ANALYSIS PLAN

IntEgrating Smoking Cessation treAtment into usual online Psychological care for people with common mEntal illness: Protocol for an online randomised feasibility and pilot study (ESCAPE Digital)

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Trial Design

This is a two-armed, pragmatic, online, randomised and controlled feasibility and pilot study, with nested qualitative research. The trial was prospectively registered on the ISRCTN registry on 02/02/2023 (ID: ISRCTN10612149, https://doi.org/10.1186/ISRCTN10612149).

Participants will be randomised to one of two treatments below (see Figure 1) using a 1:1 ratio, via an online algorithm:

1) To receive psychoeducational information about smoking and mental health and stopping smoking, as well as access to a smoking cessation programme tailored for people with mental health difficulties, alongside usual online psychological therapy (intervention);
2) To receive usual online psychological therapy followed by information about stopping smoking at the end of their participation in the study (control).

The trial procedures, including recruitment, eligibility, randomisation and intervention delivery will be conducted online via Qualtrics (https://www.qualtrics.com/uk/), an online survey platform, and SilverCloud Health by Amwell (https://www.silvercloudhealth.com/), a telehealth platform that delivers evidence-based online psychological therapy (1). Data collection will involve self-reported questionnaires, biochemical verification of smoking cessation (salivary cotinine or anabasine), information from National Health Service Improving Access to Psychological Therapies (NHS IAPT) services patient management systems and SilverCloud, and qualitative interviews. Participants will be enrolled for 6 months post-randomisation to final follow-up.

Research questions

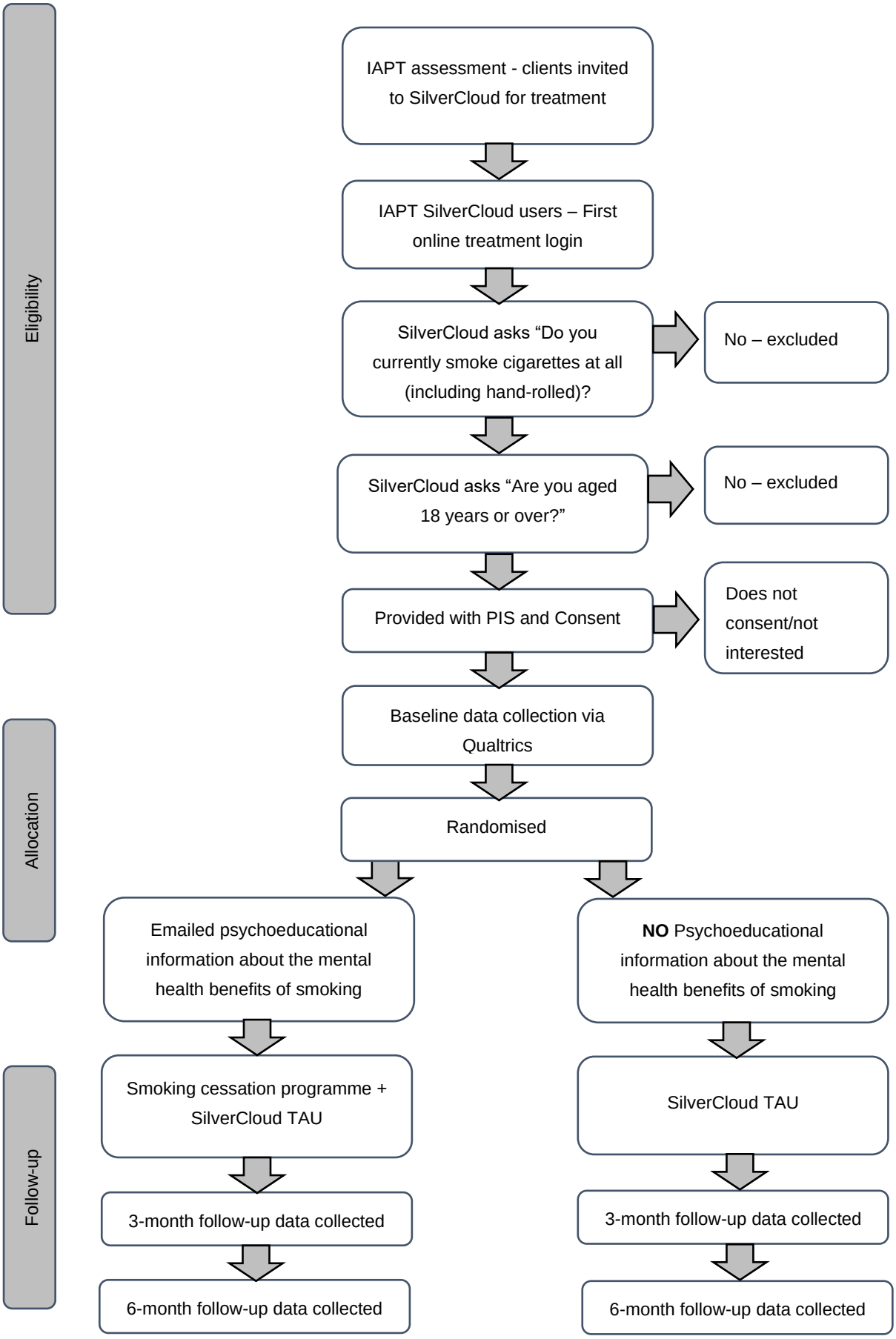
1) Is a tailored and integrated smoking cessation intervention delivered as part of usual online treatment via SilverCloud feasible and acceptable to patients and psychological wellbeing practitioners?
2) Are trial procedures feasible and acceptable in terms of recruitment, randomisation, retention, and data collection?

