telephone call - are you aware of which treatment arm the participant was allocated to?" and they responded "yes" or "no".

3.1.1. Piloting main trial outcomes - Feasibility of data collection and completeness

To see if conducting a full-scale trial is appropriate in terms of feasibility of data collection, we aimed to collect data for key outcomes that would be used to assess intervention effects in a full-scale trial.

Primary outcome: 7-day point-prevalence abstinence with biological verification
In a full-sized effectiveness trial, the primary outcome will be self-report 7-day point prevalence abstinence with biological verification at 6-months follow-up. We will class biologically verified

abstinence as participants who report to be quit for at least 7-days, with an exhaled carbon monoxide concentration equal to or less than 10 parts per million, or a cotinine level equal to or less than 10 nanograms per millilitre of saliva. We will report data this outcome at 3-months too.

Secondary outcomes: mental health and tobacco dependency measures

We have collected data using measures that are likely to be the secondary outcomes in a full-scale effectiveness trial at 3- and 6-month follow-ups: Patient Health Questionnaire (PHQ-9), Generalised Anxiety Disorder Questionnaire (GAD-7), Heaviness of Smoking Index (HIS), number of cigarettes per day (CPD), and adverse events.

Table 1 SPIRIT schedule of enrolment, interventions, and assessments

	Pre-randomisation	Randomisation	Pre-treatment	Post-Enrolment				Close
Time point	t_{-1}	t_0	t_1	t_2	t_{3-11}	t_{12}	t_{13}	t_{14}
Appointment details				IAPT appt. 1	IAPT appt. 2-10	3-motnhs	6-months	
Enrolment:								
Eligibility screen	✓							
Informed consent	✓							
Allocation	✓							
Interventions:								
Intervention				—	—	—		
Control				—	—	—		
Assessments:								
Age	✓							
Sex	✓							
Education	✓							
Ethnicity	✓							
PHQ-9			✓	✓	✓	✓	✓	
GAD-7			✓	✓	✓	✓	✓	
Heaviness of Smoking Index			✓	✓		✓	✓	
Cigarettes per day			✓	✓		✓	✓	
Previous quit attempts			✓					
Mental health co-morbidities				✓	✓			
Planned, completed and missed IAPT appointments				✓	✓	✓	✓	
IAPT treatment status (active/discontinued/completed/discharged)				✓	✓	✓	✓	
Smoking cessation treatment session (completed/not completed, and duration)				✓	✓			
Retention in smoking cessation treatment (continued/discontinued)				✓	✓	✓	✓	
Smoking cessation medication usage (type of medicine/e-cig use)				✓	✓	✓	✓	
Self-reported 7-day point-prevalence smoking cessation					✓	✓	✓	
Biologically validated 7-day point-prevalence smoking cessation						✓	✓	
Stop Smoking Service Client Satisfaction Survey						✓	✓	
Clinician Self-Report Intervention Acceptability and Satisfaction Questionnaires								✓
Adverse events			✓	✓	✓	✓	✓	

4. STATISTICAL ANALYSIS PLAN

This is a pilot and feasibility study and was not designed to test effects of the intervention on any clinical outcomes, or for differences between groups at baseline. The study was designed produce a precise estimate for the main outcome (precision calculation available in published protocol[18]).

4.1. TRIAL FLOW CHART

Participant flow through the trial will be presented in a CONSORT diagram, showing total number of participants screened, number meeting initial eligibility criteria, reasons for potentially eligible participants being excluded, number randomised, drop-outs before the end of treatment, and numbers retained in the trial at 3- and 6- month follow-up.

4.2. BASELINE AND PRE-INTERVENTION DATA

We will report means and standard deviations or numerators, denominators, and percentages where appropriate for all measures collected at baseline and pre-intervention.

4.3. MAIN ACCEPTABILITY AND FEASIBILITY OUTCOME

4.3.1. Study completion

We will present the proportion of 'study completers' in each arm with numerators and denominators, this will be calculated by: N study completers in arm/ N randomised to arm at baseline. We will use a logistic regression model to produce the odds ratio and 95% confidence interval for the effect of intervention on completion at 3- and 6- months follow-up. Random allocation will be the independent variable (coded as intervention=1, control=0). Study completion will be the dependant variable (coded as study competition=1, and study non-competition=0). We will adjust the model for any baseline differences between arms and for site. Those with missing data about study completion will be assumed to be a 'non-completer' (coded as 0).

4.4. SECONDARY ACCEPTABILITY AND FEASIBILITY OUTCOMES

4.4.1. Recruitment into the trial

We will report the recruitment rate by month, year, and site, and present this on a line graph. Descriptive statistics will be presented for the proportion of target sample size achieved, proportion of initially eligible patients who were randomised and proportion of participants lost to follow-up.

