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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-013604
Article Type:	Protocol
Date Submitted by the Author:	25-Jul-2016
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Primary Subject Heading:	Smoking and tobacco
Secondary Subject Heading:	Public health
Keywords:	e-health, smoking cessation, internet based intervention, prevention, mobile phone, efficacy

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KEY WORDS

E-health, smoking cessation, internet-based intervention, prevention, mobile phone, efficacy

WORDS COUNT : 5136

ABSTRACT

Introduction - A national smoking cessation service, Tabac Info Service, have been developed to provide an adapted quitline, web and mobile application support to smoking cessation. This paper presents the study protocol of the evaluation of the e-health part of the service (e-TIS). The primary objective is to assess the efficacy of e-TIS. The secondary objectives are to 1) describe efficacy variations in regard to users' characteristics, 2) analyze mechanisms and contextual conditions of e-TIS efficacy.

Methods and analyses - The study design is a two-arm pragmatic randomized controlled trial including a process evaluation with at least 3000 participants randomized to the intervention or to the control arm (current practices). Inclusion criteria are: being 18 years old or more, a current smoker, having completed the screening and the consent on-line forms, possessing a mobile phone and using mobile applications, wanting stop to smoking soon or later. The primary outcome is the point prevalence abstinence of 7 days at 6 months later. Data will be analyzed in Intention to treat (primary) and per protocol analyses. A logistic regression will be carried out to estimate an Odds Ratio [95% Confidence Interval] for efficacy. A multivariate multilevel analysis will explore the influence on results of patients' characteristics, contextual factors, conditions of use and behavior change techniques.

Ethics and dissemination - The study protocol was reviewed by the ethical and deontological institutional review board of the INVS (French Institute for Public Health Surveillance) on 18 April 2016. The findings of this study will allow us to understand and characterize the efficacy of e-TIS and conditions of its efficacy. These findings will be disseminated through peer-reviewed articles.

Trial registration number - The study is registered at www.clinicaltrials.gov (number = NCT02841683).

STRENGHTS AND LIMITATIONS OF THE STUDY

- Large national randomized trial in pragmatic conditions
- Process analysis within the trial using MRC framework and BCTs taxonomy in order to understand mechanisms and conditions of efficacy

INTRODUCTION

Every year, smoking causes worldwide 6.1 million deaths and an estimated 143.5 million DALYs (1). The health risks associated with smoking depend on two factors: daily consumption (2) and history of smoking. Conversely, smoking cessation is good for health and the sooner a smoker quits, the better (3,4). People who stop smoking by the age of 40 reduce their likelihood of dying from smoking-related diseases by over 90%, and by the age of 30 the figure stands at 97% (3). Those who quit at 40 live 7 years longer, and at 50 live 4 years longer (4) compared to those who do not stop. In addition, smoking cessation does not just reduce mortality; it also brings down morbidity (5).

Various types of support and treatment are available, with varying results. Examples include: individual professional counseling (6), nicotine replacement therapy, motivational interviewing (7), group behavioral therapy (8), nursing interventions (9), self-help tools (10) for patients who prefer not to seek the help of a healthcare professional, or call helplines (8), support via mobile phone text messaging (11). Other less proven methods include: acupuncture, hypnosis, physical activity, support from one's partner, and aversion therapy (12). The effectiveness of internet-based interventions is difficult to ascertain due to the number of factors involved (13).

Whatever the method used, the relapse prevention model (13) stresses the need to provide greater support in the so-called high-risk situations. All non-pharmacological treatments must therefore be tailored to the patient to deal adequately with both different immediate determinants (high-risk situations, coping skills in front of high-risk situations, outcome expectancies, and the abstinence violation effect), and the covert antecedents (lifestyle factors, stress, denial, cravings) as these factors can contribute to relapse.

Drawing on this knowledge, the CNAMTS (the French National Health Insurance Fund) and the national agency of public health (Santé Publique France - Public Health France) have come together to design, experiment and assess a new E-coaching intervention (eTIS) part of the Tabac Info Service available online and via a smartphone application. The intervention is designed to provide intensive support to all smokers who are wishing to quit. It is based on effectiveness criteria of online programs (13) but it also refers to psychosocial theories and behavioral change theories (14–20). This article describes the protocol used to assess this intervention. The protocol follows the recommendations of the CONSORT(21) and SPIRIT 2013 guidelines(22).

OBJECTIVES

The main objective of the study is to demonstrate the efficacy and the conditions of efficacy of the eTIS intervention. The latter, which involves an internet-based phone application, is complex in nature and many variables can influence its ability to deliver the desired outcome. For the purposes of our study, we have therefore followed the recommendations of the Medical Research Council (MRC) (23,24) and those of the Workgroup for Intervention Development and Evaluation Research (WIDER) (25). Not only does this involve looking at efficacy, but also at other areas that can shed light on this efficacy, such as the intervention logic, the behavioral mechanisms induced and contextual factors. The aim is to assess the intervention's key functions (26), in other words, the intervention or environmental components that determine its efficacy. To achieve this, we will draw on the taxonomy by Michie et al (27,28) which have enabled us to describe the Behavioral Change Techniques (BCTs) used in the intervention. The secondary objectives of the study are therefore to: 1) describe the possible variations in efficacy according to the smokers' background (age, sex, social class, level of education, smoking habits, presence of chronic illness etc.), 2) analyze the mechanisms and conditions relating the intervention's efficacy. This is based on how the application is used, on the external environmental or social factors that either contribute to or hinder the intervention's efficacy, and on the BCTs implemented by the smokers.

METHODS AND ANALYSES

Study design

The evaluation will be conducted as a pragmatic randomized controlled trial combined with a process analysis. The e-TIS intervention will be compared against current practices for smoking cessation as set out on a non-interactive website (ameli-sante.fr, Cnamts).

To do this, the evaluation sets out the smoking cessation treatments as recommended by the *Haute autorité de santé* (HAS; independent national scientific body with a broad remit on health and healthcare issues) and consists of two arms: the intervention arm (use of the e-TIS intervention) and a control arm (current practices).

Study setting

This pragmatic trial will involve French smokers of 18 years old or more, with or without any chronic diseases, and regardless of social background, who wish to quit smoking, whether they are ready to do so sooner or later. The e-TIS intervention is unlike other intervention in that it caters for smokers who may not have set a date for quitting and provides them with specific support.

Eligibility criteria

Inclusion criteria are: all adult smokers on the intervention who have completed the entry questionnaire and who have agreed to participate in the study between 1 January 2017 and 1 March 2017, with a mobile phone, be willing to use applications, and envisage quitting smoking (in the short, medium or long term).

Sample size

In view of previous data, for a spontaneous abstinence rate of 10% (median hypothesis between a spontaneous rate of 5% and the rate observed in the STAMP(29) study undertaken by INPES (French Institute for Health Promotion and Health Education) on highly motivated smokers (abstinence rate of 20%)), a sample of size of 1,500 subjects per group is required to show an OR of 1.5 with a power of 90% (alpha 0.05, bilateral test), meaning a total of 3,000 persons.

Recruitment

Subjects will be recruited as the e-TIS website becomes operational and over 3 full months (January - March 2017). The study will start in January 2017 and end in July 2018. Data will be collected over 12 months. Recruitment will be via France's national health insurance fund's website Ameli: www.ameli-sante.fr/arret-tabac. Subjects will log on to the Ameli website (to the home page, not to the application) where they see a banner for the study. If they click on the banner, they will be taken to the website of the study and will be invited to participate. Here they will find an information sheet along with a section where they can give their informed consent. The form also contains a few questions for the volunteers to answer (inclusion criteria). If consent is given, a confirmation email will be sent to the person (link to click on). Once they volunteers have confirmed, they will be randomized and a second email and a text message will be sent to them. These contain a password so that they can log on to the entry questionnaire (T0) for the study. And once this questionnaire is completed, the participants will be assigned to one of the study arms. Figure 1 shows the procedure.

Randomization

Automated randomization will be carried out following receipt of all necessary data, and consent by the subject to participate in the study. A Minimization software package will be used to reduce of the risk of unmatched groups and will be applied to stratify participants according to sex and age using the following parameters: two treatment arms, e-TIS (E) and Ameli.fr (A) allocated 50/50; stratified by sex (M/F) and by age (+/- 45 years old); randomly drawn for the first 30 subjects, 5% randomly drawn, 0.96 randomization factor.

Intervention

Intervention arm: Participants will be randomly assigned to one of two arms before the treatment begins. Those participants assigned to the intervention arm will be exposed to the e-TIS intervention. They start by answering a short questionnaire. In keeping with the precepts of the relapse prevention model, the treatment will be individually tailored to each smoker throughout, based on feedback collected along the way. The support process draws on the efficacy criteria of online programs (frequency and intensity of contacts, short messages, interactivity, appeal, personalization, credibility of content, share functions) and various theoretical models used in withdrawal treatments.

The intervention will primarily involve personalized interactive (push) messages via mobile phone, website platform and tablet. These messages can take the form of questionnaires, advice, messages of encouragement, situational exercises, situation assessments etc.

They are tailored to how the participant is progressing.

- Module 1 – Participants are not yet ready to quit smoking (they have yet to set a quitting date). This module is intended to increase the participants' resolve / resoluteness / resolution to quit and help them set a stopping date. Text messaging is not intense at this stage. Participants only leave this module once they have set a quitting date.
- Module 2 – Participants are ready to quit (they have set a date). This module aims to provide the best possible conditions to help participants prepare in the run-up to their quitting date. There will be intensive text messaging the day before the quitting date. Participants leave this module on the morning of their quitting date unless they choose to cancel, in which case they return to module 1.
- Module 3: Participants have stopped smoking. In this module they are given support and advice in detecting and avoiding possible relapses. For the first 7 days, push text messaging will be highly intense. From D+8 to D+28 the rhythm will drop a level, then again from D+29 to D+56, and again from D+57 to D+180.
- Module 4 – Participants have relapsed. This is a short term module whose purpose is to help willing participants to manage their relapse and return to either modules 1, 2, or 3. They can leave module 4 once they have completed a questionnaire designed to ascertain which module they should reintegrate.

This process is presented in table 1.