Objectives

Investigate the feasibility and acceptability of:

1) An online smoking cessation intervention nested into the SilverCloud mental health treatment platform
2) Trial procedures of an online randomised pilot and feasibility trial

Figure 1 Trial flow chart



Sample size

We aim to recruit 500 participants. This will be sufficient for us to assess the feasibility of adequate recruitment and retention of participants and completeness of data collection. Furthermore, we aim to calculate estimates of key parameters of clinical effectiveness for a future trial. This sample size is achievable as recruitment procedures will be automated online, and approximately 29-34% of online IAPT service users are smokers (2).

Outcomes

See Table 1 for the SPIRIT Schedule of enrolment, interventions, and assessments.

Trial procedures feasibility and acceptability outcomes

- **Total number of participants recruited** relative to target and the number of eligible SilverCloud clients, and recruitment rate: The number of participants recruited, each month, and over the whole trial period, as well as the proportion of eligible SilverCloud clients (i.e., adult smokers accessing supported treatment) who are randomised to a trial arm
- **Smoking abstinence data completeness**: Participants reached at 3- and 6-months to ascertain abstinence status
- **Saliva sample data completeness**: Returned saliva sample packs (sent to participants reporting abstinence)
- **Concordance between self-reported and biochemically validated abstinence**: Biochemical verification of abstinence measured by salivary cotinine or anabasine
- **Data completeness for depression (PHQ-9)(3) and anxiety scoring (GAD-7)(4)**: Participants reached at 3- and 6-months to ascertain PHQ-9 and GAD-7 scores
- **Participant follow-up data completeness and reminder requirement**: Participants with 3- and 6- month follow-up data, and requiring 3- and 6-month follow-up research team reminders
- **Proportion of key outcome data collected via phone**: Proportion of follow-ups who did not respond to automated prompts and completed smoking information via phone
- **Participants' views of the study procedures**:

  1. Trial satisfaction questionnaire
     - 'Why did you decide to take part in this study (select all that apply)?
       'To get stop smoking support', 'To get the shopping vouchers', 'To take part in research', 'To help my mental health', 'To help others stop smoking in the future', 'Other (please specify)'