4.4.2. Participant and PWP acceptability and satisfaction smoking cessation treatment

For each categorical subscale we will report the percentage of participants choosing each categorical answer as divided by the number of participants who completed the survey, with numerators and denominators. For continuous outcomes we will report means and standard deviations. We will report the mean and standard deviation for the total scale scores where possible.

4.4.3. Service-related feasibility outcomes

We will report descriptive statics for these outcomes as means and standard deviations, proportions as percentages with numerators and denominators. If we have adequate data (i.e., complete data with dates, we will explore the possibility of presenting service-related outcomes using Kaplan-Meier plots.

4.4.4. Smoking cessation treatment-related feasibility outcomes

We will report descriptive statistics for these outcomes as means and standard deviations, proportions as percentages with numerators and denominators. These data are only relevant to the treatment arm, so we will not report data for the control group.

4.4.5. Blinded outcome data collection

We will report the proportion of researchers reported being blinded to participant allocation status as a percentage with numerators and denominators, by trial arm.

4.4.6. Piloting main trial outcomes

We will test the primary and secondary outcomes to mimic practice for a full-scale trial. We must emphasise that as this is a feasibility study, these estimates will be too imprecise to support definitive conclusions but will be inspected for evidence of a benefit of the intervention. The proportions of participants missing each variable will be summarised in each arm and at each time point. Where these outcome data were imputed from IAPT patient management systems we will report the proportion of these data that were imputed where patients were lost to follow-up or data were missing as percentages with numerators and denominators.

Primary outcome: 7-day point-prevalence abstinence with biological verification at 6-months
We will use a logistic regression model to produce an odds ratio and 95% confidence interval for the association between trial arm and abstinence. The independent variable will be randomisation status (control=0, intervention=1), and the dependant variable will be 7-day point-prevalence abstinence with biological verification at 6-months (smoking=0, quit=1). Those with missing values will be assumed to be smokers.[22] We will adjust the model for any baseline differences between arms and for site. We will present complete case and imputed data. We will analyse these data at 3-months follow-up too.

Of particular interest to a full-scale trial will be success in obtaining smoking cessation bio-verification data. We will report proportions of missing data at 3- and 6-month follow-ups by trial arm for the number of participants who are self-reported quit with bio-verification data obtained (number of participants as biologically validated as quit/number of participants self-reported as quit).

Secondary outcomes: mental health and tobacco dependency measures

We will report descriptive statics for these outcomes as means and standard deviations, proportions as percentages with numerators and denominators. We will present complete case and imputed data, and report the proportion of missing data for each variable.

5. PROTOCOL AMENDMENTS RELEVANT TO THE ANALYSIS PLAN

5.1. AMENDMENT 1

In our original protocol we reported that follow-up would be conducted 3- and 6-months after randomisation. During the early stages of the trial, we learned that this was not the most sensible timing for data collection as waiting lists in some services were up to 1 year after the initial IAPT assessment. Therefore, we collected follow-up data at 3- and 6- months after the date of the first IAPT treatment appointment. This amendment took place on April 15, 2019.

5.2. AMENDMENT 2

We collected baseline measures prior to randomisation (ethnicity, age, sex, education) and then we collected pre-intervention measures (PHQ, GAD, HIS, CPD) two weeks prior to intervention start date. We did this because baseline measures could be collected anywhere from 3 weeks to 2 months before IAPT treatment start. Time of randomisation had to be completed opportunistically because of the long waitlist between recruitment and IAPT first appointment date and allocating the participant to a trained practitioner which had to occur before first IAPT appointment was allocated. This amendment took place on January 28, 2020.

5.3. AMENDMENT 3

We added the following outcomes since publication of the trial protocol, Generalised Anxiety Questionnaire-7 (GAD-7), “Clinician Self-Report Intervention Acceptability Questionnaire”, the “Acceptability of Intervention Measure (AIM)”, “Intervention Appropriateness Measure (IAM)”, “Feasibility of Intervention Measure (FIM)”, and “Sustainability of Intervention Measure (SIM). This amendment took place on January 30, 2020.

5.4. AMENDMENT 4

Our previously published protocol stated that we would bio-validate smoking cessation using expired carbon monoxide readings. However, the COVID-19 pandemic impacted on face-to-face data collection, so we decided to collect saliva samples for bio-validation as these were deemed “covid-safe”. This amendment took place on June 8, 2020.

5.5. AMENDMENT 5

Our previously published protocol stated that we would collect and analyse implementation data. It has not been possible to collect these data. We had tried to establish this for over two years. There was an R&D ban on Dictaphones. We managed to get an exception, but then couldn’t get local approvals, and for other sites PWPs weren’t able to record in sessions because of working from home during the COVID-19 pandemic. This amendment took place on Sept 1, 2021.

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