Table 1: eTIS support process

	Module 1 Contemplation	Module 2 Preparation	Module 3 Quitting	Module 4 Relapse

	I'm thinking of quitting	I m ready to quit	I'm quitting	I have slipped
Context	Smokers who are contemplating but who have yet to set a quit date	Smokers preparing for the quit date they have set	Smokers who have quit	Smokers who relapse
Objectives	Help smokers increase their resolve Help smokers set a quit date	Help smokers prepare in the run-up to their quit date in the best possible conditions	Provide support and advice in detecting and avoiding possible lapses/relapses	Help willing users return to modules 1, 2 or 3 Provide individual support
Level of contact throughout the intervention	Low intensity 3-4 messages per week	Intense 1 message per day One day before the quit date, messaging will be intense (3 to 4 messages).	Up to D+7 Highly intense 2 to 4 messages per day Between D+8 and D+28 ; D+29 and D+56 ; D+57 and D+180 Intensity declines	N/A

The intervention comprises 16 different activities, 13 position questionnaires and a set of email or push-app messages/notifications (roughly 170) with various purposes: welcome messages for each module entered; messages promoting activities and some of the questionnaires to come, reminders and follow-up messages as required, unidirectional messages (personalized or not) to provide advice rather than to encourage the recipient to use the application; personalized messages relating to the answers given in the different questionnaires; messages about the quitting date.

Control arm: Participants assigned to the control arm are exposed to an information page which lists smoking cessation resources readily available in France and recommended by HAS (12). This is the common practice pathway. Participants are given a link to access the page and there are 4 tabs:

- The effects of smoking: this section provides information about how tobacco affects morbidity, mortality and quality of life.

- The benefits of a smoke-free life: this section provides information about the short-, medium-, and long-term benefits of smoking cessation and how quality of life is likely to improve.
- Your current situation: this section involves conducting a small survey about the participants' smoking habits to assess their levels of consumption, dependency, and motivation to quit.
- How to quit smoking: this section informs smokers about the various cessation methods recommended by HAS and how to apply for them.

Primary outcome

For the main analysis, the primary endpoint is a minimum 7-day point abstinence at 6 months.

Point prevalence abstinence (PPA) is considered the most appropriate measure for intervention evaluation studies. The National Interagency Council on Smoking and Health recommends PPA for a minimum 24h at 3 months, 7-day abstinence at 6 months and 30 days at 12 months (30). Biochemical validation will not be used; for most situations, and particularly in community-based interventions (vs clinical interventions) and with an adult population(30), the misreporting rates are relatively low, typically near zero and seldom exceeding 5%. In such settings biochemical validation of the study is not necessary given its cost and its lack of acceptance (30).

Secondary outcomes

The secondary endpoints for the main analysis are:

- minimum 24-hour point abstinence at 3 months
- minimum 30-day point abstinence at 12 months
- number and duration of quit attempts
- progress through the 4 modules in the intervention (module changes and length of stay in each).

Other data

Other data will be collected in order to characterize consumption, dependency, determinants of abstinence, and the process. This will allow us to explain the results obtained and to achieve our secondary objectives. Table 2 sets out these data:

Table 1 – Other variables

Types of variable	Variables

Socio-demographic	Age Sex Marital status Living alone or not Living with child/children Planning a family or adoption Socio-professional categories (INSEE scale level 1 in 8 grades) Level of education
Co-morbidity	Receiving treatment for a chronic disease or not
Dependency and consumption (Fagerstrom test (31) in two questions)	Length of time between waking up and consuming Number of cigarettes/day Age at time of first smoke Daily consumption or not
Motivation (numerical scale of 1 to 10 as recommended by HAS(12)	Importance of quitting Abstinence self-efficacy
Experience of quitting	Experience of being supported
Support Preferences (12)	List of HAS-recommended treatments including electronic cigarettes
External factors	Psychological and environmental factors beneficial to cessation (access to other methods; social support including support groups, friends and relatives, influence of a third party; combined work and personal life events) Psychological and environmental factors adverse to cessation
Mechanisms/components of the intervention	Number and types of BCTs encountered by the participant in his/her attempts to quit (28,32,33)(28,32,34) TIS usage data: number of connections, frequency of activity use, progress through the modules

Data collection

Primary and secondary outcomes collection: The measures in both arms will be internet-based. Data will be collected via self-reporting questionnaires at set times (T+3, 6 and 12 months).

Other data collection: The measures in both arms will be internet-based except for data relating to e-TIS components which only concerns the intervention arm (E).

Data will be collected from 4 sources: an inclusion questionnaire (technical variables), an initial self-reporting questionnaire at T0, 3 follow-up self-reporting questionnaires (T+3, 6 and 12 months), and routine collection via the internet platform of e-TIS. In the T0 questionnaire,

the data collected will be differentiated according to the entry point into the intervention (1 to 4). In the follow-up questionnaire, the data collected will be differentiated according the participant's status: has stopped smoking or not.

At each milestone, an email and text message will be sent as a reminder. Throughout the study, there will be routine and ongoing data collection via the system for the intervention arm only (E).

Analysis plan

The efficacy will be analyzed using blind analysis by comparison at 3, 6, 12 months in both arms using the primary and secondary endpoints. In the main analysis, data will be analyzed by Intention-to-treat and then by Per-protocol analyses. For the main analysis, those participants lost to follow-up (those who don't answer the questionnaires) will be considered smokers. For the secondary analysis, we will only consider those who will not be lost to follow-up. The efficacy analysis will be blinded to the randomization group, but the processes and mechanisms by their nature will be analyzed openly. The proportion of quitters in each arm will be estimated, as well as an OR and its 95% confidence interval by logistic univariate regression. We will also conduct an analysis on efficacy in sub-groups using the following predefined variables: Socio-professional classification, sex, age, point of entry onto the intervention. Multiple imputation methodologies will be used to limit the amount of possible missing data.

To assess the processes, we will clarify the intervention components (the BCTs used in e-TIS) and the environmental components (beneficial and adverse factors for cessation) to which the subjects have been exposed. We will also look into how e-TIS has been used (frequency and duration of use, the activities performed). To conduct this analysis, we will proceed in 3 stages:

Stage 1 – Clarify the intervention theory: This involves attributing one or several BCTs to each contact between the user and the e-TIS intervention, which will establish the generic intervention theory of the said intervention (components) (35,36).

Each user will go through the intervention in his or her own way and this intervention theory will come across differently according to a combination of contextual factors including the route taken and the use of the website. This all leads to different intervention doses (number and type of BCTs to which the user is exposed) and to different response doses (module changes, end of platform use, smoking cessation, relapse, etc.) (37).

Stage 2 – Describe the route taken by users in the intervention arm: In this stage we will describe the user's or user's routes within the e-TIS intervention, looking at the combinations of BCTs to which users are exposed (number, type, associations), the types of environmental

and social factors encountered (social support, substitutes, life events, etc.) and the use of the e-TIS platform. From this we will be able to identify the most common routes used through the intervention.

Stage 3 – Analyze the influence of user characteristics, processes, context and exposure to BCTs on the outcome: Here we will compare and contrast the routes identified, with emphasis on the most common ones, using primary and secondary endpoints. The aim is to analyze the influence of user characteristics, processes, context and exposure to BCTs on the outcome in terms of abstinence, quit attempts and progress through the modules.

This purpose of this analysis is to clarify how the generic theory best applies to the different users going through the intervention. It will therefore enable us to assess the mechanisms and conditions of the theory's efficacy, in relation to options for the degree of intervention, exposure to context and to the different dose responses. To achieve this, we will conduct multivariate, multi-level statistical analysis, stratified by point of entry, and adjusted to the variables relating to user characteristics.

Ethical considerations and dissemination

Participants must give their informed consent to participate in the study. They will be informed that they can refuse and drop out at any time. Subjects in the control arm will be asked to register to the e-TIS website once they have been deemed suitable for treatment via an initial evaluation. The data collected and processed in this study will be done so in compliance with the Act of 6 January 1978 on Data Processing, Data Files and Individual Liberties, as amended by the Act 2014-801 of 6 August 2004. The CNAMTS has a compliance undertaking with the CNIL (national body for data protection) as set out by Decree no. 2012-1249 of 9 November 2012 in the Conseil d'Etat (Council of State) which authorizes public health insurance funds (CNAMTS) to implement healthcare prevention and support programs for their beneficiaries.

The study protocol was reviewed by the ethical and deontological institutional review board of the INVS on 18 April 2016. All the proposals and recommendations put forward by the ethics committee have been followed and integrated into the amended version of the protocol.

DISCUSSION

Behavioral change interventions are complex, with outcomes depending as much on the intervention itself as on participant characteristics and the context of intervention delivery (24,26,38). In the case, this variability is borne out in the literature - the demonstrated effects are very heterogeneous due to the influence of the population characteristics, the way the

intervention is used by participants, and the context in which it is used. This is further compounded by the fact that the intervention is dematerialized and that each participant has a unique experience of it.

In view of the above, participant compliance should be improved and the support provided within the intervention should be fully tailored to the circumstances of each participants. For this to happen, we will need to work on two levels: intervention design, and evaluation design. Consequently the intervention has been based on data from literature and from the most used theoretical models used for helping people to quit. We have developed an evaluation protocol that no only allows us to conduct a thorough assessment of the intervention's efficacy via the RCT, but also seeks to clarify the conditions of its efficacy. These conditions relate to the participants; the different components of the TIS used by the participants; the psychological, social and environmental factors possibly affecting the participants during the study. To guide us, we use the references currently in use for evaluating complex interventions.

In this respect we hope both to contribute to better demonstrating the efficacy of online and mobile phone interventions, and to influence prevention strategies through an understanding of compliance and change phenomena.

ACKNOWLEDGMENTS

The authors wish to thank Jocelyn COURTOIS (CNAMTS), Eliane ALBUISSON, Marc BORIE and Geoffroy CAGNINACCI (CHU de Nancy), Viêt NGUYEN-THANH (Santé Publique France) and the Sociéte Française de Tabacologie for their technical help.

AUTHORS' CONTRIBUTIONS

LC and FA deals with the scientific coordination of the whole study; PB, IV, AP and PA designed the e-TIS intervention; LC prepared the first draft; all authors reviewed and contributed to the article.

COMPETING INTERESTS

We have read and understood BMJ policy on declaration of interests and declare that we have no competing interests.

REGISTRATION

The study is registered at www.clinicaltrials.gov (number = NCT02841683). The full trial protocol can be accessed on demand to the corresponding author.

FUNDING

This study is funded by the CNAMTS for the period 2016/2018.