- ‘How satisfied were you with the following parts of the study’: ‘The information provided about the study’; ‘The explanation of how I would be randomly allocated to receive one of two treatments’; ‘The number of questionnaires you had to complete’; ‘The length of questionnaires you had to complete’; ‘The ease of completing the questionnaires’; ‘The use of email to send questionnaires’; ‘Additional follow up by the research team (e.g., by phone)’; ‘The overall experience of taking part in the study’, using Likert scale: ‘Very unsatisfied’, ‘Unsatisfied’, ‘Unsure’, ‘Satisfied’, ‘Very satisfied’
- ‘Based on your experience of taking part in this study, how likely would you be to’: ‘Recommend taking part in this study to family or friends’; ‘Take part in a similar study run by the same people’, using Likert scale: ‘Very unlikely, ‘Unlikely, ‘Unsure’, ‘Likely, ‘Very Likely’

2. Qualitative interviews with participants will explore participant perceptions of randomisation and data collection procedures

- **Mental health practitioners’ views of the study procedures**: Qualitative interviews will explore their perceptions of data collection procedures and randomisation

Intervention feasibility and acceptability outcomes

A key early indicator of effectiveness is the proportion of people who report making a quit attempt, which can be measured in each arm of the trial. The outcome here is defined as a quit attempt lasting at least 24 hours. The outcome is recorded as the primary outcome measure on the ISRCTN Registry and is a key measure of intervention feasibility.

- **Self-reported quit attempt**
  ‘Have you made a serious attempt to stop smoking (lasting at least 24 hours) in the last two weeks/three months [post-allocation t1-t5/3-month follow up survey]?’ ‘Yes’, ‘No’
- **Engagement with the SilverCloud programme(s)**: Use of the SilverCloud smoking cessation (intervention arm only) and usual mental health (all participants) programmes, e.g., length of support, frequency (number of logins) and duration (time spent) of programme use, programme completion
- **Self-reported smoking cessation medicine or e-cigarette use**:
  ‘Are you currently using any stop smoking medication or e-cigarettes?’ ‘Yes, ‘No’, ‘If yes to the above, please specify (select all that apply): gum, inhalator, mouth spray, nasal spray, lozenge, mini lozenge, micotab, Bupropion (Zyban), e-cigarettes’
- **Proportion of people completing their mental health treatment**: Participants’ discharge status; and completion of mental health treatment
- **Number of attended/missed IAPT appointments**

- **Participants' views of the intervention**:
  1. Modified version of the Stop Smoking Service Patient Satisfaction Survey (5) (intervention arm participants only)
  - 'At the start of the study, we emailed you information about smoking, mental health, how quitting smoking can help your mental heath and how to get help from your SilverCloud smoking cessation programme. Please could you provide below, any thoughts you have about this information and any suggestions about how it could be improved. [free text]'
  - 'Overall, how satisfied were you with the SilverCloud smoking cessation programme?', using Likert scale: 'Very unsatisfied', 'Unsatisfied', 'Unsure', 'Satisfied', 'Very satisfied'
  - 'Would you recommend the smoking cessation programme to other smokers who want to stop smoking?' 'No', 'Unsure', 'Yes'
  - 'Did you discuss smoking or quitting with your SilverCloud supporter (e.g., during reviews with your psychological wellbeing practitioner)?' 'No', 'Yes', 'I didn't have / didn't contact a SilverCloud supporter' [If 'yes': 'How satisfied are you with how supportive staff have been?', using Likert scale: 'Very unsatisfied', 'Unsatisfied', 'Unsure', 'Satisfied', 'Very satisfied']
  - 'How helpful has the information and advice been that was provided in the smoking cessation programme?', using Likert scale: 'Very unhelpful', 'Unhelpful', 'Unsure', 'Helpful', 'Very helpful'
  - 'Was the information that you were given about the choice of stop smoking medication helpful?' 'No', 'Unsure', 'Yes'
  - 'How did you get your medication?' 'GP prescription', 'Chemist/pharmacy', 'Other (please specify)', 'I did not use stop smoking medication' [If used: 'Was it easy to get hold of your stop smoking medication?' 'No', 'Unsure', 'Yes'
  - 'We really value your feedback, please write below: Any changes to the smoking cessation programme that you would like to see; Anything that you particularly liked about the smoking cessation programme; Anything else that you think it would be useful for us to know. [free text]'
  2. Qualitative interviews with: a) participants, to explore their perceptions of: accessing the smoking cessation programme via SilverCloud alongside usual psychological treatment, acceptability of the smoking cessation treatment, positive and negative impacts of smoking cessation treatment on IAPT usual care and mental health recovery; b) mental health practitioners, to explore their perceptions of: the acceptability of the smoking cessation treatment, acceptability