LEGENDS OF FIGURES

Figure 1: Recruitment procedure

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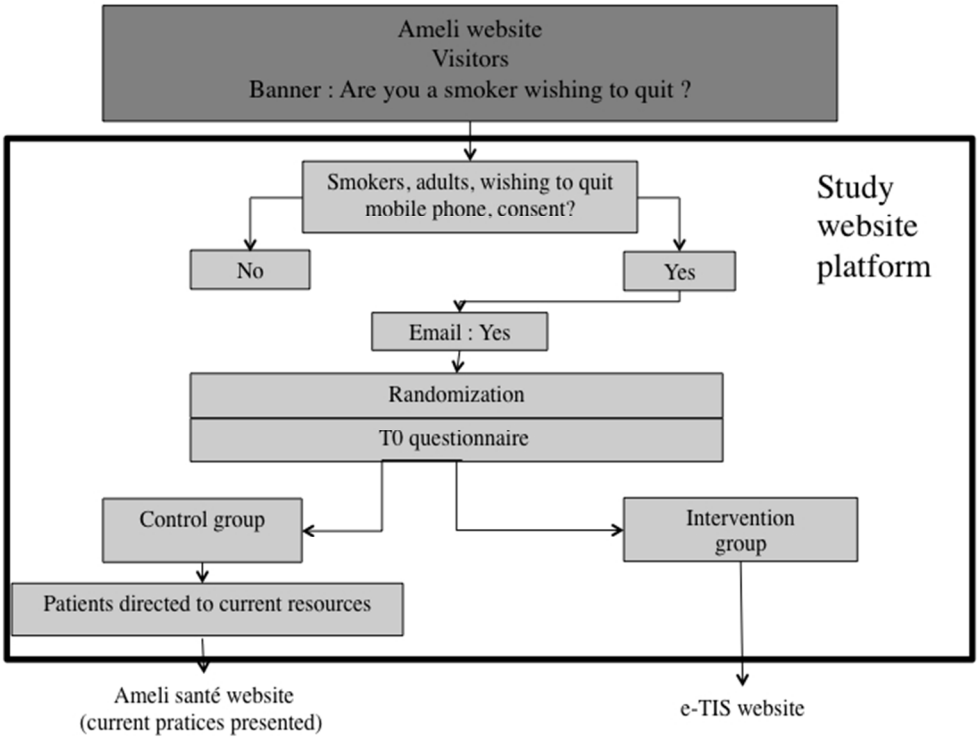

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CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3
	2b	Specific objectives or hypotheses	3/4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	4
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	5
Participants	4a	Eligibility criteria for participants	5
	4b	Settings and locations where the data were collected	4
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	5
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	8
	6b	Any changes to trial outcomes after the trial commenced, with reasons	8
Sample size	7a	How sample size was determined	5
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	5
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	5
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	5
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	5
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	5

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	NA
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	10/11
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	10/11
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	NA because protocol article
	13b	For each group, losses and exclusions after randomisation, together with reasons	NA because protocol article
Recruitment	14a	Dates defining the periods of recruitment and follow-up	NA because protocol article
	14b	Why the trial ended or was stopped	NA because protocol article
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	NA because protocol article
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	NA because protocol article
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	NA because protocol article
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	NA because protocol article
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	NA because protocol article
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	NA because

			protocol article
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	NA because protocol article
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	NA because protocol article
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	NA because protocol article
Other information			
Registration	23	Registration number and name of trial registry	2 and 13
Protocol	24	Where the full trial protocol can be accessed, if available	13
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	13

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

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A STUDY PROTOCOL FOR A PRAGMATIC RANDOMIZED CONTROLLED TRIAL EVALUATING EFFICACY OF A SMOKING CESSATION E- INTERVENTION "TABAC INFO SERVICE": EE-TIS TRIAL

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-013604.R1
Article Type:	Protocol
Date Submitted by the Author:	11-Nov-2016
Complete List of Authors:	Cambon, Linda; Ecole des Hautes Etudes en Sante Publique, Chaire de Recherche en prévention des cancers Bergman, Pierre; Caisse nationale de l'assurance maladie des travailleurs salaries Lefaou, Anne Laurence; Centre Addiction, Hôpital Européen Georges Pompidou, Pôle Psychiatrie-Addictologie, Hôpitaux Universitaires Paris-Ouest; Societé Francophone de Tabacologie Vincent, Isabelle; Caisse nationale de l'assurance maladie des travailleurs salaries Lemaitre, Beatrice; Société Francophone de Tabacologie Pasquereau, Anne; Santé Publique France Arwidson, Pierre; Santé Publique France Thomas, Daniel; Université Paris VI CHU Pitié-Salpêtrière; APHP, Institut de cardiologie, Hôpital de la Pitié-Salpêtrière ALLA, François; EA 4360 Apemac, Université de Lorraine
Primary Subject Heading:	Smoking and tobacco
Secondary Subject Heading:	Public health
Keywords:	e-health, smoking cessation, internet based intervention, prevention, mobile phone, efficacy

A STUDY PROTOCOL FOR A PRAGMATIC RANDOMIZED CONTROLLED TRIAL EVALUATING EFFICACY OF A SMOKING CESSATION E- INTERVENTION "TABAC INFO SERVICE": EE-TIS TRIAL

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KEY WORDS

E-health, smoking cessation, internet-based intervention, prevention, mobile phone, efficacy

WORDS COUNT: 4076

ABSTRACT

Introduction - A French national smoking cessation service, Tabac Info Service, has been developed to provide an adapted quitline and a web and mobile application involving personalized contacts (e.g. questionnaires, advice, activities, messages) to support smoking cessation. This paper presents the study protocol of the evaluation of the application (e-TIS). The primary objective is to assess the efficacy of e-TIS. The secondary objectives are to 1) describe efficacy variations with regard to users' characteristics, 2) analyze mechanisms and contextual conditions of e-TIS efficacy.

Methods and analyses - The study design is a two-arm pragmatic randomized controlled trial including a process evaluation with at least 3000 participants randomized to the intervention or to the control arm (current practices). Inclusion criteria are: aged 18 years or over, current smoker, having completed the on-line consent forms, possessing a mobile phone with android or apple systems and using mobile applications, wanting to stop smoking sooner or later. The primary outcome is the point prevalence abstinence of 7 days at 6 months later. Data will be analyzed in Intention to treat (primary) and per protocol analyses. A logistic regression will be carried out to estimate an Odds Ratio [95% Confidence Interval] for efficacy. A multivariate multilevel analysis will explore the influence on results of patients' characteristics (sex, age, education and socio-professional levels, dependency, motivation, quit experiences) and contextual factors, conditions of use, behavior change techniques.

Ethics and dissemination - The study protocol was reviewed by the ethical and deontological institutional review board of the French Institute for Public Health Surveillance on 18 April 2016. The findings of this study will allow us to characterize the efficacy of e-TIS and conditions of its efficacy. These findings will be disseminated through peer-reviewed articles.

Trial registration number - The study is registered at www.clinicaltrials.gov (number NCT02841683).

STRENGHTS AND LIMITATIONS OF THE STUDY

- Large national randomized trial in pragmatic conditions
- Process analysis within the trial using MRC framework and BCTs taxonomy in order to understand mechanisms and conditions of efficacy

INTRODUCTION

Every year, smoking causes 6.1 million deaths worldwide and an estimated 143.5 million DALYs (1). Health risks associated with smoking depend on two factors: daily consumption (2) and duration of smoking. Conversely, smoking cessation is good for health and the sooner a smoker quits, the better (3,4). People who stop smoking by the age of 40 reduce their likelihood of dying from smoking-related diseases by over 90%, and by the age of 30 the figure stands at 97% (3). Those who quit at 40 live 7 years longer, and at 50 live 4 years longer (4) compared to those who do not quit. In addition, smoking cessation does not just reduce mortality; it also brings down morbidity (5).

Various types of support and treatment are available, with varying results. Best evidence examples include: individual professional counseling (6), nicotine replacement therapy (NRT), motivational interviewing (7), group behavioral therapy (8), nursing interventions (9), self-help tools (10) for patients who prefer not to seek the help of a healthcare professional, or call helplines (8), support via mobile phone text messaging (11). Whatever the method used, the relapse prevention model (12) stresses the need to provide greater support in the so-called high-risk situations. Non-pharmacological treatments must therefore be tailored to the patient to deal adequately with both different immediate determinants (high-risk situations, coping skills in front of high-risk situations, outcome expectancies, and the abstinence violation effect), and the covert antecedents (lifestyle factors, stress, denial, cravings) as these factors can contribute to relapse.

Drawing on this knowledge, the CNAMTS (the French National Health Insurance Fund) and the national agency of public health (Santé Publique France - Public Health France) with the support of the French smoking cessation specialists association (Société Francophone de Tabaccologie) have come together to design, experiment and assess a new E-coaching intervention named e-TIS. The intervention is a mobile phone application designed to provide intensive support to smokers who are wishing to quit, including those who are not currently trying to. It is based on the effectiveness criteria of online programs (12), psychosocial and behavioral change theories (13–19) and the expertise from SFT members. E-TIS aims, therefore, to help smokers to progress through different stages (contemplation, intention, action), by providing tailored activities, self-reporting exercises, tips and social or psychological support, reassurance and motivational text messages. All these contacts are adapted to individual characteristics and level of progress. This article describes the protocol used to assess it. The protocol follows the recommendations of the CONSORT(20) and SPIRIT 2013 guidelines(21).

OBJECTIVES

The primary objective is to assess the efficacy of e-TIS. The secondary objectives are to 1) describe efficacy variations with regard to users' characteristics, 2) analyze mechanisms and contextual conditions of e-TIS efficacy.

METHODS AND ANALYSES

Rationale

The intervention is complex and many variables influence the outcomes. To achieve the secondary objectives of the study, we have followed the recommendations of the Medical Research Council (MRC) (22,23) and the Workgroup for Intervention Development and Evaluation Research (WIDER) (24). In 2000, the MRC published a framework, updated in 2012 (25) concerning the evaluation of complex interventions. The framework stresses the need to base the intervention on a theory in order to understand which components are effective and in which conditions.

In 2007, following the 21st annual conference of the European Health Psychology Society, the WIDER issued a consensus statement which outlined that specific behavioral change intervention (BCI) reporting has to be used in conjunction with the CONSORT statement. The philosophy is that greater clarity about the functional components of behavior change interventions is essential to ensure that interventions are delivered to influence outcomes. The WIDER recommendations are now an established framework for identifying and describing the essential components for detailed reporting of BCIs. In line with these frameworks, our second objective is to assess the intervention's key functions (26), in other words, the environmental or intervention components that determine its efficacy. To achieve this, we will draw on the taxonomy by Michie et al (27,28) which has enabled us to describe the Behavioral Change Techniques (BCTs) used in the intervention. We will also report the external environmental or social factors and consider additional individual characteristics that could influence the efficacy of the intervention.

Study design

The evaluation will be conducted as a pragmatic randomized controlled trial combined with a process analysis. The e-TIS intervention will be compared against current practices for smoking cessation as set out on a non-interactive website (ameli-sante.fr, Cnamts).

To do this, the evaluation sets out the smoking cessation treatments as recommended by the *Haute Autorité de Santé* (HAS); independent national scientific body with a broad remit on

health and healthcare issues) and consists of two arms: the intervention arm (use of the e-TIS intervention) and a control arm (current practices).

Study setting

This pragmatic trial takes place in France on a national level. The application was launched in October 2016. The evaluation will take place between 1 January 2017 and 1 March 2017.

Eligibility criteria

Inclusion criteria are: all adult smokers, who have completed the on-line consent form, agreeing to participate in the study, possessing a mobile phone using apple and android system, willing to use applications, and envisaging quitting smoking (in the short, medium or long term). An inclusion questionnaire is included with the consent form to screen potential participants (smoker or not, age, sex, wish to stop smoking, smartphone use) and to identify the technical characteristics for setting up the study (e.g. randomization), such as email and phone number.

Sample size

The required sample size was calculated using an hypothesis of an abstinence rate of 10% in the control group (intermediate situation between a spontaneous rate of 5% and the rate of 20% observed in the STAMP study (29)). For a spontaneous rate of 10%, a sample of size of 1,500 subjects per group is required to show an OR of 1.5 with a power of 90% (alpha 0.05, bilateral test), meaning a total of 3,000 persons.

Recruitment

Subjects will be recruited as the e-TIS website becomes operational and over 3 full months (January - March 2017). The study will start in January 2017 and end in July 2018. Data will be collected over 12 months. Recruitment will be via France's national health insurance fund's website Ameli: www.ameli-sante.fr. Subjects will log on to the Ameli website where they see a banner for the study. If they click on the banner, they will be taken to the website of the study and will be invited to participate. Here they will find an information sheet along with a section where they can give their informed consent. The consent form contains the inclusion questionnaire.. If consent is given, a confirmation email will be sent to the person (link to click on). Once the volunteers have confirmed, they will be randomized, and a second email and a text message will be sent to them. These contain a password so that they can log on to the entry questionnaire (T0) for the study. And once this questionnaire is completed, the participants will be assigned to one of the study arms. Figure 1 shows the procedure. Given that the Ameli website has an average of 1.8 million single visits per month and the prevalence of smokers in the French adult population is above 30%(30), we could estimate that approximately 600,000 smokers will be connected in a three-month

period. The inclusion period can be adapted to the actual number of people volunteering. Please note that during the first month of operation of E-TIS, 33,000 persons downloaded this application, which is an argument for the feasibility of the inclusion process.

Randomization

Automated randomization will be carried out following receipt of all necessary data, and consent by the subject to participate in the study. A minimization software package will be used to reduce of the risk of unmatched groups and will be applied to stratify participants according to sex and age using the following parameters: two treatment arms, e-TIS (E) and Ameli.fr (A) allocated 50/50; stratified by sex (M/F) and by age (+/- 45 years old); drawn for the first 30 subjects, 5% drawn, 0.96 randomization factor.

Intervention

Intervention arm: Participants will be assigned to one of two arms before the treatment begins. Those participants assigned to the intervention arm will be exposed to the e-TIS intervention. In keeping with the precepts of the relapse prevention model, the treatment will be individually tailored to each smoker throughout, based on feedback collected along the way. The support process draws on the efficacy criteria of online programs (frequency and intensity of contacts, short messages, interactivity, appeal, personalization, credibility of content, share functions) and various theoretical models used in withdrawal treatments.

The intervention will primarily involve personalized interactive (push) contacts via mobile phone, website platform and tablet. These contacts are questionnaires, advice, activities, and text messages. The intervention comprises 16 different activities and 8 position questionnaires with different purposes. The position questionnaires are designed to help smokers to progress : A questionnaire to guide participants through the modules ; a questionnaire about smoker status; a customization questionnaire (presence of other smokers, e-cigarette use, cannabis consumption, contraceptive methods, pregnancy, just gave birth, cardiovascular or respiratory diseases, previous quit attempts) ; a dependency questionnaire; a questionnaire about support preferences; a questionnaire about withdrawal symptoms; a questionnaire about self-efficacy; a questionnaire about craving.

The purposes of the 16 activities are:

AC1 - Decisional balance: to define and prioritize the pros and cons of quitting.

AC2 - Fears and obstacles: to identify fears and obstacles associated with quitting and to obtain some information or reassurance about smoking cessation.

AC3 - The cigarette log: to report daily cigarette consumption and define the cigarettes really appreciated and important and furthermore difficult to leave.

AC4 – Cost of smoking: to be aware of the cost of smoking (modules 1 and 2) and the savings to be made if one quits (module 3).

AC5 - Quit date choice: To help the smoker choose the best time to attempt quitting, and to enroll the support of others who should be aware of the quit date.

AC6 – My motivations: to review the smoker's motivation to take the decision to stop smoking (module 1), strengthen this (module 2), to reiterate the decision to quit and provide encouragement throught the cessation process (module 3).

AC7 - TNS: to facilitate the use of nicotine replacement therapies (NRT), improve knowledge about them.

AC8 – Social support: to use friends' videos as a way to gain the support of the smoker's entourage.

AC9 – Craving: to obtain ideas of occupations, through videos, to manage craving; to play games, to receive practical advice, and information about stress management techniques, use of NRTs etc.

AC10 - Progress and benefits: to track progress in smoking cessation and visualize it since the beginning

AC11 – Stress management: to provide various stress and emotion management techniques

AC12 - Q & A: to send questions to a smoking cessation specialist at the Tabac Info Service platform

AC13 – Telephone directory: to find a smoking cessation specialist

AC14 - Click to call: to call a smoking cessation specialist at the Tabac Info Service platform

AC15 – Weight management: Tips on weight management

AC16 – Quit checklist: once the quit date has been set, the smoker receives advice to make a plan to quit. He/she can refer to it and check off the tasks completed.

There is also a set of email or push-app text messages/notifications (roughly 170) with various purposes: welcome messages for each module; messages promoting activities and questionnaires, reminders and follow-up messages, unidirectional messages (personalized or not) to provide advice and encouragement to use the application; personalized messages relating to the answers at the different questionnaires; messages about the quitting date.

In addition, all contacts are tailored to the answers from the 8 position questionnaires in the application, and on the smoker's progress through the 4 of the application's modules:

- Module 1 – Participants are not yet ready to quit smoking (they have yet to set a quit date). This module is intended to increase the participants' resolve / resoluteness /

resolution to quit and help them set a stopping date. Participants only leave this module once they have set a quitting date. Tailoring: Text messaging is not intense at this stage and activities mainly designed to enhance motivation, report pros and cons, reach a balanced decision, etc.

- Module 2 – Participants are ready to quit (they have set a date). This module aims to provide the best possible conditions to help participants prepare in the run-up to their quitting date. Participants leave this module on the morning of their quitting date unless they choose to cancel, in which case they return to module 1. Tailoring: Text messaging will be intensive the day before the quit date and activities are mainly aimed at providing social support, pharmacological support, at setting challenges, etc.
- Module 3: Participants have stopped smoking. In this module they are given support and advice in detecting and avoiding possible relapses. Tailoring: Text messaging will be highly intense. Activities are focused on reassurance, social comparison, social support and information about relapses , etc.,
- Module 4 – Participants have relapsed. This is a short term module whose purpose is to help willing participants to manage their relapse and return to either modules 1, 2, or 3. They can leave module 4 once they have completed a questionnaire designed to ascertain which module they should reintegrate. Tailoring: activities and text messaging aim to reassure and remotivate the smoker.

This process is presented in table 1.

Table 1: eTIS support process

	Module 1 Contemplation	Module 2 Preparation	Module 3 Quitting	Module 4 Relapse
	I'm thinking of quitting	I'm ready to quit	I'm quitting	I have slipped
Context	Smokers who are contemplating but who have yet to set a quit date	Smokers preparing for the quit date they have set	Smokers who have quit	Smokers who relapse
Objectives	Help smokers increase their resolve Help smokers set a quit date	Help smokers prepare in the run-up to their quit date in the best possible conditions	Provide support and advice in detecting and avoiding possible lapses/relapses	Help willing users return to modules 1, 2 or 3 Provide individual support

Level of contact throughout the intervention	Low intensity 3-4 messages per week	Intense 1 message per day One day before the quit date, messaging will be intense (3 to 4 messages).	Up to D+7 Highly intense 2 to 4 messages per day Between D+8 and D+28 ; D+29 and D+56 ; D+57 and D+180 Intensity declines	N/A

Control arm: Participants assigned to the control arm are exposed to an information page which lists smoking cessation resources readily available in France and recommended by HAS (31). This is the common practice pathway. Participants are given a link to access the page and there are 4 tabs:

- The effects of smoking: this section provides information about how tobacco affects morbidity, mortality and quality of life.
- The benefits of a smoke-free life: this section provides information about the short-, medium-, and long-term benefits of smoking cessation and how quality of life is likely to improve.
- Your current situation: this section involves conducting a small survey about the participants' smoking habits to assess their levels of consumption, dependency, and motivation to quit.
- How to quit smoking: this section informs smokers about the various cessation methods recommended by HAS and how to apply for them.

Primary outcome

For the main analysis, the primary endpoint is a minimum 7-day point abstinence at 6 months. To define the 6 month follow up, we follow the recommendations of the Cochrane review on internet-based intervention and mobile interventions (11,12) and of the European Medicines Agency (32). Point prevalence abstinence (PPA) is considered the most appropriate measure for intervention evaluation studies(33). The National Interagency Council on Smoking and Health recommends PPA for a minimum 24h at 3 months, 7-day abstinence at 6 months and 30 days at 12 months (34). Biochemical validation will not be used; for most situations, and particularly in community-based interventions (vs clinical interventions) and with an adult population(34), the misreporting rates are relatively low,

typically near zero and seldom exceeding 5%. In such settings biochemical validation of the study is not necessary given its cost and its lack of acceptance (34).