of data collection procedures, positive and negative impacts of smoking cessation treatment on IAPT usual care and mental health recovery

Pilot clinical outcomes

- **Smoking abstinence**: Abstinence at 3- and 6-months follow-up (4-week abstinence, biochemically validated; 12-week prolonged abstinence between 3 and 6 months, biochemically validated, respectively). Self-reported abstinence is defined as not smoking more than 5 cigarettes during the abstinence period (31):
  'Have you smoked in the last 4/12 weeks?' 'No, not even a puff', 'Yes, just a few puffs', 'Yes, between 1-5 cigarettes', 'Yes, more than 5 cigarettes'
  Biochemical validation of saliva samples will be analysed by ACM Bioanalytical Services. Salivary cotinine (cut-off 15ng/ml) will be measured in participants who do not report using nicotine products. Anabasine (cut-off <1ng/ml) will be measured in participants who report using nicotine products.
- **Depression and anxiety**: Patient Health Questionnaire (PHQ-9) scores; General Anxiety Disorder Questionnaire (GAD-7) scores
- **Quality of life**: EQ visual analogue scale (EQ VAS) from the EuroQuol three-dimensional questionnaire (EQ 5D 3L)(6)
  'We would like to know how good or bad your health is TODAY. The scale is numbered from 0 to 100. 0 means the worst health you can imagine. 100 means the best health you can imagine. Please mark on the scale to indicate how your health is TODAY.'

Other

- **Other smoking support**
  Intervention arm: 'In the last 3 months, have you accessed any additional support to stop smoking. We're interested in support outside of the SilverCloud smoking cessation programme (e.g. local stop smoking service, online support, digital app)?' 'Yes', 'No' [If yes, please specify]
  Control arm: 'In the last 3 months, have you accessed any support to stop smoking (e.g. local stop smoking service, online support, digital app)?' 'Yes', 'No' [If yes, please specify]

Baseline demographic variables

- Age: Years
- Gender: 'man', 'woman', 'non-binary', 'I identify as [free text]'