Secondary outcomes

Following the same references (11,12,32,33), we have defined the secondary endpoints for the main analysis :

- Continuous abstinence at 6 months
- Continuous abstinence at 12 months
- Minimum 24-hour point abstinence at 3 months
- Minimum 30-day point abstinence at 12 months
- Number and duration of quit attempts
- Progress through the 4 modules in the intervention (module changes and length of stay in each).

Other data

Other data will be collected in order to characterize consumption, dependency, determinants of abstinence, and the process. This will allow us to explain the results obtained and to achieve our secondary objectives. Table 2 sets out these data:

Table 2 – Other variables

Types of variable	Variables
Socio-demographic	Age Sex Marital status Living alone or not Living with child/children Planning a family or adoption Socio-professional categories (INSEE scale level 1 in 8 grades) Level of education
Co-morbidity	Receiving treatment for a chronic disease or not
Dependency and consumption **(Fagerstrom test (35) in two questions)**	Length of time between waking up and consuming Number of cigarettes/day Age at time of first smoke Daily consumption or not
Motivation (numerical scale of 1 to 10 as	Importance of quitting Abstinence self-efficacy

recommended by HAS(31)	
Experience of quitting	Experience of being supported
Support Preferences (31)	List of HAS-recommended treatments including electronic cigarettes
External factors	Psychological and environmental factors beneficial to cessation (access to other methods; social support including support groups, friends and relatives, influence of a third party; combined work and personal life events) Psychological and environmental factors adverse to cessation
Mechanisms/components of the intervention	Number and types of BCTs encountered by the participant in his/her attempts to quit (36–39) TIS usage data: number of connections, frequency of activity use, progress through the modules

Data collection

Primary and secondary outcomes collection: The measures in both arms will be internet-based. Data will be collected via self-reporting questionnaires at set times (T+3, 6 and 12 months).

Other data collection: The measures in both arms will be internet-based except for data relating to e-TIS components which only concerns the intervention arm (E).

Data will be collected from 4 sources: an inclusion questionnaire (technical variables), an initial self-reporting questionnaire at T0, 3 follow-up self-reporting questionnaires (T+3, 6 and 12 months), and routine collection via the internet platform of e-TIS. In the T0 questionnaire, the data collected will be differentiated according to the entry point into the intervention (1 to 4). In the follow-up questionnaire, the data collected will be differentiated according the participant's status: has stopped smoking or not. Table 3 describes how each measure will be recorded.

Table 3: Recording procedures

Types of measures	Inclusion questionnaire (associated with the consent form)	Questionnaire T0	Questionnaire T3, T6, T12	Extracted from the application (position questionnaires or uses of the e-TIS components)
Primary outcomes			• Minimum 7-day point abstinence at 6 months	
Secondary outcomes			• Continuous abstinence at 6 month • Continuous abstinence at 12 month • Minimum 24-hour point abstinence at 3 months • Minimum 30-day point abstinence at 12 months • Number and duration of quit attempts	• Progress through the 4 modules in the intervention
Others variables	• Technical variables (e-mail, phone number, date of entry) • Socio-demographic : sex	• Socio-demographic variables excepted sex • Dependency and consumptions variables • Motivation variables <u>Specifically for control group :</u> • Comorbidity variables • Experience of quitting • Support preferences	• Dependency and consumptions variables • Motivation variables • Added support using • External factors	<u>Specifically for intervention group</u> : • Comorbidity variables • Experience of quitting • Support preferences • Mechanisms/components of the intervention

At each follow-up point, an email and text message will be sent twice as a reminder. Throughout the study, there will be routine and ongoing data collection via the system for the intervention arm only (E).

Analysis plan

The efficacy will be analyzed using blind analysis by comparison at 3, 6, 12 months in both arms using the primary and secondary endpoints. In the main analysis, data will be analyzed by Intention-to-treat and then by Per-protocol analyses. For the main analysis, those participants lost to follow-up (those who don't answer the questionnaires) will be considered smokers as recommended (40). For the secondary analysis, we will only consider those who will not be lost to follow-up. The efficacy analysis will be blinded to the randomization group, but the processes and mechanisms by their nature will be analyzed openly. The proportion of quitters in each arm will be estimated, as well as an OR and its 95% confidence interval by logistic univariate regression. We will also conduct an analysis on efficacy in sub-groups using the following predefined variables: Socio-professional classification, sex, age, point of entry onto the intervention. Multiple imputation methodologies will be used to limit the amount of possible missing data.

To assess the processes, we will clarify the intervention components (the BCTs used in e-TIS) and the environmental components (beneficial and adverse factors for cessation) to which the subjects have been exposed. We will also look into how e-TIS has been used (frequency and duration of use, the activities performed). To conduct this analysis, we will proceed in 3 stages:

Stage 1 – Characterize the intervention theory: This involves attributing one or several BCTs to each contact, such as a message, an activity and a questionnaire, between the user and the e-TIS intervention, which will establish the generic intervention theory of the said intervention (components) (41,42). This will be carried out by a multidisciplinary committee. It will take 3 iterative steps: 1/ two groups of researchers will attribute BCTs to contacts, 2/ both groups will compare their results and draw a consensus and 3/ researchers will present their results to the committee which will in turn draw a consensus. All components of e-TIS will be identified as universal BCTs of the taxonomy.

Each user will go through the intervention in his or her own way and this intervention theory will come across differently according to a combination of contextual factors including the pathway taken and the use of the website. This all leads to different intervention doses (number and type of BCTs to which the user is exposed) and to different response doses (module changes, end of platform use, smoking cessation, relapse, etc.) (43).

Stage 2 – Describe the pathway of users in the intervention arm: In this stage we will describe the user pathways within the e-TIS intervention, looking at the combinations of BCTs to which users are exposed (number, type, associations), the types of environmental and social factors encountered (social support, substitutes, life events, etc.) and the use of the e-TIS platform. From this we will be able to identify the most common pathway used through the intervention.

Stage 3 – Analyze the influence of user characteristics, processes, context and exposure to BCTs on the outcome: Here we will compare and contrast the pathways identified, with emphasis on the most common ones, using primary and secondary endpoints. The aim is to analyze the influence of users' characteristics (such as socio-demographic, dependency, motivation, quit attempts or experiences, added support, etc.), contextual factors and exposure to BCTs on the outcome in terms of abstinence, quit attempts and progress through the modules.

This purpose of this analysis is to clarify how the generic theory best applies to the different users going through the intervention. It will therefore enable us to assess the mechanisms and conditions of the theory's efficacy, in relation to options for the degree of intervention, exposure to context and to the different dose responses. To achieve this, we will conduct multivariate, multi-level statistical analysis, stratified by point of entry, and adjusted to the variables relating to user characteristics (see above).

Ethical considerations and dissemination

Participants must give their informed consent to participate in the study. They will be informed that they can refuse and drop out at any time. Subjects in the control arm will be asked to register to the e-TIS website once they have been deemed suitable for treatment via an initial evaluation. The data collected and processed in this study will be done so in compliance with the Act of 6 January 1978 on Data Processing, Data Files and Individual Liberties, as amended by the Act 2014-801 of 6 August 2004. The CNAMTS has a compliance undertaking with the CNIL (national body for data protection) as set out by Decree no. 2012-1249 of 9 November 2012 in the Conseil d'Etat (Council of State) which authorizes public health insurance funds (CNAMTS) to implement healthcare prevention and support programs for their beneficiaries.

The study protocol was reviewed by the ethical and deontological institutional review board of the INVS on 18 April 2016. All the proposals and recommendations put forward by the ethics committee have been followed and integrated into the amended version of the protocol.

DISCUSSION

Behavioral change interventions are complex, with outcomes depending as much on the intervention itself as on participant characteristics and the context of intervention delivery (23,26,44). In the case, this variability is borne out in the literature - the demonstrated effects are very heterogeneous due to the influence of the population characteristics, the way the intervention is used by participants, and the context in which it is used. This is further compounded by the fact that the intervention is dematerialized and that each participant has a unique experience of it.

In view of the above, participant compliance should be improved and the support provided within the intervention should be fully tailored to the circumstances of each participants. For this to happen, we will need to work on two levels: intervention design, and evaluation design. Consequently the intervention has been based on data from literature and from the most used theoretical models used for helping people to quit. We have developed an evaluation protocol that no only allows us to conduct a thorough assessment of the intervention's efficacy via the RCT, but also seeks to clarify the conditions of its efficacy. These conditions relate to the participants; the different components of the TIS used by the participants; the psychological, social and environmental factors possibly affecting the participants during the study. To guide us, we use the references currently in use for evaluating complex interventions.

In this respect we hope both to contribute to better demonstrating the efficacy of online and mobile phone interventions, and to influence prevention strategies through an understanding of compliance and change phenomena.

ACKNOWLEDGMENTS

The authors wish to thank Jocelyn COURTOIS (CNAMTS), Eliane ALBUISSON, Marc BORIE and Geoffroy CAGNINACCI (CHU de Nancy), Viêt NGUYEN-THANH (Santé Publique France).

AUTHORS' CONTRIBUTIONS

LC and FA deals with the scientific coordination of the whole study; PB, IV, AP, LAL, BL, TD and PA designed the e-TIS intervention; LC prepared the first draft; all authors reviewed and contributed to the article.

COMPETING INTERESTS

We have read and understood BMJ policy on declaration of interests and declare that we have no competing interests.

REGISTRATION

The study is registered at www.clinicaltrials.gov (number = NCT02841683). The full trial protocol can be accessed on demand to the corresponding author.

FUNDING

This study is funded by the CNAMTS for the period 2016/2018.

LEGENDS OF FIGURES

Figure 1: Recruitment procedure

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CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3
	2b	Specific objectives or hypotheses	3/4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	4
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	5
Participants	4a	Eligibility criteria for participants	5
	4b	Settings and locations where the data were collected	4
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	5
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	8
	6b	Any changes to trial outcomes after the trial commenced, with reasons	8
Sample size	7a	How sample size was determined	5
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	5
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	5
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	5
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	5
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	5

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	NA
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	10/11
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	10/11
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	NA because protocol article
	13b	For each group, losses and exclusions after randomisation, together with reasons	NA because protocol article
Recruitment	14a	Dates defining the periods of recruitment and follow-up	NA because protocol article
	14b	Why the trial ended or was stopped	NA because protocol article
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	NA because protocol article
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	NA because protocol article
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	NA because protocol article
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	NA because protocol article
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	NA because protocol article
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	NA because

			protocol article
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	NA because protocol article
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	NA because protocol article
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	NA because protocol article
Other information			
Registration	23	Registration number and name of trial registry	2 and 13
Protocol	24	Where the full trial protocol can be accessed, if available	13
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	13

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

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A STUDY PROTOCOL FOR A PRAGMATIC RANDOMIZED CONTROLLED TRIAL EVALUATING EFFICACY OF A SMOKING CESSATION E- INTERVENTION "TABAC INFO SERVICE": EE-TIS TRIAL

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-013604.R2
Article Type:	Protocol
Date Submitted by the Author:	09-Jan-2017
Complete List of Authors:	Cambon, Linda; Ecole des Hautes Etudes en Sante Publique, Chaire de Recherche en prévention des cancers Bergman, Pierre; Caisse nationale de l'assurance maladie des travailleurs salaries Lefaou, Anne Laurence; Centre Addiction, Hôpital Européen Georges Pompidou, Pôle Psychiatrie-Addictologie, Hôpitaux Universitaires Paris-Ouest; Societé Francophone de Tabacologie Vincent, Isabelle; Caisse nationale de l'assurance maladie des travailleurs salaries Lemaitre, Beatrice; Société Francophone de Tabacologie Pasquereau, Anne; Santé Publique France Arwidson, Pierre; Santé Publique France Thomas, Daniel; Université Paris VI CHU Pitié-Salpêtrière; APHP, Institut de cardiologie, Hôpital de la Pitié-Salpêtrière ALLA, François; EA 4360 Apemac, Université de Lorraine
Primary Subject Heading:	Smoking and tobacco
Secondary Subject Heading:	Public health
Keywords:	e-health, smoking cessation, internet based intervention, prevention, mobile phone, efficacy

A STUDY PROTOCOL FOR A PRAGMATIC RANDOMIZED CONTROLLED TRIAL EVALUATING EFFICACY OF A SMOKING CESSATION E- INTERVENTION "TABAC INFO SERVICE": EE-TIS TRIAL

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KEY WORDS

E-health, smoking cessation, internet-based intervention, prevention, mobile phone, efficacy

WORDS COUNT: 4498

ABSTRACT

Introduction - A French national smoking cessation service, Tabac Info Service, has been developed to provide an adapted quitline and a web and mobile application involving personalized contacts (e.g. questionnaires, advice, activities, messages) to support smoking cessation. This paper presents the study protocol of the evaluation of the application (e-TIS). The primary objective is to assess the efficacy of e-TIS. The secondary objectives are to 1) describe efficacy variations with regard to users' characteristics, 2) analyze mechanisms and contextual conditions of e-TIS efficacy.

Methods and analyses - The study design is a two-arm pragmatic randomized controlled trial including a process evaluation with at least 3000 participants randomized to the intervention or to the control arm (current practices). Inclusion criteria are: aged 18 years or over, current smoker, having completed the on-line consent forms, possessing a mobile phone with android or apple systems and using mobile applications, wanting to stop smoking sooner or later. The primary outcome is the point prevalence abstinence of 7 days at 6 months later. Data will be analyzed in Intention to treat (primary) and per protocol analyses. A logistic regression will be carried out to estimate an Odds Ratio [95% Confidence Interval] for efficacy. A multivariate multilevel analysis will explore the influence on results of patients' characteristics (sex, age, education and socio-professional levels, dependency, motivation, quit experiences) and contextual factors, conditions of use, behavior change techniques.

Ethics and dissemination - The study protocol was reviewed by the ethical and deontological institutional review board of the French Institute for Public Health Surveillance on 18 April 2016. The findings of this study will allow us to characterize the efficacy of e-TIS and conditions of its efficacy. These findings will be disseminated through peer-reviewed articles.

Trial registration number - The study is registered at www.clinicaltrials.gov (number NCT02841683).

STRENGHTS AND LIMITATIONS OF THE STUDY

- Large national randomized trial in pragmatic conditions
- Process analysis within the trial using MRC framework and BCTs taxonomy in order to understand mechanisms and conditions of efficacy

INTRODUCTION

Every year, smoking causes 6.1 million deaths worldwide and an estimated 143.5 million DALYs (1). Health risks associated with smoking depend on two factors: daily consumption (2) and duration of smoking. Conversely, smoking cessation is good for health and the sooner a smoker quits, the better (3,4). People who stop smoking by the age of 40 reduce their likelihood of dying from smoking-related diseases by over 90%, and by the age of 30 the figure stands at 97% (3). Those who quit at 40 live 7 years longer, and at 50 live 4 years longer (4) compared to those who do not quit. In addition, smoking cessation does not just reduce mortality; it also brings down morbidity (5).

Various types of support and treatment are available, with varying results. Best evidence examples include: individual professional counseling (6), nicotine replacement therapy (NRT), motivational interviewing (7), group behavioral therapy (8), nursing interventions (9), self-help tools (10) for patients who prefer not to seek the help of a healthcare professional, or call helplines (8), support via mobile phone text messaging (11). Whatever the method used, the relapse prevention model (12) stresses the need to provide greater support in the so-called high-risk situations. Non-pharmacological treatments must therefore be tailored to the patient to deal adequately with both different immediate determinants (high-risk situations, coping skills in front of high-risk situations, outcome expectancies, and the abstinence violation effect), and the covert antecedents (lifestyle factors, stress, denial, cravings) as these factors can contribute to relapse.

Drawing on this knowledge, the CNAMTS (the French National Health Insurance Fund) and the national agency of public health (Santé Publique France - Public Health France) with the support of the French smoking cessation specialists association (Société Francophone de Tabaccologie) have come together to design, experiment and assess a new E-coaching intervention named e-TIS. The intervention is a mobile phone application designed to provide intensive support to smokers who are wishing to quit, including those who are not currently trying to. It is based on the effectiveness criteria of online programs (12), psychosocial and behavioral change theories (13–19) and the expertise from SFT members. E-TIS aims, therefore, to help smokers to progress through different stages (contemplation, intention, action), by providing tailored activities, self-reporting exercises, tips and social or psychological support, reassurance and motivational text messages. All these contacts are adapted to individual characteristics and level of progress. This article describes the protocol used to assess it. The protocol follows the recommendations of the CONSORT(20) and SPIRIT 2013 guidelines(21).

OBJECTIVES

The primary objective is to assess the efficacy of e-TIS. The secondary objectives are to 1) describe efficacy variations with regard to users' characteristics, 2) analyze mechanisms and contextual conditions of e-TIS efficacy.

METHODS AND ANALYSES

Rationale

The intervention is complex and many variables influence the outcomes. To achieve the secondary objectives of the study, we have followed the recommendations of the Medical Research Council (MRC) (22,23) and the Workgroup for Intervention Development and Evaluation Research (WIDER) (24). In 2000, the MRC published a framework, updated in 2012 (25) concerning the evaluation of complex interventions. The framework stresses the need to base the intervention on a theory in order to understand which components are effective and in which conditions.

In 2007, following the 21st annual conference of the European Health Psychology Society, the WIDER issued a consensus statement which outlined that specific behavioral change intervention (BCI) reporting has to be used in conjunction with the CONSORT statement. The philosophy is that greater clarity about the functional components of behavior change interventions is essential to ensure that interventions are delivered to influence outcomes. The WIDER recommendations are now an established framework for identifying and describing the essential components for detailed reporting of BCIs. In line with these frameworks, our second objective is to assess the intervention's key functions (26), in other words, the environmental or intervention components that determine its efficacy. To achieve this, we will draw on the taxonomy by Michie et al (27,28) which has enabled us to describe the Behavioral Change Techniques (BCTs) used in the intervention. We will also report the external environmental or social factors and consider additional individual characteristics that could influence the efficacy of the intervention.

Study design

The evaluation will be conducted as a pragmatic randomized controlled trial combined with a process analysis. The e-TIS intervention will be compared against current practices for smoking cessation as set out on a non-interactive website (ameli-sante.fr, Cnamts).

To do this, the evaluation sets out the smoking cessation treatments as recommended by the *Haute Autorité de Santé* (HAS); independent national scientific body with a broad remit on

health and healthcare issues) and consists of two arms: the intervention arm (use of the e-TIS intervention) and a control arm (current practices).

Study setting

This pragmatic trial takes place in France on a national level. The application was launched in October 2016. The evaluation will take place between 1 January 2017 and 1 March 2017.

Eligibility criteria

Inclusion criteria are: all adult smokers, who have completed the on-line consent form, agreeing to participate in the study, possessing a mobile phone using apple and android system, willing to use applications, and envisaging quitting smoking (in the short, medium or long term). An inclusion questionnaire is included with the consent form to screen potential participants (smoker or not, age, sex, wish to stop smoking, smartphone use) and to identify the technical characteristics for setting up the study (e.g. randomization), such as email and phone number.

Sample size

The required sample size was calculated using a hypothesis of a 10% abstinence rate at the six-month follow-up (similar to the rate observed in the StopAdvisor trial (29). Given a rate of 10% in the control group, a sample of 1,500 subjects per group is required to show an OR of 1.5 (i.e. a rate of 14% in the intervention group) with a power of 90% (alpha 0.05, bilateral test), meaning a total of 3,000 persons (30).

Recruitment

Subjects will be recruited as the e-TIS website becomes operational and over 3 full months (January - March 2017). The study will start in January 2017 and end in July 2018. Data will be collected over 12 months. Recruitment will be via France's national health insurance fund's website Ameli: www.ameli-sante.fr. Subjects will log on to the Ameli website where they see a banner for the study. If they click on the banner, they will be taken to the website of the study and will be invited to participate. Here they will find an information sheet along with a section where they can give their informed consent. The consent form contains the inclusion questionnaire.. If consent is given, a confirmation email will be sent to the person (link to click on). Once the volunteers have confirmed, they will be randomized, and a second email and a text message will be sent to them. These contain a password so that they can log on to the entry questionnaire (T0) for the study. And once this questionnaire is completed, the participants will be assigned to one of the study arms. Figure 1 shows the procedure. Given that the Ameli website has an average of 1.8 million single visits per month and the prevalence of smokers in the French adult population is above 30%(31), we could estimate that approximately 600,000 smokers will be connected in a three-month

period. The inclusion period can be adapted to the actual number of people volunteering. Please note that during the first month of operation of E-TIS, 33,000 persons downloaded this application, which is an argument for the feasibility of the inclusion process.