- Ethnicity: ‘Asian or Asian British’, ‘Black, Black British, Caribbean or African’, ‘Mixed or multiple ethnic groups’, ‘White’, ‘Other ethnic group’
- Highest level of education: ‘Higher Education or professional / vocational equivalents (e.g., post-school diploma, university degree)’, ‘A levels or vocational level 3 or equivalents (e.g., school exams age 18)’, ‘GCSE / O Level grade A*-C or vocational level 2 or equivalents (e.g., school exams age 16)’, ‘Qualifications at level 1 and below (e.g., essential work-based skills)’, ‘Other qualifications: level unknown’, or ‘No qualifications’
- Heaviness of smoking index (HSI)(7):
  ‘How soon after you wake up do you smoke your first cigarette?’ ‘within 5 minutes’, ‘6-30 minutes’, ’31-60 minutes’, ‘more than 60 minutes’
  ‘How many cigarettes do you usually smoke per day?’ ‘10 or less’, ‘11 to 20’, ‘21 to 30’, ‘31 or more’
- Cigarettes per day: ‘Please write down the number of cigarettes you usually smoke per day in the box below [free text]’
- Stop smoking medication or e-cigarette use:
  ‘Are you currently using any stop smoking medication or e-cigarettes (e.g., nicotine replacement therapy (NRT) patch or gum)?’ ‘Yes’, ‘No’
  ‘If yes to the above, please specify (select all that apply)’: ‘patch’, ‘gum’, ‘inhalator’, ‘mouth spray’, ‘nasal spray’, ‘lozenge’, ‘mini lozenge’, ‘microtab’, ‘Bupropion (Zyban)’, ‘e-cigarettes’
- Previous stop smoking medication or e-cigarette use:
  ‘Have you used stop smoking medication or e-cigarettes previously?’ ‘Yes’, ‘No’
  ‘If yes to the above, please specify (select all that apply)’: ‘patch’, ‘gum’, ‘inhalator’, ‘mouth spray’, ‘nasal spray’, ‘lozenge’, ‘mini lozenge’, ‘microtab’, ‘Bupropion (Zyban)’, ‘Varenicline (champix)’, ‘e-cigarettes’
- Previous quit attempts: ‘Have you quit smoking for at least 24 hours in the last 12 months?’ ‘Yes’, ‘No’
- Primary mental health reason for treatment and any physical/mental comorbidities: Collected from the IAPT patient management system

Table 1 SPIRIT Schedule of enrolment, interventions, and assessments

	Pre-allocation	Allocation	Post-allocation[b]					Follow up		Trial end
	t0		t1	t2	t3	t4	t5	3-m	6-m	
Enrollment										
Eligibility screen	x									
Informed consent	x									
Allocation		x								
Intervention										
Treatment			x	x	x	x	x			
Control			x	x	x	x	x			
Assessments										
Age	x									
Gender	x									
Ethnicity	x									
Education	x									
Heaviness of Smoking Index (HSI)	x									
Previous quit attempts	x									
Primary mental health condition	x									
Physical and mental health comorbidities	x									
(Previous and) current use of smoking cessation medicine/e-cigarette use	x		x	x	x	x	x	x	x	
Patient Health Questionnaire (PHQ-9)[a]	x		x	x	x	x	x	x	x	
General Anxiety Disorder Questionnaire (GAD-7)[a]	x		x	x	x	x	x	x	x	
EQ visual analogue scale (EQ VAS)	x							x	x	
Self-reported smoking cessation (prolonged 12-week, and 4-weeks abstinent)								x	x	
Saliva sample (for those reporting cessation)								x	x	
Self-reported quit attempt			x	x	x	x	x	x		
Engagement with SilverCloud programme(s): Mental health treatment (treatment as usual) and smoking cessation (intervention arm only), e.g., frequency, duration, logins, logoffs, time spent, pages viewed			x	x	x	x	x			
Completion of SilverCloud programme(s)			x	x	x	x	x	x	x	
Stop Smoking Service Patient Satisfaction Survey (intervention arm only)								x		
Qualitative interviews with participants (intervention arm only)									x	x
Qualitative interviews with IAPT staff								x	x	x
Number of attended IAPT appointments (SilverCloud reviews and any other clinical contact)			x	x	x	x	x	x	x	
Number of missed IAPT appointments (DNAs) (SilverCloud reviews and any other clinical contact)			x	x	x	x	x	x	x	
Discharge/completion of IAPT treatment status			x	x	x	x	x	x	x	
Trial satisfaction questionnaire									x	

[a]PHQ-9 and GAD-7 assessments will be collected via SilverCloud for pre- and post-allocation time points, and directly from participants (online/by telephone) for 3- and 6-month follow ups; [b]Five post-allocation time-points will be scheduled at fortnightly intervals after randomisation. These may differ from the timing of review sessions with the mental health service (which vary from approximately weekly over six weeks to fortnightly over 12 weeks).