Randomization

Automated randomization will be carried out following receipt of all necessary data, and consent by the subject to participate in the study. A minimization software package will be used to reduce of the risk of unmatched groups and will be applied to stratify participants according to sex and age using the following parameters: two treatment arms, e-TIS (E) and Ameli.fr (A) allocated 50/50; stratified by sex (M/F) and by age (+/- 45 years old); drawn for the first 30 subjects, 5% drawn, 0.96 randomization factor.

Intervention

Intervention arm: Participants will be assigned to one of two arms before the treatment begins. Those participants assigned to the intervention arm will be exposed to the e-TIS intervention. In keeping with the precepts of the relapse prevention model, the treatment will be individually tailored to each smoker throughout, based on feedback collected along the way. The support process draws on the efficacy criteria of online programs (frequency and intensity of contacts, short messages, interactivity, appeal, personalization, credibility of content, share functions) and various theoretical models used in withdrawal treatments.

The intervention will primarily involve personalized interactive (push) contacts via mobile phone, website platform and tablet. These contacts are questionnaires, advice, activities, and text messages. The intervention comprises 16 different activities and 8 position questionnaires with different purposes. The position questionnaires are designed to help smokers to progress : A questionnaire to guide participants through the modules ; a questionnaire about smoker status; a customization questionnaire (presence of other smokers, e-cigarette use, cannabis consumption, contraceptive methods, pregnancy, just gave birth, cardiovascular or respiratory diseases, previous quit attempts) ; a dependency questionnaire; a questionnaire about support preferences; a questionnaire about withdrawal symptoms; a questionnaire about self-efficacy; a questionnaire about craving.

The purposes of the 16 activities are:

AC1 - Decisional balance: to define and prioritize the pros and cons of quitting.

AC2 - Fears and obstacles: to identify fears and obstacles associated with quitting and to obtain some information or reassurance about smoking cessation.

AC3 - The cigarette log: to report daily cigarette consumption and define the cigarettes really appreciated and important and furthermore difficult to leave.

AC4 – Cost of smoking: to be aware of the cost of smoking (modules 1 and 2) and the savings to be made if one quits (module 3).

AC5 - Quit date choice: To help the smoker choose the best time to attempt quitting, and to enroll the support of others who should be aware of the quit date.

AC6 – My motivations: to review the smoker's motivation to take the decision to stop smoking (module 1), strengthen this (module 2), to reiterate the decision to quit and provide encouragement throught the cessation process (module 3).

AC7 - TNS: to facilitate the use of nicotine replacement therapies (NRT), improve knowledge about them.

AC8 – Social support: to use friends' videos as a way to gain the support of the smoker's entourage.

AC9 – Craving: to obtain ideas of occupations, through videos, to manage craving; to play games, to receive practical advice, and information about stress management techniques, use of NRTs etc.

AC10 - Progress and benefits: to track progress in smoking cessation and visualize it since the beginning

AC11 – Stress management: to provide various stress and emotion management techniques

AC12 - Q & A: to send questions to a smoking cessation specialist at the Tabac Info Service platform

AC13 – Telephone directory: to find a smoking cessation specialist

AC14 - Click to call: to call a smoking cessation specialist at the Tabac Info Service platform

AC15 – Weight management: Tips on weight management

AC16 – Quit checklist: once the quit date has been set, the smoker receives advice to make a plan to quit. He/she can refer to it and check off the tasks completed.

There is also a set of email or push-app text messages/notifications (roughly 170) with various purposes: welcome messages for each module; messages promoting activities and questionnaires, reminders and follow-up messages, unidirectional messages (personalized or not) to provide advice and encouragement to use the application; personalized messages relating to the answers at the different questionnaires; messages about the quitting date.

In addition, all contacts are tailored to the answers from the 8 position questionnaires in the application, and on the smoker's progress through the 4 of the application's modules:

- Module 1 – Participants are not yet ready to quit smoking (they have yet to set a quit date). This module is intended to increase the participants' resolve / resoluteness /

resolution to quit and help them set a stopping date. Participants only leave this module once they have set a quitting date. Tailoring: Text messaging is not intense at this stage and activities mainly designed to enhance motivation, report pros and cons, reach a balanced decision, etc.

- Module 2 – Participants are ready to quit (they have set a date). This module aims to provide the best possible conditions to help participants prepare in the run-up to their quitting date. Participants leave this module on the morning of their quitting date unless they choose to cancel, in which case they return to module 1. Tailoring: Text messaging will be intensive the day before the quit date and activities are mainly aimed at providing social support, pharmacological support, at setting challenges, etc.
- Module 3: Participants have stopped smoking. In this module they are given support and advice in detecting and avoiding possible relapses. Tailoring: Text messaging will be highly intense. Activities are focused on reassurance, social comparison, social support and information about relapses , etc.,
- Module 4 – Participants have relapsed. This is a short term module whose purpose is to help willing participants to manage their relapse and return to either modules 1, 2, or 3. They can leave module 4 once they have completed a questionnaire designed to ascertain which module they should reintegrate. Tailoring: activities and text messaging aim to reassure and remotivate the smoker.

Participants start with the module adapted to their stage with regard to tobacco consumption (i.e. Module 1: Participants are not yet ready to quit smoking; Module 2: Participants are ready to quit; Module 3: Participants have stopped smoking; Module 4: Participants have relapsed.)

This process is presented in table 1.

Table 1: eTIS support process

	Module 1 Contemplation	Module 2 Preparation	Module 3 Quitting	Module 4 Relapse
	I'm thinking of quitting	I'm ready to quit	I'm quitting	I have slipped
Context	Smokers who are contemplating but who have yet to set a quit date	Smokers preparing for the quit date they have set	Smokers who have quit	Smokers who relapse
Objectives	Help smokers	Help smokers	Provide	Help willing

	increase their resolve Help smokers set a quit date	prepare in the run-up to their quit date in the best possible conditions	support and advice in detecting and avoiding possible lapses/relapses	users return to modules 1, 2 or 3 Provide individual support
Level of contact throughout the intervention	Low intensity 3-4 messages per week	Intense 1 message per day One day before the quit date, messaging will be intense (3 to 4 messages).	Up to D+7 Highly intense 2 to 4 messages per day Between D+8 and D+28 ; D+29 and D+56 ; D+57 and D+180 Intensity declines	N/A

Control arm: Participants assigned to the control arm are exposed to an information page which lists smoking cessation resources readily available in France and recommended by HAS (32). This is the common practice pathway. Participants are given a link to access the page and there are 4 tabs:

- The effects of smoking: this section provides information about how tobacco affects morbidity, mortality and quality of life.
- The benefits of a smoke-free life: this section provides information about the short-, medium-, and long-term benefits of smoking cessation and how quality of life is likely to improve.
- Your current situation: this section involves conducting a small survey about the participants' smoking habits to assess their levels of consumption, dependency, and motivation to quit.
- How to quit smoking: this section informs smokers about the various cessation methods recommended by HAS and how to apply for them.

Primary outcome

For the main analysis, the primary endpoint is a minimum 7-day point abstinence at 6 months. To define the 6 month follow up, we follow the recommendations of the Cochrane review on internet-based intervention and mobile interventions (11,12) and of the European Medicines Agency (33). Point prevalence abstinence (PPA) is considered the most appropriate measure for intervention evaluation studies(34). The National Interagency

Council on Smoking and Health recommends PPA for a minimum 24h at 3 months, 7-day abstinence at 6 months and 30 days at 12 months (35). Biochemical validation will not be used; for most situations, and particularly in community-based interventions (vs clinical interventions) and with an adult population(35), the misreporting rates are relatively low, typically near zero and seldom exceeding 5%. In such settings biochemical validation of the study is not necessary given its cost and its lack of acceptance (35).

Secondary outcomes

Following the same references (11,12,33,34), we have defined the secondary endpoints for the main analysis :

- Continuous abstinence at 6 months
- Continuous abstinence at 12 months
- Minimum 24-hour point abstinence at 3 months
- Minimum 30-day point abstinence at 12 months
- Number and duration of quit attempts
- Progress through the 4 modules in the intervention (module changes and length of stay in each).

Other data

Other data will be collected in order to characterize consumption, dependency, determinants of abstinence, and the process. This will allow us to explain the results obtained and to achieve our secondary objectives. Table 2 sets out these data:

Table 2 – Other variables

Types of variable	Variables
Socio-demographic	Age Sex Marital status Living alone or not Living with child/children Planning a family or adoption Socio-professional categories (INSEE scale level 1 in 8 grades) Level of education
Co-morbidity	Receiving treatment for a chronic disease or not
Dependency and	Length of time between waking up and consuming Number of cigarettes/day

consumption **(Fagerstrom test (36) in two questions)**	Age at time of first smoke Daily consumption or not
Motivation (numerical scale of 1 to 10 as recommended by HAS(32)	Importance of quitting Abstinence self-efficacy
Experience of quitting	Experience of being supported
Support Preferences (32)	List of HAS-recommended treatments including electronic cigarettes
External factors	Psychological and environmental factors beneficial to cessation (access to other methods; social support including support groups, friends and relatives, influence of a third party; combined work and personal life events) Psychological and environmental factors adverse to cessation
Mechanisms/components of the intervention	Number and types of BCTs encountered by the participant in his/her attempts to quit (37–40) TIS usage data: number of connections, frequency of activity use, progress through the modules

Data collection

Primary and secondary outcomes collection: The measures in both arms will be internet-based. Data will be collected via self-reporting questionnaires at set times (T+3, 6 and 12 months).

Other data collection: The measures in both arms will be internet-based except for data relating to e-TIS components which only concerns the intervention arm (E).

Data will be collected from 4 sources: an inclusion questionnaire (technical variables), an initial self-reporting questionnaire at T0, 3 follow-up self-reporting questionnaires (T+3, 6 and 12 months), and routine collection via the internet platform of e-TIS. In the T0 questionnaire, the data collected will be differentiated according to the entry point into the intervention (1 to 4). In the follow-up questionnaire, the data collected will be differentiated according the participant's status: has stopped smoking or not. Table 3 describes how each measure will be recorded.