Outcome analysis

This is a pilot and feasibility study; the statistical analysis described below will be conducted to produce precise estimates for the main outcomes in an effectiveness trial and should not be interpreted as a test of effects of the intervention on the pilot clinical outcomes.

Definition of population for analysis

Statistical analyses will be performed on an intention-to-treat (ITT) basis, with participants being analysed in the study arms to which they were allocated, regardless of levels of adherence to the intervention. Due to the automated online randomisation, it is not anticipated that any participants could receive a different intervention to that intended.

Trial flow chart

A CONSORT flow chart will be constructed to show the number of participants screened for eligibility, meeting eligibility criteria, excluded (with reasons), randomised, treated and followed-up.

Baseline data

For each trial arm, we will report means, proportions and a relevant measure of variance for each baseline variable.

Feasibility and acceptability outcomes

We will use descriptive statistics to report the key feasibility and acceptability outcomes outlined below. All raw data will be reported in tables for the treatment and control arms. We will report percentages and/or the median for categorical variables, and the mean and standard deviation for continuous variables.

- *Proportion of eligible SilverCloud clients (i.e., adult smokers accessing supported treatment) who enrol in trial:* We will report the proportion of eligible clients who are randomised to a trial arm (for each site and overall)
- *Recruitment to the trial:* The number of participants recruitment for each site, and the total proportion recruited relative to the target, will be reported for each trial arm
- *Rate of recruitment:* The number of participants recruited each month will be reported and plotted on a line graph for the total trial time period
- *Smoking abstinence data completeness*: We will report the number and proportion of people reached at 3- and 6-months from whom we ascertain abstinence status, relative to the number randomised at baseline

- *Saliva sample data completeness*: We will report the number and proportion of saliva sample packs that are i) returned, and ii) yield a measure of cotinine or anabasine, relative to a) the number that report abstinence, and b) the number of packs that are sent to people reporting abstinence (i.e., those who provide their address)
- *Concordance between self-reported and biochemically validated abstinence:* We will report the number and proportion of abstinence self-reports at 3- and 6-months that are biochemically verified by salivary cotinine (cut off 15ng/ml) or anabasine (cut off 1ng/ml) levels
- *Participant follow-up reminder requirement and data completeness:* We will report the number and proportion of participants with 3- and 6- month follow-up data, relative to the number randomised at baseline; and the number and proportion of participants requiring research team reminders at 3- and 6-month follow-up; we will report the number and proportion of participants requiring reminders at 3- and 6-months as well as and the mean number of reminders required at 3- and 6-months
- *Mental health data completeness*: We will report the number and proportion of people reached at 3- and 6-months to provide depression (PHQ-9) and anxiety (GAD-7) scores, relative to the number randomised at baseline
- *Self-reported quit attempts:* We will report the number and proportion of participants who report a quit attempt at any time point. We will compare categorical outcome values [No quit attempts=0; Yes 1+ quit attempt=1] between trial arms using logistic regression modelling. We will report odds ratios and 95% confidence intervals from regression models.
- *Engagement with the SilverCloud programmes:* We will report the mean and range for the length of support, frequency (number of logins), duration (time spent) and extent (number of pages viewed) of programme use for both the mental health and smoking cessation programmes, and we will report the proportion of each programme completed
- *Self-reported stop smoking medication and e-cigarette use:* We will report the number and proportion of participants who report using stop smoking aid(s) at any time point. We will compare categorical outcome values [No medication or e-cigarette use=0, Yes medication or e-cigarette use=1] between trial arms using logistic regression modelling. We will report odds ratios and 95% confidence intervals from regression models.
- *Proportion of people completing a course of treatment and discharge status*: We will report the number and proportion of people completing their IAPT treatment relative

to the number randomised at baseline for each trial arm; as well as number and proportion of participants according to the possible discharge statuses

- *Mental health treatment engagement:* We will report the mean and number of attended and missed IAPT appointments
- *Self-reported intervention (intervention arm only) and trial satisfaction*: We will report the number, percentage and median to describe the distribution of responses

Progression criteria

The following outcomes will be used to indicate whether it would be feasible to progress to an effectiveness trial without significant modification of the intervention or trial procedures.