Table 3: Recording procedures

Types of measures	Inclusion questionnaire (associated with the consent form)	Questionnaire T0	Questionnaire T3, T6, T12	Extracted from the application (position questionnaires or uses of the e-TIS components)
Primary outcomes			• Minimum 7-day point abstinence at 6 months	
Secondary outcomes			• Continuous abstinence at 6 month • Continuous abstinence at 12 month • Minimum 24-hour point abstinence at 3 months • Minimum 30-day point abstinence at 12 months • Number and duration of quit attempts	• Progress through the 4 modules in the intervention
Others variables	• Technical variables (e-mail, phone number, date of entry) • Socio-demographic : sex	• Socio-demographic variables excepted sex • Dependency and consumptions variables • Motivation variables <u>Specifically for control group :</u> • Comorbidity variables • Experience of quitting • Support preferences	• Dependency and consumptions variables • Motivation variables • Added support using • External factors	<u>Specifically for intervention group</u> : • Comorbidity variables • Experience of quitting • Support preferences • Mechanisms/components of the intervention

At each follow-up point, an email and text message will be sent twice as a reminder. Throughout the study, there will be routine and ongoing data collection via the system for the intervention arm only (E).

Analysis plan

The efficacy will be analyzed using blind analysis by comparison at 3, 6, 12 months in both arms using the primary and secondary endpoints. In the main analysis, data will be analyzed by Intention-to-treat and then by Per-protocol analyses. For the main analysis, those participants lost to follow-up (those who don't answer the questionnaires) will be considered smokers as recommended (12,33,41). For the secondary analysis, we will only consider those who will not be lost to follow-up. The efficacy analysis will be blinded to the randomization group, but the processes and mechanisms by their nature will be analyzed openly. The proportion of quitters in each arm will be estimated, as well as an OR and its 95% confidence interval by logistic univariate regression. We will also conduct an analysis on efficacy in sub-groups using the following predefined variables: Socio-professional classification, sex, age, point of entry onto the intervention. Multiple imputation methodologies will be used to limit the amount of possible missing data.

To assess the processes, we will clarify the intervention components (the BCTs used in e-TIS) and the environmental components (beneficial and adverse factors for cessation) to which the subjects have been exposed. We will also look into how e-TIS has been used (frequency and duration of use, the activities performed). To conduct this analysis, we will proceed in 3 stages:

Stage 1 – Characterize the intervention theory: This involves attributing one or several BCTs to each contact, such as a message, an activity and a questionnaire, between the user and the e-TIS intervention, which will establish the generic intervention theory of the said intervention (components) (42,43). This will be carried out by a multidisciplinary committee. It will take 3 iterative steps: 1/ two groups of researchers will attribute BCTs to contacts, 2/ both groups will compare their results and draw a consensus and 3/ researchers will present their results to the committee which will in turn draw a consensus. All components of e-TIS will be identified as universal BCTs of the taxonomy.

Each user will go through the intervention in his or her own way and this intervention theory will come across differently according to a combination of contextual factors including the pathway taken and the use of the website. This all leads to different intervention doses (number and type of BCTs to which the user is exposed) and to different response doses (module changes, end of platform use, smoking cessation, relapse, etc.) (44).

Stage 2 – Describe the pathway of users in the intervention arm: In this stage we will describe the user pathways within the e-TIS intervention, looking at the combinations of BCTs to which users are exposed (number, type, associations), the types of environmental and social factors encountered (social support, substitutes, life events, etc.) and the use of the e-TIS platform. From this we will be able to identify the most common pathway used through the intervention. To identify cluster of participants following similar pathway we will use the SAS Proc Traj (45). This procedure is a specialized application of finite mixture modeling designed to identify clusters of individuals following similar progressions of an outcome over time (or trajectory). Outcome variable will be smoking status (i.e. abstinence, quit attempts); time-varying dependent covariables will be BCTs used, progress through the modules and other factors measured during follow-up.

Stage 3 – Analyze the influence of user characteristics, processes, context and exposure to BCTs on the outcome: The clusters developed stage 2 will be used as dependent variables in a model designed to analyze the influence of users' characteristics (e.g. socio-demographic, dependency, motivation, quit attempts or experiences, added support, contextual factors) on the trajectory. For that we will use a multivariate, multi-level (i.e. participants, entry module and identified pathway) statistical analysis using the SAS Proc Mixed (46).The purpose of this analysis is to clarify how the generic theory best applies to the different users going through the intervention. It will therefore enable us to assess the mechanisms and conditions of the theory's efficacy, in relation to options for the degree of intervention, exposure to context and to the different dose responses.

Ethical considerations and dissemination

Participants must give their informed consent to participate in the study. They will be informed that they can refuse and drop out at any time. Subjects in the control arm will be asked to register to the e-TIS website once they have been deemed suitable for treatment via an initial evaluation. The data collected and processed in this study will be done so in compliance with the Act of 6 January 1978 on Data Processing, Data Files and Individual Liberties, as amended by the Act 2014-801 of 6 August 2004. The CNAMTS has a compliance undertaking with the CNIL (national body for data protection) as set out by Decree no. 2012-1249 of 9 November 2012 in the Conseil d'Etat (Council of State) which authorizes public health insurance funds (CNAMTS) to implement healthcare prevention and support programs for their beneficiaries.

The study protocol was reviewed by the ethical and deontological institutional review board of the INVS on 18 April 2016. All the proposals and recommendations put forward by the

ethics committee have been followed and integrated into the amended version of the protocol.

DISCUSSION

Behavioral change interventions are complex, with outcomes depending as much on the intervention itself as on participant characteristics and the context of intervention delivery (23,26,47). In the case, this variability is borne out in the literature - the demonstrated effects are very heterogeneous due to the influence of the population characteristics, the way the intervention is used by participants, and the context in which it is used. This is further compounded by the fact that the intervention is dematerialized and that each participant has a unique experience of it.

In view of the above, participant compliance should be improved and the support provided within the intervention should be fully tailored to the circumstances of each participants. For this to happen, we will need to work on two levels: intervention design, and evaluation design. Consequently the intervention has been based on data from literature and from the most used theoretical models used for helping people to quit. We have developed an evaluation protocol that no only allows us to conduct a thorough assessment of the intervention's efficacy via the RCT, but also seeks to clarify the conditions of its efficacy. These conditions relate to the participants; the different components of the TIS used by the participants; the psychological, social and environmental factors possibly affecting the participants during the study. To guide us, we use the references currently in use for evaluating complex interventions.

In this respect we hope both to contribute to better demonstrating the efficacy of online and mobile phone interventions, and to influence prevention strategies through an understanding of compliance and change phenomena.

ACKNOWLEDGMENTS

The authors wish to thank Jocelyn COURTOIS (CNAMTS), Eliane ALBUISSON, Marc BORIE and Geoffroy CAGNINACCI (CHU de Nancy), Viêt NGUYEN-THANH (Santé Publique France).

AUTHORS' CONTRIBUTIONS

LC and FA deals with the scientific coordination of the whole study; PB, IV, AP, LAL, BL, TD and PA designed the e-TIS intervention; LC prepared the first draft; all authors reviewed and contributed to the article.

COMPETING INTERESTS

We have read and understood BMJ policy on declaration of interests and declare that we have no competing interests.

REGISTRATION

The study is registered at www.clinicaltrials.gov (number = NCT02841683). The full trial protocol can be accessed on demand to the corresponding author.

FUNDING

This study is funded by the CNAMTS for the period 2016/2018.

LEGENDS OF FIGURES

Figure 1: Recruitment procedure

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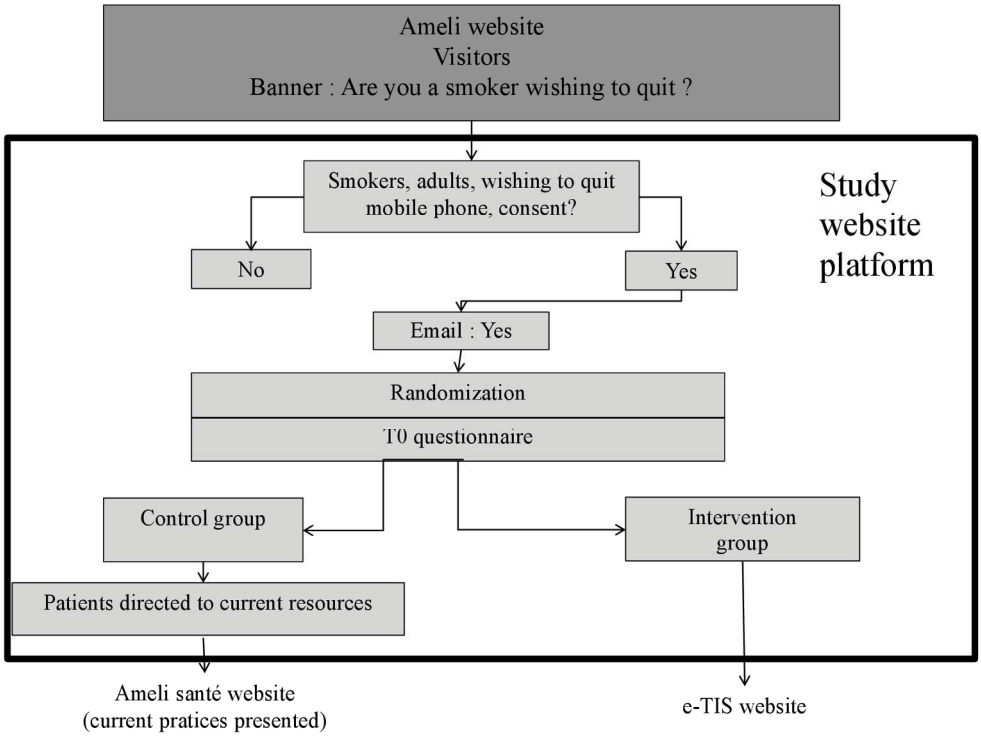

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CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3
	2b	Specific objectives or hypotheses	3/4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	4
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	5
Participants	4a	Eligibility criteria for participants	5
	4b	Settings and locations where the data were collected	4
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	5
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	8
	6b	Any changes to trial outcomes after the trial commenced, with reasons	8
Sample size	7a	How sample size was determined	5
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	5
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	5
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	5
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	5
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	5

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	NA
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	10/11
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	10/11
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	NA because protocol article
	13b	For each group, losses and exclusions after randomisation, together with reasons	NA because protocol article
Recruitment	14a	Dates defining the periods of recruitment and follow-up	NA because protocol article
	14b	Why the trial ended or was stopped	NA because protocol article
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	NA because protocol article
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	NA because protocol article
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	NA because protocol article
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	NA because protocol article
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	NA because protocol article
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	NA because

			protocol article
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	NA because protocol article
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	NA because protocol article
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	NA because protocol article
Other information			
Registration	23	Registration number and name of trial registry	2 and 13
Protocol	24	Where the full trial protocol can be accessed, if available	13
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	13

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.