Criteria	Red	Amber	Green
Proportion of eligible SilverCloud clients (i.e., adult smokers) who enrol in trial	<15%	15-19%	≥20%
Recruitment compared with target	<60%	60-79%	≥80%
Data completeness of future trial outcomes (i.e., self-reported abstinence status, depression and anxiety scores)	<50%	50-69%	≥70%
Behavioural marker of engagement with smoking cessation programme: self-reported quit attempt(s) in intervention group	<5%	5-7%	≥8%

Piloting main trial clinical outcomes

The outcome measures that we intend to assess in an effectiveness trial (biochemically validated smoking abstinence, depression and anxiety scores, quality of life score) will be piloted in this feasibility study. Raw data will be reported in tables for the treatment and control arms. We will report percentages and/or the median for categorical variables, and the mean and standard deviation for continuous variables. We will compare continuous mental health and quality of life outcome values between trial arms at 3- and 6-months using linear regression modelling, with adjustment for baseline values. We will report coefficients and 95% confidence intervals from regression models. We will compare categorical abstinence outcome values [smoking (>5 cigarettes)=0, quit (smoking 0-5 cigarettes)=1] between trial arms at 3- and 6-months using logistic regression modelling. We will report odds ratios and 95% confidence intervals from regression models. We will present complete case and imputed data. Those with missing smoking outcome data will be assumed to be smokers.

Missing data

We will report data missingness for all variables. Mid-assessment survey (2, 4, 6, 8, 10 weeks post randomisation) data will be treated as missing if no data has been collected within a 13-day visit window after the survey link has been sent. Follow-up survey data will

be treated as missing if no data has been collected within a 28-day visit window after the survey link has been sent.

Qualitative data analysis

We will aim to conduct up 15 interviews with SilverCloud users and 15 with IAPT staff, to be spaced evenly across the trial period. The purpose will be to inform a future effectiveness trial (rather than data saturation). Interviews will be conducted online via Teams and audio files will be exported in mp4 format. Interview data will be transcribed automatically via Teams and / or securely transferred to, and transcribed by, a University approved and GDPR compliant transcription service. To ensure the quality of data transcription a researcher will do a check of audio data against the transcripts. The audio recordings will then be deleted. The data will be analysed using thematic analysis, applying the framework method as outlined below (8):

1. *Transcription*: verbatim transcription of audio recordings will be conducted (see above)
2. *Familiarisation with the interview*: member(s) of the research team will re-listen to or re-read interviews in full
3. *Coding*: member(s) of the research team will independently read the transcripts line by line and record initial codes (words or phrases) on printed transcripts to describe key elements of the interview and highlighting possible interpretations; we will use a mixture of deductive coding (i.e., informed by the study objectives) and inductive coding (i.e., identified in the interview data)
4. *Developing a working analytical framework*: after the first few interviews have been coded, we will collate a list of codes with brief definitions, combine similar codes and organise codes into categories
5. *Applying the framework*: we will code new transcripts according to the framework, adding any new codes and updating the framework throughout the process, we will import the transcripts and framework into NVivo and code each transcript
6. *Charting data into the framework matrix*: we will develop a framework matrix in Excel using a separate tab for each category, with a column for each code and a row for each interview, we will review the text for each code for each interview and summarise in each matrix cell with any (anonymised) direct quotes
7. *Interpreting the data*: we will identify overarching connections and differences to develop potential explanations for emerging patterns across the matrix as a whole and form the central interpretative themes

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